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Clinical presentation and treatment of orthopaedic implant-associated infection

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Abstract. Zimmerli W (Interdisciplinary Unit of Orthopaedic Infections, Kantonsspital Baselland, University of Basel, Liestal, Switzerland). Clinical presentation and treatment of orthopaedic implant-associated infection (Review). *J Intern Med* 2014; **276**: 111–119.

Orthopaedic implants are highly susceptible to infection. The aims of treatment of infection associated with internal fixation devices are fracture consolidation and prevention of chronic osteomyelitis. Complete biofilm eradication is not the primary goal, as remaining adherent microorganisms can be removed with the device after fracture consolidation. By contrast, in periprosthetic joint infection (PJI), biofilm elimination is required. Surgical treatment of PJI includes debridement with retention, one- or two-stage exchange and removal without reimplantation. In addition, prolonged antibiotic treatment, preferably with an agent that is effective against biofilm bacteria, is required. Rifampicin is an example of an antibiotic with these properties against staphylococci. However, to avoid the emergence of resistance, rifampicin must always be combined with another antimicrobial agent. With this novel treatment approach, orthopaedic implant-associated infection is likely to be eradicated in up to 80–90% of patients. Because most antibiotics have a limited effect against biofilm infections, novel prophylactic and therapeutic options are needed. Surface coating with antimicrobial peptides that reduce bacterial attachment and biofilm formation can potentially prevent implant-associated infection. In addition, quorum-sensing inhibitors are a novel therapeutic option against biofilm infections.

Keywords: biofilm, fluoroquinolone, internal fixation, prosthetic joint infection, rifampicin, *Staphylococcus aureus*.

Introduction

Orthopaedic implants are mainly used for bone fixation and joint replacement [1–3]. Internal fixation devices are only temporarily needed and can be removed after healing of a bone fracture. Prosthetic joints replace the irreversibly damaged articulation, mainly in patients with osteoarthritis or inflammatory arthritis [4]. The aim of joint replacement is alleviation of pain and improvement of function. With increasing life expectancy, increasingly more patients suffer from osteoarthritis and therefore need joint replacement. By contrast, a decreasing number of patients with rheumatoid arthritis require arthroplasty, due to the availability of efficacious disease-modifying drugs [4]. Artificial joints are kept in the body as long as their function is intact and the patient is free of pain. Between 1990 and 2007, the number of total hip replacements in the USA increased two-fold to 200 000, and the number of total knee arthroplasties increased almost five-fold to 550 000 [5]. In Finland, the number of hip replacements increased from 5000 to 9200, and of knee replacements from 3000 to 9100 between 1995 and 2009 [4]. These figures show a significant increase in joint replacement on both sides of the Atlantic; however, the indication for knee replacement is clearly less strict in the USA, as compared to Finland where an equal number of hips and knees were replaced in 2009.

Implanted foreign bodies are highly susceptible to bacterial and fungal infection. This is due to locally compromised host defence [6–9]. The risk of infection after internal fixation is between 0.4% and up to 16.1% according to the type of fracture (closed or varying degrees of open infection) [10, 11]. After joint replacement, periprosthetic joint infections (PJIs) occur in 0.3–1.7%, in 0.5–2% and in 2–9% of patients after total replacement of the hip, knee and ankle, respectively [12, 13]. The economic burden of PJI is steadily increasing, because the number of prosthetic joints is increasing and also because implants can be infected via the

bloodstream (i.e. the haematogenous route) as long as they remain in the body (see below) [14–17].

Rapid detection of infection is of paramount importance because delaying the start of treatment of PJI may result in the loss of the device [18, 19]. Here, the classification, clinical presentation and management of orthopaedic device-related infections will be reviewed.

Classification

Internal fixation devices

Infections associated with internal fixation devices can be classified according to their pathogenesis: exogenous, haematogenous and contiguous. Exogenous infections occur either in the perioperative period or as a consequence of a penetrating event (e.g. joint tap). There is a persistent lifelong risk of haematogenous seeding on orthopaedic devices [20]. However, the risk is clearly lower on internal fixation devices than on artificial joints [14]. Infections can also be classified according to the time interval between surgery and clinical manifestation. Early infections are mainly caused by virulent microorganisms, such as *Staphylococcus aureus*, and diagnosed within <3 weeks after implantation of the orthopaedic device. Delayed infections are typically due to less virulent bacteria, such as coagulase-negative staphylococci, and develop between 3 and 10 weeks. Finally, late infections occur more than 10 weeks after implantation and are either caused by haematogenous seeding or by recurrence of inadequately treated early infection [21].

PJIs

The classical definition of wound infection by the Centers for Disease Control and Prevention should not be used for implant-associated infections because superficial and deep (implant-associated) wound infections cannot be reliably clinically differentiated [22, 23]. Therefore, the Infectious Disease Society of America (IDSA) proposed a definition, which is summarized in Table 1 [18, 19, 23–26]. Traditionally, PJIs are classified as early (<3 months after surgery), delayed (3–24 months after surgery) and late (>2 years after surgery) infections [18, 19]. However, this classification is not useful for planning the therapeutic management of PJIs. We have therefore proposed a novel classification, which considers surgical treatment concepts (Table 2) [27]. Acute haematogenous PJIs of <3 weeks' duration and early postinterventional PJIs occurring within 1 month after implantation can generally be treated with implant retention (see below) [18, 28]. By contrast, in patients with a chronic PJI, the biofilm adhering to the implant generally cannot be eliminated by antimicrobial agents. Therefore, the implant has to be removed and/or replaced [18, 19, 29].

Clinical presentation

Internal fixation devices

The clinical presentation of infections associated with internal fixation devices is multifaceted [21] and depends on (i) the preceding trauma and/or surgical procedures, (ii) the anatomical localization, (iii) the quality of bone and surrounding soft tissue, (iv) the time interval between microbial inoculation (trauma, surgery) and manifestation of infection and (v) the type of microorganism. Early postoperative infection (<3 weeks) is generally characterized by erythema, local hyperthermia, protracted wound healing and a secreting wet wound. Thus, wound healing disturbances after internal fixation are highly suspicious of early

Table 1 *Diagnostic criteria for periprosthetic joint infection (PJI)*[a] *[19]*

• Presence of a sinus tract communicating with the prosthetic joint
• Presence of purulence without another known aetiology surrounding the prosthetic device
• Acute inflammation consistent with infection on histopathological examination of periprosthetic tissue
• Elevated leukocyte count in the synovial fluid and/or predominance of neutrophils [24–26]
• Growth of identical microorganisms in at least two intraoperative cultures or a combination of preoperative aspiration and intraoperative cultures in the case of a microorganism of low virulence (e.g. coagulase-negative staphylococci, *Propionibacterium acnes*). In the case of a virulent microorganism (e.g. *Staphylococcus aureus, Escherichia coli*), growth in a single specimen from synovial fluid, periprosthetic tissue and/or sonication fluid may also represent PJI. However, if there is growth only in one single specimen, other criteria for infection must be present [19].

[a]At least one of the five criteria is required for the diagnosis of PJI.

Table 2 *Novel classification of periprosthetic joint infection (PJI) [27]*

Type of PJI	Characteristics
Acute haematogenous	Infection with a duration of symptoms of 3 weeks or less after an uneventful postoperative period
Early postinterventional	Infection that manifests within 1 month after an invasive procedure such as surgery or arthrocentesis
Chronic	Infection with symptoms that persist for more than 3 weeks, beyond the early postinterventional period

infection and should be managed as such. The first step is always debridement surgery for diagnostic and therapeutic purposes. Delayed (3–10 weeks) or chronic (≥10 weeks) infections are typically due to low-virulence microorganisms such as coagulase-negative staphylococci. However, they may also result from inadequate treatment of early infection. If a patient with wound healing disturbance is treated with a short course of antibiotics without debridement surgery, clinical signs of suppressed early infection typically reappear at a later time. Delayed and chronic infections manifest as persistent pain and/or signs of local inflammation, such as erythema, swelling or intermittent drainage of pus (sinus tract) (Fig. 1, left panel). Radiologically, delayed consolidation (Fig. 1, right panel, large arrow), pseudoarthrosis, bone sequesters and soft-tissue calcification (Fig. 1, right panel, small yellow arrows) can be observed.

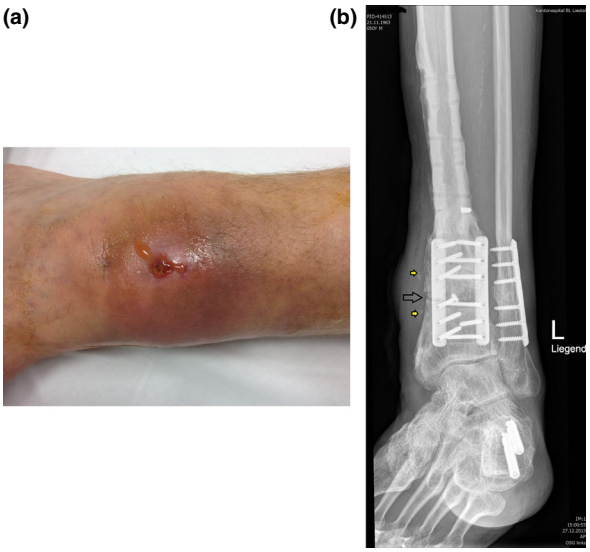

Fig. 1 *A 50-year-old man with chronic implant-associated osteomyelitis due to Staphylococcus aureus. In 2003, the patient underwent internal fixation after fracture of the left lower leg; this was followed in 2007 by revision surgery because of malunion. In July 2013, he underwent valgisation osteotomy of the distal tibia and fibula because of consolidation in malposition of the axis. Left panel: the presence in December 2013 of local inflammation, erythema, swelling and sinus tract. Right panel: insufficient bone healing (large black arrow) and tissue calcification (small yellow arrows) 5 months after internal fixation.*

PJIs

Acute PJIs occurring after seeding from the bloodstream are typically preceded by a systemic infection such as sepsis, skin and soft-tissue infection, pneumonia or enterocolitis [15, 30, 31]. However, the first signs may also be new-onset joint pain, initially without local inflammation, after clinically asymptomatic bacteraemia [32]. The sepsis syndrome is only observed in one-third of patients. However, in most patients, the C-reactive protein level is >75 mg/L [33]. The most common aetiological agents are *S. aureus*, haemolytic streptococci and Gram-negative bacilli [15, 18, 34, 35].

Early postoperative PJIs are typically exogenously acquired either during implantation or in the early postoperative period before the patient's drains have been removed. The risk is especially high in patients suffering from a secreting or a gaping wound. Local signs of wound infection and pain predominate (Fig. 2). In exogenous staphylococcal PJI, a temperature >38.3 °C is present in only one-quarter of patients, and the sepsis syndrome in <10% [33]. All patients with acute symptoms, regardless the time after implantation of the orthopaedic device, require prompt diagnostic work-up because the chance of retaining the implant is high if the duration of symptoms is short (see below) [18, 19, 28, 36].

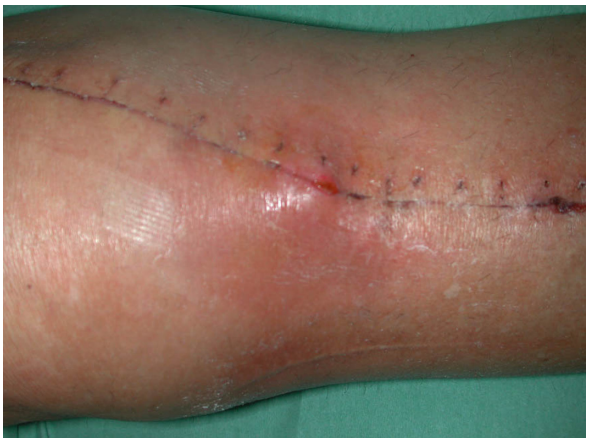

Fig. 2 *Three weeks after a total knee replacement because of osteoarthritis in a 69-year-old man. Postoperative wound healing disturbances with protracted secretion, erythema and hyperthermia of the knee. Follow-up revealed early postoperative periprosthetic joint infection caused by Staphylococcus aureus. After treatment with debridement and implant retention, follow-up for >2 years was uneventful.*

Chronic PJIs are either exogenously or haematogenously acquired. Chronic exogenous infections lasting ≥1 month are acquired during the perioperative period. They are typically caused by microorganisms of low virulence, including coagulase-negative staphylococci and *Propionibacterium acnes*. These microorganisms generally cause low-grade infections, which are diagnosed with a considerable delay. Chronic PJIs are characterized by chronic joint effusion, pain due to inflammation or implant loosening (Fig. 3), local erythema and hyperthermia, and occasionally by recurrent or permanent sinus tracts. Typically, routine follow-up markers such as C-reactive protein and/or erythrocyte sedimentation rate do not normalize after surgery and fluctuate within a slightly elevated range.

Risk of haematogenous implant-associated infection

During bacteraemia, intravascular devices, such as artificial heart valves or vascular prostheses, are a favourite site for bacterial seeding [37, 38]. Therefore, whether extravascular foreign bodies are also at risk during episodes of bacteraemia is questionable. Implants are highly susceptible to infection. It has been shown that the risk of infection is >100 000-fold increased by the presence of a foreign body [7, 39]. This is due to a

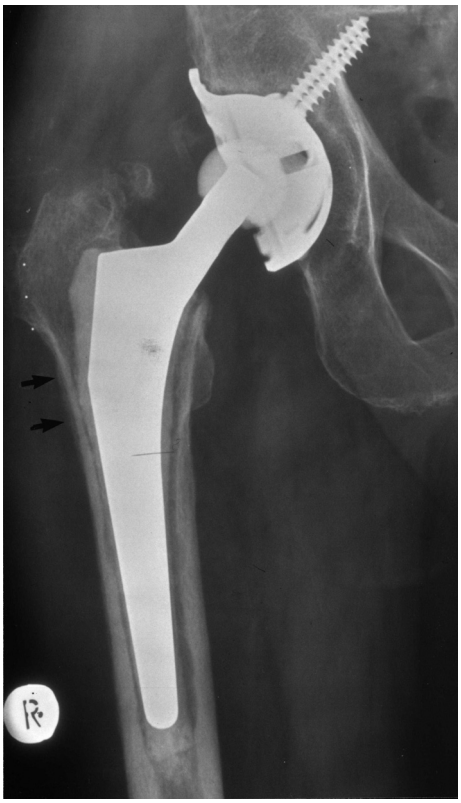

Fig. 3 *Nine months after treatment with a hip prosthesis because of osteoarthritis in a 73-year-old man. After surgery, he experienced continuing pain in his prosthetic hip joint. Clinically, there were no signs of inflammation. A plain radiograph revealed signs of early loosening and periosteal reaction (arrows). The patient was diagnosed with chronic periprosthetic hip joint infection due to Staphylococcus epidermidis* and was treated with one-stage exchange *and a 3-month course of antibiotics (rifampin plus levofloxacin).*

locally acquired granulocyte defect around implants, caused by so-called 'frustrated phagocytosis' [6, 8]. Therefore, it is highly probable that any implant is at risk of infection during episodes of bacteraemia. Indeed, Blomgren *et al.* [40, 41] showed in a rabbit model that knee prostheses could be infected by the haematogenous route. We quantified the risk of bacterial seeding in the guinea pig tissue cage infection model [42]. With an *S. aureus* bacteraemia of 1000 CFU per mL blood, 42% of subcutaneous implants could be selectively infected. With a lower bacterial density in the bloodstream, no extravascular devices were infected. However, at a higher bacterial load, bacterial seeding was not selective; in addition to

implants, kidney, liver, spleen and lungs were also infected. In summary, implants are a common site of bacterial seeding at a bacterial density occurring during *S. aureus* bacteraemia (1000 CFU/mL blood) but not at lower levels such as during dental treatment (<50 CFU/mL blood) [16, 43].

Internal fixation devices

Most infections associated with internal fixation devices are acquired exogenously, typically in the perioperative period. Infections via the bloodstream can occur at any time after surgery and have been mainly observed after bacteraemia due to *S. aureus* or *Salmonella* spp. [20, 44]. The risk of bacterial seeding on an internal fixation device during *S. aureus* bacteraemia has been shown to be at least 7% [14, 45].

PJIs

Haematogenous PJI can be defined as infection manifesting for more than 2 years following implantation after a previously uneventful course. In addition, if the first signs of PJI follow an episode of documented bacteraemia or an infection at a distant focus, it can be considered to be haematogenously acquired, regardless of the time interval after surgery. The risk of haematogenous PJI is highest during the first 2 years after implantation (5.9 episodes per 1000 joint-years), but persists throughout the lifetime of the prosthetic joint (2.3 episodes per 1000 joint-years) [17]. In most case series, the fraction of patients with haematogenous versus exogenous PJI is not reported. In our cohort of patients with total knee and hip arthroplasty, 37.5% and 33.3% of the episodes, respectively, were acquired haematogenously [12, 46]. If only patients with PJI due to *S. aureus* are considered, the fraction of haematogenous infection was as high as 70% [33].

In three different studies of patients with *S. aureus* sepsis with a non-infected artificial joint, haematogenous seeding on the implant was been observed in 34–39% of cases [14, 15, 45]. In patients with multiple prosthetic joints, *S. aureus* occasionally even causes oligoarthritis [15]. Taken together, the findings suggest that calculating the rate of PJI only during a 2-year period after surgery seriously underestimates the rate, because of the lifelong risk of infection. For this reason, the absolute number of PJIs increases not only in relation to the number of implanted artificial joints, but also to the total joint-years of use.

Treatment

Surgical management of infection associated with internal fixation devices

The aims of treating infection associated with internal fixation devices are fracture consolidation and prevention of chronic osteomyelitis. In contrast to PJI, complete eradication of infection associated with internal fixation devices is not the primary goal, as long as the persistent biofilm does not impair bone healing. Complete healing generally occurs as soon as the foreign material is removed after fracture consolidation. Stability of the fracture is crucial for preventing and treating device-associated infection [47]. Therefore, maintenance of stable internal fixation devices has been suggested; however, success rates vary between 68% and 100% [28, 48, 49]. This wide variation is probably due to the type of antibiotics used, as the choice of appropriate antimicrobial agents is crucial for the treatment of biofilm infection (see below).

The principal aims of surgical management are debridement and stabilization. The technique of debridement includes diagnostic biopsy for microbiological and histological evaluation. In addition, thorough removal of pus, necrotic tissue, dead bone, abscess membranes and granulation tissue is important. If the fracture is still stable and the patient is not suffering from sepsis, the device can be maintained. Otherwise, it must be replaced either by another internal or by an external fixation device. In the case of chronic osteomyelitis with damage to the skin and soft tissues, orthopaedic procedures should be combined with a plastic and reconstructive intervention [50].

Surgical management of PJIs

The traditional surgical treatment of PJI is a two-stage exchange of the device. The first intervention includes thorough removal of necrotic tissue, bone cement and all prosthetic material. The patient is treated with antibiotics during the implant-free period, before the new artificial joint is implanted [51]. Because this procedure is invasive and generally leads to functional impairment, less-invasive treatment approaches have been increasingly used [52]. However, less-invasive procedures (one-stage exchange and debridement with retention) have

higher failure rates if the selection of patients is not appropriate, that is, if patients with sinus tracts or loose implants are treated with retention [53–57]. During the last two decades, we have developed an algorithm for the optimal surgical therapy of patients with different presentations of PJI [18, 36]. In brief, four curative procedures are available: debridement with retention; one-stage exchange; two-stage exchange involving a short interval between steps; and two-stage exchange with a long interval. According to this algorithm, only patients with acute haematogenous infections diagnosed within 3 weeks and patients with early infection up to 1 month after surgery can be successfully treated with implant retention [27]. Therefore, rapid diagnosis is of paramount importance. In all other patients, the implant must be removed to obtain a high chance of cure. The details of these procedures have recently been reported and are beyond the scope of this review [58]. If the appropriate intervention is selected for each patient, the cure rate is above 80% for all four procedures [12, 46]. Patients not qualifying for any of these interventions can be treated with a palliative procedure, that is, implant removal without replacement or, currently in a small minority, amputation. In addition, in patients with a very high surgical risk, long-term suppressive antimicrobial therapy without surgery may be an option [18].

Choosing the least invasive treatment that cures infection is the most rational approach. Because no controlled study comparing the different surgical options has been conducted, treatment recommendations are based on cohort studies, case series and expert opinion. From these data, international guidelines have been developed [19].

Antimicrobial therapy

In contrast to many other infections, such as pneumonia or urinary tract infection, PJIs never spontaneously heal. Even long-term antimicrobial therapy frequently fails [53]. Until recently, it has been generally considered that PJI cannot be cured without removal of the device. However, if risk factors for failure are considered and appropriate antibiotics used, many PJIs can be treated with implant retention [12, 18, 28, 46].

Implant-adherent bacteria persist as a biofilm [6]. Such bacteria are in a stationary phase of growth because oxygen and glucose are limited in biofilms [59]. Therefore, successful treatment of implant-associated infection should consider this property of the microorganisms. *In vitro* studies revealed that most antimicrobial agents have a minimal bactericidal concentration (MBC), which is much higher during the stationary than the logarithmic phase of growth [32, 60–69]. In addition, antibiotics with a high stationary MBC are not able to clear bacteria adhering to sinter glass beads [64, 70, 71]. The high stationary-phase MBCs and the lack of efficacy against adherent bacteria are predictive of the failure of antibiotics in implant-associated infections [28, 32, 35]. To date, only two classes of drugs have shown the properties that are needed for efficacious elimination of biofilm bacteria. Rifampicin and other rifamycins act on biofilm staphylococci [28, 69, 72–75] and fluoroquinolones on Gram-negative bacilli [32, 35, 66]. Clinical details of the antimicrobial treatment of PJI have been reported recently [6, 58].

Requirements for prevention and treatment of biofilm infections

Most antimicrobial agents have a limited efficacy against biofilm infections; therefore, novel preventive and therapeutic options are needed. Implant materials that inhibit biofilm formation at their surface would be an attractive option. However, in an animal model, it was shown that the type of metal used (titanium versus stainless steel) had only a minor effect on susceptibility to staphylococcal infection [76]. It is conceivable that susceptibility to infection does not vary for different materials because a foreign device is coated with host proteins as soon as it is implanted and thereby remains in contact with interstitial fluid and blood. Some of these proteins, such as fibronectin, fibrin and laminin, act as receptors for staphylococci [77, 78]. Indeed, in the absence of host proteins, surface properties alter bacterial adhesion, but convincing *in vivo* differences have not been reported (for review see [79]). Thus, the coating proteins are more important in terms of adhesion of microorganisms than the material of the device. Therefore, adhesion could be better prevented by an implant coating with monoclonal antibodies against fibronectin than an antiadhesive material [80]. Surface coating with antibiotics may prevent infection. This concept has been proven in central venous catheters coated with rifampicin/minocycline [81]. However, the risk of selecting antibiotic-resistant microorganisms by this technique is considerable. Therefore, other nonantibiotic substances such as silver or antimicrobial peptides should be recommended.

Preclinical *in vitro* and *in vivo* data are favourable [82–84]; however, clinical data are still lacking.

Regarding new therapeutic options, agents with efficacy against biofilms are urgently needed. The quorum-sensing inhibitor RNAIII-inhibiting peptide is such a compound. However, preclinical data are controversial, and clinical data are still lacking. This peptide seems to act prophylactically, but not against established biofilms [85, 86]. Analysing specific crucial bacterial genes in biofilms may enable novel antimicrobial agents specifically acting against biofilms, and therefore against implant-associated infections, to be detected in the future.

Conclusions

Infections associated with internal fixation devices and with prosthetic joints have similar clinical properties. Both are biofilm infections, which are generally accompanied by osteomyelitis. Haematogenous seeding on osteosynthesis material is rare, whereas it is fairly common on prosthetic joints. The risk is especially high with *S. aureus* bacteraemia. Infections associated with internal fixation devices can be treated with implant retention, as long as the fracture is stable. By contrast, retention of an artificial joint is only successful in the case of acute haematogenous or early postoperative PJIs. Rifampicin is still the only drug with high activity against implant-associated staphylococci, and fluoroquinolones are the only active agents against Gram-negative bacilli associated with orthopaedic implants. Surgical treatment should follow a well-defined treatment algorithm. Prevention may be achieved in the future by implant coating with novel substances. Additionally, novel antimicrobial agents that act specifically on established implant-adherent biofilms are required.

Conflict of interest statement

The author has no conflict of interests to declare.

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