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Diagnosis and treatment of infections associated with fracture-fixation devices

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KEYWORDS:
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Summary[1] The pathogenesis of infections associated with fracture-fixation devices is related to microorganisms growing in biofilms, which render these infections difficult to treat. These infections are classified as early (< 2 weeks), delayed (2–10 weeks) or late infections (> 10 weeks) according to the implant surgery. Most infections are caused by staphylococci and are acquired during trauma (in penetrating injuries) or subsequent fracture-fixation procedures. A combination of clinical, laboratory, histopathology, microbiology, and imaging studies are usually needed to accurately diagnose infection. Magnetic resonance imaging (MRI) and computed tomography (CT) scans are often used to diagnose infection and plan surgical treatment. Positron emission tomography (PET) and PET-CT are promising new tools for diagnosing implant-associated osteomyelitis. The treatment goal is achieving bone consolidation and avoiding development of chronic osteomyelitis. Successful treatment requires adequate surgical procedures combined with 6–12 weeks of antimicrobial therapy acting on adhering stationary-phase microorganisms. In chronic osteomyelitis, orthopedic and plastic-reconstructive surgery is combined in the same procedure or within a short time span. In this article, pathogenesis, classification, diagnosis, and treatment of infections associated with intramedullary nails, external-fixation pins, plates, and screws are reviewed.

Introduction

Orthopedic devices are increasingly used for fracture fixation, including intramedullary nails, external-fixation pins, plates, and screws. In the United States, about 2 million fracture-fixation devices are inserted annually [1]. The use of single shot antimicrobial prophylaxis or preemptive therapy for third degree open fractures has substantially decreased the frequency of implant-associated infections [2]. On average, about 5% of initially inserted internal fixation devices become infected and the average cost of combined medical and surgical treatment is estimated at US$ 15,000 [1]. The incidence of infection after internal fixation of closed fractures is generally lower (1–2%), whereas the incidence may exceed 30% after fixation of open fractures [3–6].

Due to the absence of well-designed studies with a sufficient follow-up period, diagnosis and treatment of implant-associated infections is mainly based on tradition, personal experience, and liability aspects, and therefore differs substantially between institutions and countries. In this review, we discuss pathogenesis, classification, diagnosis, and treatment of fracture-fixation devices.

[1] Abstracts in German, French, Italian, Spanish, Japanese, and Russian are printed at the end of this supplement.

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Pathogenesis

Implant-associated infections are typically caused by microorganisms growing in biofilms [7]. These microorganisms live clustered together in a highly hydrated extracellular matrix attached to a surface (Fig 1). Depletion of metabolic substances and/or waste product accumulation in biofilms causes microbes to enter into a slow- or nongrowing (stationary) state, rendering them up to 1,000 times more resistant to most antimicrobial agents than their planktonic (free-living) counterparts [8, 9].

Adherence of microorganisms to the surface of the implant involves rapid attachment to the surface by specific factors (such as adhesins) or nonspecific factors (such as surface tension, hydrophobicity, and electrostatic forces) [10]. This initial phase of adherence is followed by an accumulative phase during which bacterial cells adhere to each other and form a biofilm. The presence of a foreign body has been shown to significantly increase susceptibility to infection. For example, the minimal infecting dose of *Staphylococcus aureus*, causing an abscess in guinea pigs, was more than 100,000-fold lower in the vicinity of subcutaneous devices than in skin without an implant [11]. The increased susceptibility to infection is at least partially due to a locally acquired granulocyte defect induced by phagocytic mechanisms [11, 12].

Infections associated with internal fracture fixation generally occur exogenously by the pen-

Classification	Characteristic
According to the route of infection	
• Perioperative	Inoculation of microorganisms into the surgical wound during surgery or immediately thereafter
• Contiguous	Wound contamination due to penetrating trauma (open fractures) or from an adjacent focus of infection (skin and soft-tissue lesions)
• Hematogenous	Microbial spread through blood or lymph from a distant focus of infection (eg, skin, lung, urinary tract)
According to the onset of symptoms after implantation	
• Early infection (< 2 weeks)	Predominantly acquired during trauma or implant surgery, caused by highly virulent organisms (eg, *S. aureus*, Gram-negative bacilli)
• Delayed infection (2–10 weeks) and late infection (> 10 weeks)	Predominantly acquired during trauma or implant surgery and caused by low virulence organisms (eg, coagulase-negative staphylococci); occasionally caused by hematogenous seeding from remote infections

Table 1: Classification of infections associated with fracture fixation devices.

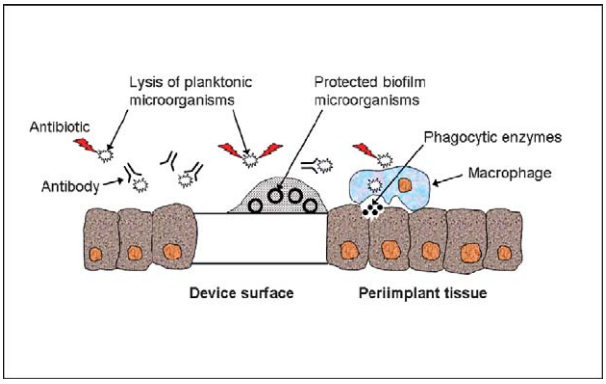

Fig 1: Representation of planktonic microorganisms, killed by antibiotics and the immune system, and biofilm microorganisms, attached to a surface and protected in an extracellular matrix.

Microorganism	Frequency (%)
Staphylococcus aureus	30
Coagulase-negative staphylococci	22
Gram-negative bacilli	10
Anaerobes	5
Enterococci	3
Streptococci	1
Polymicrobial	27
Unknown	2

Table 2: Commonly identified microorganisms causing infections associated with fracture-fixation devices (adapted from Trampuz et al [17]).

etrating trauma itself (preoperatively), during insertion of the fixation device (intraoperatively), or during disturbed wound healing (postoperatively) [13–15]. Hematogenous infection is less frequent and is mainly caused by bacteremia originating from the skin, and respiratory, dental, and urinary tract infection (Table 1) [16]. The most common microorganisms causing implant-associated infections are shown in Table 2. In a retrospective study of 132 consecutive patients with an internal-fixation-device-associated infection, more than one pathogen was isolated in 27%; the most common pathogens were *S. aureus* (30%), coagulase-negative staphylococci (22%), and Gram-negative bacilli (10%) [17].

Classification

Infections after internal fixation are classified into those with early (less than 2 weeks), delayed (2–10 weeks), and late onset (more than 10 weeks) (Table 1) [18–20]. Infections with delayed and late manifestations are usually grouped together, since their clinical presentation, treatment, and prognosis are similar [21].

Early infection: Leading clinical signs of early infections are persisting local pain, erythema, edema, wound healing disturbance, large hematoma, and fever. Highly virulent organisms (eg, *S. aureus*, Gram-negative bacilli) are frequent agents of early infection. In cases of wound healing disturbance, necrosis of the wound edges or postoperative hematoma and infection must be actively sought (see diagnostic procedures below) [22, 23].

Delayed and late infection: Persisting or increasing pain, pseudoarthrosis, implant loosening, and occasionally development of a sinus tract are hallmarks of a delayed infection. However, clinical signs and symptoms of infection may be entirely lacking. Delayed and late infections are mainly caused by microorganisms of low virulence (eg, coagulase-negative staphylococci). Alternatively, manifestation of infection due to any microorganism may be delayed because initial antimicrobial treatment was not sufficient for complete microbial eradication. Late infection may be caused by a low inoculum or the low virulence of microorganisms introduced during penetrating trauma or perioperatively with an insidious onset of systemic or local symptoms. In contrast to prosthetic joint infections, hematogenous infection of the fracture-fixation devices occur less frequently [24].

Diagnosis

No single routinely used test is sufficiently accurate to diagnose infection. Therefore, a combination of clinical, laboratory, histopathology, microbiology, and imaging studies is usually required.

Laboratory signs of inflammation

Blood leukocyte count and differential are neither sufficiently sensitive nor specific to predict infection. After surgery, C-reactive protein (CRP) is elevated and returns to normal within weeks. Therefore, in the postoperative period, repeated measurements are more informative than a single value. A secondary increase of CRP, after an initial postoperative decline, is highly suggestive of infection.

Microbiology and histopathology

Preoperative aspirate of fluid accumulation and intraoperative tissue cultures provide the most accurate specimens for detecting the infecting microorganism. At least three intraoperative tissue areas should be sampled and paired for microbiology and histopathology. The degree of infiltration with acute inflammatory cells may vary considerably between specimens from the same patient. Therefore, areas with the most florid inflammatory changes should be assessed. Swabs should be avoided because of low sensitivity. It is important to discontinue any antimicrobial therapy at least two weeks before tissue sampling for culture, if possible [25]. Perioperative prophylaxis at revision surgery should not be started until after the tissue specimens have been collected for culture [26]. If the implanted material is removed, it can be cultured in enrichment broth media. However, the risk of contamination during processing is high. The use of sonication to dislodge microorganisms from the surface of explanted devices may increase the sensitivity of the culture [27, 28]. Quantitative molecular methods such as polymerase chain reaction (PCR) may further facilitate diagnosis as an extremely sensitive diagnostic method [7].

Imaging studies

Imaging plays an inferior role in early infection, whereas it is useful in delayed and late infections to assess the extent of infection.

Plain x-ray: Examination of serial plain x-rays after implantation is helpful, but is neither sensitive nor specific for infection. Implant loosening may indicate either instability or infection, although in case of early loosening, infection is a more probable cause. Similarly, widening of the fracture gap may be caused by infection or a lack of blood supply to the fractured bone ends. Ultrasonography may detect fluid accumulations around the implant and can be used to guide joint aspiration and drainage procedures.

Nuclear imaging: 3-phase skeletal scintigraphy with ^{99m}Tc has little value in acute fractures and in the early postoperative period. This method detects increased bone remodeling, which is normally present after fracture and around the implant during at least the first postoperative year. A lack of ^{99m}Tc accumulation indicates devascularization and dead bone. Skeletal scintigraphy cannot differentiate aseptic loosening from infection. Scintigraphy with ^{99m}Tc-labelled monoclonal antibodies demonstrates a higher accuracy for detection of infection. Overall, nuclear medicine imaging techniques are sensitive, but their specificity in evaluating implant-associated infection is still controversial.

Computed tomography (CT) gives additional information on the extent of bone necrosis. **Magnetic resonance imaging (MRI)** displays an improved resolution for soft tissue abnormalities compared to CT or radiography and greater anatomical detail than radionuclide scans. The main disadvantages of CT and MRI are imaging interferences in the vicinity of metal implants. **Positron emission tomography** (PET) and PET-CT appear to be valuable new techniques in the diagnosis of implant-associated osteomyelitis [29]. They are based on the detection of radiation from the emission of positrons emitted from a radioactive substance administered to the patient. The combined imaging of PET-CT should result in far fewer false diagnoses.

Treatment

Surgical therapy

The goals of treating infection associated with internal fixation devices are consolidation of the fracture and prevention of chronic osteomyelitis. Thus, in contrast to prosthetic joint associated infection, complete eradication of infection is not the primary goal, since the device can be removed after consolidation. The nature of the surgical intervention in patients with infected fracture-fixation devices depends on the type of device, the presence or absence of bone union, and the patient's underlying condition [1]. If the implant is stable, debridement with retention of the fracture-fixation device combined with long-term antibiotic treatment is reasonable [30, 31]. Where there is dead tissue or abundant purulence, repeated debridement is usually required.

Delayed wound closure is generally associated with microbial contamination. Therefore, free tissue transfer may be considered for exposed bone or hardware. If wound edges become necrotic, local excision and split skin grafting is indicated. As hematoma provides a suitable growth medium for microorganisms, painful or fluctuating blood collections should be revised with appropriate microbiological investigation.

In cases of chronic osteomyelitis associated with a fixation device, surgical therapy should always include both orthopedic and plastic-reconstructive intervention since neither exclusive soft-tissue covering nor exclusive bone repair has a fair chance of curing long-standing bone infection, which is often complicated by sinus tracts and bone sequesters. Longer duration of infection and larger areas of involved bone or soft tissue require more radical surgical intervention and longer antimicrobial treatment, and are associated with a worse outcome [32].

Currently, only one randomized placebo-controlled study has investigated the treatment of infection associated with orthopedic devices [30]. All patients were treated with debridement and device retention, and long-term antibiotic treatment with ciprofloxacin plus either placebo or rifampin was administered. In those patients who tolerated long-term antibiotic therapy, the cure rate of staphylococcal orthopedic-implant-associated infections with ciprofloxacin plus rifampin was 100% [30]. In this study, complete eradication of all surface adhering microorganisms was tested by culturing the removed fixation device in broth. The results of this study have been confirmed in a recent prospective observational study showing a probability of survival without treatment failure of 86% at three years [31]. In both studies, patients with internal fixation devices and prosthetic joints were included. In a recent retrospective study of 132 consecutive patients with infection associated with internal fixation devices, 88% had a successful outcome after more than one year (86% with debridement and device retention and 91% with device removal) [17].

Direct exchange includes removing the old fixation device and implantating a new one during the same surgical procedure. If resistant or difficult-to-treat microorganisms are causing the infection (eg, methicillin-resistant *S. aureus* (MRSA), small-colony variants of

staphylococci, enterococci, quinolone-resistant *Pseudomonas aeruginosa* or fungi), complete hardware removal and external fixation is preferable.

Pin-track infection: In a retrospective study of 285 patients with external fixation, the incidence of pin-track infection was on average 11%. The incidence of infection was 4% for ring fixators, 13% for unilateral fixators, and 20% for hybrid fixators [33]. Erythema surrounding the external fixation pins is a frequent finding, usually only representing local irritation of the surrounding soft tissue. Occasionally, necrotic bone fragments form a ring sequester [34]. Surgical treatment of pin-track infection usually consists of removing the infected pins and a short course of antibiotics. If bone union has not yet occurred; new pins should be inserted at a distant site. Alternatively, internal fixation (eg, medullary nail) can be inserted. Coating the pins with hydroxyapatite appears to improve the amount of bone contacting the bone-pin interface [35].

Osteomyelitis after plating: After plating, devascularized areas may occur at the interface between the plate and bone and between the plate and soft tissue, even after preservation of the periosteum. Necrotic and infected bone fragments will eventually demarcate and sequestrate, with loss of stability and an infected nonunion. Infections associated with subcutaneous plate fixations produce early clinical symptoms, whereas those associated with submuscular or subfascial plates are often recognized only at a late time point.

Osteomyelitis after intramedullary nailing: Unreamed and reamed nailing may lead to partial necrosis of the central parts of the bone cortex. Dead bone prevents normal fracture healing, and in cases of infection may lead to an infected nonunion that is hard to salvage [36, 37]. Infection of intramedullary nails is often associated with nonunion of bone and requires removal of the infected nail, insertion of external-fixation pins, and if necessary, subsequent insertion of a replacement nail. Antimicrobial-impregnated beads may be inserted into the canal for a limited period of time (eg, ten days). Where there is insufficient fracture healing, bridging of the fracture site with external fixation may be used to prevent recurrence of the fracture.

Antimicrobial therapy

If no antibiotic with efficacy on adherent bacteria is available (see below), treatment with implant retention is generally only suppressive, operating until the implants can be definitively removed. In such cases, antibiotics should be discontinued at least two weeks before removing the implants to collect reliable intraoperative tissue specimens for culture. If intraoperative cultures are positive, antimicrobial treatment should be continued for about 4–6 weeks after hardware removal to avoid development of chronic osteomyelitis.

Suggested antimicrobial treatment according to the pathogen and its antimicrobial susceptibility is summarized in Table 3 [38]. The suggested treatment duration is 3 months in cases of device retention and 6 weeks after removal of the infected fixation device [30]. Intravenous treatment should be administered for the first 2–4 weeks, followed by oral therapy to complete the treatment course.

The optimal antimicrobial therapy is best defined in staphylococcal implant infections, and includes rifampin in susceptible staphylococcal strains [30]. Rifampin has an excellent activity on slow-growing and adherent staphylococci, and has proved its activity in several additional clinical studies [31, 39, 40]. It must always be combined with another drug to prevent emergence of resistance in staphylococci. Quinolones are excellent combination drugs because of their good bioavailability, activity, and safety. Newer quinolones such as moxifloxacin, levofloxacin and gatifloxacin have a better *in-vitro* activity against quinolone-susceptible staphylococci compared to that of ciprofloxacin. However, when given alone, levofloxacin was unable to eliminate adherent staphylococci in vitro or in vivo [41].

Other anti-staphylococcal drugs have been combined with rifampin, such as cotrimoxazole or minocycline or fusidic acid, but they have been less intensively studied [42]. Daptomycin has been tested in an animal model of implant-associated infections, where it showed similar efficacy to glycopeptides (vancomycin or teicoplanin) [43]. Linezolid is active against virtually all gram-positive cocci, including methicillin-resistant staphylococci and vancomycin-resistant enterococci (VRE). A retrospective study looked at 20 consecutive patients treated with linezolid for orthopedic infections, 15 of whom had an orthopedic device [44]. At a mean follow-up of 276 days, 55% achieved clinical cure and 35% had clinical improvement but received long-term antimicrobial suppressive therapy. Adverse events during therapy occurred frequently; reversible myelosuppression in 40% of patients and irreversible peripheral neuropathy in 5%. In another review, long-term use of linezolid (> 28 days) was associated with severe, but reversible peripheral and optic neuropathy [45, 46].

In conclusion, the treatment goals of infections associated with fracture-fixation devices are bone

Microorganism	Antimicrobial Agent[1]	Dose	Route
S. aureus or coagulase-negative staphylococci			
• Methicillin-susceptible	Rifampin plus (flu)cloxacillin[2]	450 mg every 12 h 2 g every 6 h	PO/IV IV
	for 2 weeks, followed by		
	Rifampin plus ciprofloxacin or levofloxacin	450 mg every 12 h 750 mg every 12 h 750 mg every 24 h to 500 mg every 12 h	PO PO PO
• Methicillin-resistant	Rifampin plus vancomycin	450 mg every 12 h 1 g every 12 h	PO/IV IV
	for 2 weeks, followed by		
	Rifampin plus ciprofloxacin[3] or levofloxacin[3] or teicoplanin[4] or fusidic acid or cotrimoxazole or minocycline	450 mg every 12 h 750 mg every 12 h 750 mg every 24 h to 500 mg every 12 h 400 mg every 24 h 500 mg every 8 h 1 forte tablet every 8 h 100 mg every 12 h	PO PO PO PO IV/IM PO PO PO
Streptococcus spp.	Penicillin G[2] or ceftriaxone	5 million U every 6 h 2 g every 24 h	IV IV
	for 4 weeks, followed by		
	Amoxicillin	750-1000 mg every 8 h	PO
Enterococcus spp. (penicillin-susceptible)	Penicillin G or ampicillin or amoxicillin plus aminoglycoside[5]	5 million U every 6 h 2 g every 4–6 h	IV IV IV
	for 2–4 weeks, followed by		
	Amoxicillin	750–1000 mg every 8 h	PO
Enterobacteriaceae (quinolone-susceptible)	Ciprofloxacin	750 mg every 12 h	PO
Nonfermenters (eg, *Pseudomonas aeruginosa*)	Cefepime or ceftazidime plus aminoglycoside[5]	2 g every 8 h	IV IV
	for 2–4 weeks, followed by		
	Ciprofloxacin	750 mg every 12 h	PO
Anaerobes[6]	Clindamycin	600 mg every 6–8 h	IV
	for 2–4 weeks, followed by		
	Clindamycin	300 mg every 6 h	PO
Mixed infections (without methicillin-resistant staphylococci)	Amoxicillin/clavulanic acid or piperacillin/tazobactam or imipenem or meropenem	2.2 g every 8 h 4.5 g every 8 h 500 mg every 6 h 1 g every 8 h	IV IV IV IV
	for 2–4 weeks, followed by individual regimens according to antimicrobial susceptibility		

Table 3: Treatment of implant-associated infections (adapted from Zimmerli et al [38]).
PO = orally; IV = intravenously; IM = intramuscularly, forte tablet: trimethoprim 160 mg plus sulfamethoxazole 800 mg.

[1] For total duration of antimicrobial treatment see text.
[2] In patients with delayed hypersensitivity, cefazolin (2 g every 8 h IV) can be administered. In patients with immediate hypersensitivity, penicillin should be replaced by vancomycin (1 g every 12 h IV).
[3] Methicillin-resistant *S. aureus* (MRSA) should **not** be treated with quinolones since antimicrobial resistance may emerge during treatment.
[4] First 1–3 days of treatment, teicoplanin dose should be increased to 800 mg IV.
[5] Aminoglycosides can be administered in a single daily dose.
[6] Alternatively, penicillin G (5 million U every 6 h IV) or ceftriaxone (2 g every 24 h IV) can be used for Gram-positive anaerobes (eg, *Propionibacterium acnes*), and metronidazole (500 mg every 8 h IV or PO) for Gram-negative anaerobes (eg, *Bacteroides spp.*).

consolidation and prevention of chronic osteomyelitis. Successful treatment requires a combination of an adequate surgical procedure combined with prolonged antimicrobial therapy acting, if possible, on adhering stationary-phase microorganisms growing in biofilms.

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