

# Infection after fracture fixation: current surgical and microbiological concepts

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## **Abstract**

One of the most challenging complications in trauma surgery is infection after fracture fixation (IFF). IFF may result in permanent functional loss or even amputation of the affected limb in patients who may otherwise be expected to achieve complete, uneventful healing. Over the past decades, the problem of implant related bone infections has garnered increasing attention both in the clinical as well as preclinical arenas; however this has primarily been focused upon prosthetic joint infection (PJI), rather than on IFF. Although IFF shares many similarities with PJI, there are numerous critical differences in many facets including prevention, diagnosis and treatment. Admittedly, extrapolating data from PJI research to FFI has been of value to the trauma surgeon, but we should also be aware of the unique challenges posed by IFF that may not be accounted for in the PJI literature.

This review summarizes the clinical approaches towards the diagnosis and treatment of IFF with an emphasis on the unique aspects of fracture care that distinguish IFF from PJI. Finally, recent developments in anti-infective technologies that may be particularly suitable or applicable for trauma patients in the future will be briefly discussed.

**Key Words:** Infection after fracture fixation, implant-related infection, infected non-union, complications, biofilm, antibiotic therapy

## **Introduction**

The operative fixation of skeletal fractures can be highly complex due to the unpredictable nature of the bone damage, the multitude of concomitant injuries that may need to be considered and the frequency of life-threatening situations in emergency care. One of the most feared and challenging complications in the

treatment of musculoskeletal trauma patients is infection after fracture fixation (IFF), which can delay healing, lead to permanent functional loss, or even amputation of the affected limb.

Treating IFF may also result in significant socio-economic costs and can result in protracted recovery periods for affected patients [1]. Recent studies showed median costs per patient double to over 108'000 USD per patient when infected [2] with reported treatment success rates of only between 70 and 90% [3, 4]. The incidence of IFF has been tracked in numerous small-scale studies, with values from the 1980's and 90's indicating that the infection rate may range from as low as approximately 1% after operative fixation of closed low-energy fractures, to more than 30% in complex open tibia fractures [5, 6]. Over the past decades, it appears that there has been a steady reduction in the overall incidence of infection [7]. However, the question must be asked as to whether or not we have reached a plateau on what can be achieved by current protocols [8]. The persistence of the problem, and the somewhat unsatisfactory treatment outcomes, suggests that neither prophylaxis nor treatment of IFF is completely effective despite best practice, and further improvements should be sought.

Much of the surgical and medical treatment concepts currently applied to IFF have been adopted from prosthetic joint infection (PJI) treatment algorithms. Specific data, tailored towards the musculoskeletal trauma patient, is comparatively scarce. IFF and PJI do indeed have similar clinical properties, however there are important distinctions between the elective arthroplasty patient and the trauma patient, both in terms of risk of infection at the primary surgery, and in treatment options. Clearly, there is likely to be significant differences in the soft tissues overlying the surgical site: the fracture patient may have significant soft tissue damage or compromised vasculature secondary to the trauma, which is less common in elective arthroplasty patients. This vascular and soft tissue damage can impair access of the host defences and antibiotic therapy to the affected areas. Open fracture wounds are also certainly contaminated with an unknown variety and abundance of contaminating bacteria that are not present in elective patients. Furthermore, trauma patients may also require repeated visits to the OR for definitive fixation, second look, or plastic surgery for soft tissue flaps, which are not routine in primary arthroplasty. Amongst the most obvious technical differences in IFF is the presence of a fracture and the

need for biomechanical stability in order for it to heal. Clinical guidelines highlight the fact that construct stability is important not only for prevention, but also for treatment of IFF [9, 10]. Furthermore, in contrast to PJI, fracture fixation devices may be removed after osseous healing and therefore complete immediate eradication of infection is not always the primary goal and suppressive antibiotic therapy may be an option in advance of later implant removal when treatment outcome and success is likely to be improved. Finally, identification of infecting pathogens may be possible by joint puncture prior to surgical intervention in the case of PJI, however, biopsies are more often taken intraoperatively for IFF, which can delay or complicate diagnosis of IFF.

Preclinical research studies looking into the risk and progression of bone infection specifically in trauma-relevant models are also scarce [11-13], and few specific innovations have been translated from the academic arena and made available to the musculoskeletal trauma surgeon [14-16]. In this review, we summarize the preventative, diagnostic and therapeutic guidelines for IFF with an emphasis on the unique aspects of fracture care that distinguish IFF from PJI. Furthermore, we summarize the latest preclinical and clinical research innovations regarding prevention and treatment of IFF.

## **Definition and classification**

### **Definition**

Accurately estimating the impact of fracture related complications has been hampered by the lack of clear definitions for complications such as nonunion or infection. To date, there are no available standard criteria and a lack of consensus regarding the definition of IFF. This is in contrast to the situation for PJI, where a definition is available [17]. The trauma literature often cites the Centers for Disease Control (CDC)-guidelines for surgical site infection (SSI). The CDC definition divides SSIs into superficial, deep incisional and organ/space [18]. Furthermore, osteomyelitis is stated separately. As the fracture nor the implant taken into account, the complexity of an infected traumatic fracture is not completely covered by these guidelines. The problem becomes clear when reviewing the clinical literature. Some studies have cited the CDC-guidelines without a specific description of osteomyelitis

[19, 20]; others use these guidelines but include their own additional inclusion criteria such as purulent drainage or other clinical signs [21]. Perhaps due to the lack of suitable definitions for trauma patients, there are also authors who do not define infection [22] and others who provide a unique custom-made definition [23]. Interestingly, this issue was already mentioned by Arens *et al.* in 1996 [24], wherein the authors stated: *'It is astonishing that in all papers in which infection is mentioned, the term 'infection' is not defined'*. A better understanding and description of the definition of IFF is therefore a needed first step towards improving scientific reporting and evaluation of routine clinical data, as well as aid in the evaluation of novel prevention and treatment strategies [25].

## **Classification**

Although there is a lack of clear definitions, there is a widely accepted classification scheme for IFF [26, 27]. Willeneger and Roth classified IFF in the 1980's according to the time of onset into three groups: those with an early (less than 2 weeks), delayed (2–10 weeks), and late onset (more than 10 weeks) infection [27]. This classification has been adopted widely and is important because it has an influence on treatment decisions made by physicians [26]. Although infections with delayed and late manifestations may be combined [26], a trisection of this classification seems more appropriate. The relative frequency of infections of each type is not available from the published literature, but would represent an interesting validation of the classification scheme should such data become available. In the following section, this classification will be discussed, with particular reference to onset of IFF, biofilm formation and, importantly for the trauma surgeon, fracture-healing status (Figure 1).

### **Early infection (< 2 weeks)**

Early IFFs are often a clinical diagnosis since the patient generally presents with classic signs of infection (rubor, calor, dolor, tumor and functio laesa), wound healing disturbances, large hematomas, and accompanying systemic signs of infection such as fever and lethargy. Highly virulent organisms, like *Staphylococcus aureus*, are frequent causative agents of early infection [26]. Within this timeframe, it is commonly considered that the causative bacteria may already have formed a biofilm, although this biofilm may still be in an 'immature' phase.

With regard to bone involvement and healing, preclinical models have shown that at one-week post-inoculation, the bone does not show signs of osteomyelitis or osteolysis (Figure 2), despite the presence of bacteria. Furthermore, bone healing is in the 'inflammatory or soft callus stage' [28], and so there will be no fracture stability at this early stage. As discussed later, these pathophysiological conditions (active infection without radiographic signs of fracture stability) have significant treatment consequences due to the importance of fracture healing for successful treatment outcomes.

#### Delayed infection (2 – 10 weeks)

Patients with delayed infections can present with symptoms consistent with either early or late infections. For example, hematomas, which may be expected in earlier stages, may still be present after 3 weeks, or alternatively, a fistula can also present itself after 9 weeks, which may be more often associated with late infections.

There are several important distinctions from early infections. Delayed infections are typically due to less virulent bacteria, such as *Staphylococcus epidermidis* [26], and as the duration of infection extends, biofilms mature and become more resistant to antibiotic therapy and host defenses.

In terms of fracture healing, preclinical studies show that normal bone healing takes up to 10 weeks [29], with a 'hard callus stage' that is situated between 3-16 weeks [28, 30]. In case of infection, this changes significantly. Experimental studies have shown that *S. epidermidis* inoculation into a fracture gap in the rat can lead to non-union rates of 83-100% at 8 weeks [31]. Bilgili *et al.* could prove, in a similar approach, that IFF was associated with weaker callus formation [32]. These observations, in combination with the fact that bacterial bone invasion and inflammation ('osteomyelitis') often occur within 2 - 10 weeks (Figure 2), explain why treatment choices are often different compared to early onset infections where fracture healing may not have commenced, and bone involvement may still be minimal.

#### Late infection (> 10 weeks)

Many patients with late infections can present with subtle symptoms, compromised functionality and stress dependent pain, localized swelling and erythema or a draining sinus tract, mostly lacking systemic manifestation [33, 34]. In patients presenting with compromised functionality and stress dependent pain, infection with

low-virulence microorganisms should always be considered a possible cause (a clinically silent infection) [33]. Late, as delayed, IFF is primarily caused by microorganisms of low virulence like *S. epidermidis* [26].

Compromised fracture healing is a frequent observation in late infections and although bone healing may have taken place in some cases, severe inflammation and osteolysis with osteomyelitis lead to instability of the osteosynthesis (Figure 2). Periosteal new bone formation around the periphery of the infected area produces an involucrum that further walls off the infection [35]. These changes often necessitate extensive and repeated debridements, resulting in bone defects.

## Diagnosis

The diagnosis of IFF is challenging and based on a combination of various diagnostic criteria: past medical history, host physiology, clinical presentation, laboratory tests, imaging modalities and culturing of intraoperative tissue samples. Local signs of infection should be considered an IFF until proven otherwise. Signs such as a draining fistula from the implant or pus drainage are considered definitive signs of infection.

### Evaluation of host physiology

The detailed examination of patients with a suspected IFF includes a clinical assessment, and complete medical history, as well as an evaluation of the host local and systemic risk factors. High-risk injuries including open fractures with severe soft-tissue damage, a previous history of infection or a compromised host physiology [36]. Characteristics of compromised host physiology, such as chronic immune suppression (diabetes, malignancy, severe liver or renal disease, alcoholism), impairment of local vascularity and soft-tissue integument or deficiency in wound healing, should not only influence the risk assessment for infection, it should also influence treatment concepts [37]. Therefore, treating surgeons should be reluctant to perform complex reconstructive procedures in patients where these high-risk host factors are identified [33, 38].

### Laboratory examination

White blood cell count (WBC) with differential and neutrophil count display low sensitivity and specificity for diagnosing IFF [26, 39]. Persistent elevation or a secondary rise in C-reactive protein (CRP) can be an indicator for IFF [40, 41].

## **Microbiology**

IFF is mostly due to bacterial communities growing in protected biofilms on the foreign material and in necrotic bone tissue [42]. These localized grouped bacteria are often metabolically quiescent, which makes them difficult to identify and culture [43, 44]. Cultures taken from an open wound at the time of initial fracture fixation do not correlate with an eventual later infection and should be avoided [45, 46]. Similarly, swab cultures at the time of revision surgery do not reliably represent the pathogens in the bone [47, 48] and are therefore not recommended. In case of suspected infection, at least three bone biopsies should be taken close to the implant and in regions of macroscopically perceived infection such as necrotic bone tissue or non-unions [26]. If the same microorganism is cultured in at least two separate biopsies, it is believed to be relevant. In case of virulent species such as *S. aureus* or *E. coli*, a single positive biopsy may already sufficiently represent an infection [17]. If involvement of an adjacent joint is suspected, joint fluid for analysis (cell count, cultures) should be aspirated. Whenever possible, antibiotics should be avoided for at least 2 weeks before microbiological culturing, since this can transform specific bacterial species into viable but non-culturable forms [49] and cultures may therefore become falsely negative [50]. There is still an on-going debate about the duration of culture incubation: from 7 up to 14 days of incubation can be reasonable [51, 52], balancing the risk of missing a difficult to culture pathogen with the risk of culturing an irrelevant contaminant.

If implanted hardware is removed during surgery, these should be sent to the microbiological laboratory for sonication and cultivation of sonication fluid, if possible. Sonication is believed to detach the biofilm-encased bacteria from the implant and disrupt the biofilms themselves, thereby rendering the bacteria amenable for cultivation. This method has proved to increase the yield of positive cultures, especially after pre-treatment with antibiotics [53-56].

Although culturing is still believed to be the gold standard for microbiologic assessment, molecular methods are increasingly being added to identify difficult to



culture or non-culturable bacteria. Especially after antibiotic pre-treatment, detecting pathogens with polymerase chain reaction (PCR) has proven to be a valuable complementation [57-59]. However, the high resolution and sensitivity of PCR comes along with the risk of false-positive results from contaminants [60, 61]. Furthermore, it commonly cannot distinguish between live or dead bacteria and does not provide broad information about susceptibility to antibiotics, except of the presence of specific resistance genes [62].

### **Histology**

Routine diagnostics of IFF may include histological analysis of several tissue samples, that were taken intra-operatively from the site of suspected infection and/or non-union [63]. The histological examination allows differentiation between acute and chronic infection, proof of necrotic bone and detection of malignancy and delivers in combination with microbiological analysis important clues on the presence of a bone infection [33].

### **Imaging**

Serial radiographs are the first method of choice in complications after fracture fixation to gain a primary overview of the anatomy and to judge fracture healing status, implant positioning, possible implant failure, limb alignment and bone quality [64]. However, plain radiographs are not suitable to differentiate between septic and aseptic changes in active infections [26, 65]. In chronic infections, areas with a suspected bone infection may display sequestration, cortical irregularities, bone resorption and bone/callus formation [33, 65]. For more precise planning of the surgical procedure, computed tomography (CT) provides more detail about bone architecture to evaluate fracture pattern, new bone formation and necrotic bone as well as implant loosening and delivers additional evidence for infection: cortical bone reaction, presence of sequestration or intraosseous fistula and abscess formation in the adjacent soft-tissue [33, 66, 67].

Magnetic resonance imaging (MRI) is the method of choice to evaluate soft-tissue involvement and gives additional information about intramedullary infection manifestation [39]. However in cases of IFF, metal artefacts impair correct evaluation

and scarring or edema in postoperative/posttraumatic bone defects may mimic an infection [68].

Nuclear imaging modalities are often included in the diagnostic pathway of these type of infections [69, 70]. Nuclear imaging is using radioactive radiopharmaceuticals to visualize and trace (patho-) physiological changes, such as fracture healing, bone remodelling and inflammatory response to an infection. The combination of these functional imaging studies with morphological imaging, such as CT in one device is called hybrid imaging (SPECT/CT). It allows precise localization of the suspected infection and facilitates the discrimination between bone and soft-tissue infection [70]. Bone scintigraphy, usually performed with technetium-99m-diphosphonates ( $^{99m}\text{Tc}$ ) is positive for osteomyelitis in the case of focal hyperaemia or hyperperfusion and focally increased bone activity [70]. Since these physiological changes are also involved in fracture healing, it cannot discriminate between infection and posttraumatic bone formation. Therefore, bone scintigraphy has limited value in the diagnosis of IFF [26, 39, 70]. WBC imaging, using *in vitro* labeled leucocytes is a promising technique to identify bacterial infections, but is not routinely available due to complex *in vitro* labeling [70].  $^{18}\text{F}$ -fluoro-desoxy-glucose PET (FDG-PET), is very useful in musculoskeletal infections to visualize and precisely localize the infection with a high sensitivity and specificity [70]. Its role in IFF still remains inconclusive and has to be determined.

## Treatment

### General considerations

The central aims of treating IFF are shown in Table 1. Remember that every case of IFF is to be considered as a unique case, since there is no standard procedure that can be routinely applied to every patient.

In contrast to PJI, fracture fixation devices can be removed after healing has occurred, thereby removing the biofilm and resulting in a high chance of clearance of the infection. Therefore, complete eradication of infection is not always the primary goal. Suppressive therapy with antibiotics can be an established alternative in certain cases [3, 26, 71]. In order to tailor the appropriate treatment strategy, a number of important questions should be considered (Table 2) [1, 26, 39].

Taking these considerations into account, the above-mentioned aims can be achieved by two main surgical principles:

- I. Irrigation, debridement and retention of the implant combined with antibiotic therapy.
- II. Debridement, implant removal or exchange (one or multiple stages) with accompanied antibiotic therapy.

In very rare cases, especially in compromised hosts with serious infections, healing cannot be achieved and salvage procedures, such as amputation or establishment of a continuous fistula, may be the only treatment alternatives.

Regardless of which of the two main principles was chosen, the treating surgeon has to apply the above-mentioned diagnostic tools (CRP, radiographic analysis, etc.) to develop a long-term treatment concept as part of a multidisciplinary team. This treatment concept encompasses debridement, fracture- and soft-tissue management and antibiotic therapy (systemic/local). Carefully considered debridement is the cornerstone of treatment and involves the excision of necrotic and infected (bone- and soft-) tissue, evaluation of the osteosynthetic construct (stability), removal of foreign bodies (e.g. sequestrs, broken screws, sutures) and acquisition of multiple tissue samples for diagnostics [72]. Radical debridement should not be limited by concerns of creating bone or soft-tissue defects [33], one must compare debridement to '*Oncologic resections*'. Leaving a high concentration of pathogens ('cancer cells') in a specific surgical area, will lead to recurrence of the disease. When multiple operative stages are planned, these defects should be temporarily filled with a spacer ('dead-space management'). Finally, an adequate soft-tissue coverage is essential. This often means involvement of plastic surgeons in the process, for e.g. free-flaps.

## **Antibiotic treatment considerations**

Systemic antibiotic therapy

In general, antibiotic therapy can either be curative or suppressive. In the latter case, the antibiotics control the infection until the fracture is healed and the implant can be removed [26]. Antibiotics should always be tailored to the recovered bacteria and their antibiotic susceptibility pattern (see Table 3).

After surgical debridement, an initial intravenous therapy is started to achieve a rapid reduction of the bacterial load at the site of infection. After approximately 2 weeks of intravenous therapy, a switch to oral therapy with good bioavailability is suggested (see Table III) [73-75]. In case of treatment with aim of cure, the total treatment duration is usually 6 weeks after removal of implants or 12 weeks if implants stay in place [26, 72]. In case of treatment with aim of suppression, duration of therapy is linked with the time for the fracture to stabilize/heal and should commonly be continued for 4-6 weeks after implant removal. This is particularly recommended in infections with virulent bacteria such as *S. aureus* or *Escherichia coli* in order to prevent or treat chronic osteomyelitis. When implants are retained, a curative treatment is generally only effective with a biofilm-active antibiotic, which has so far only been shown for rifampicin against staphylococci [76-78] and for quinolone against Gram-negative bacteria [79-81]. Importantly, rifampicin must always be combined with a second antibiotic due to otherwise rapid development of resistance. For the same reason rifampicin should not be started before an initial bacterial load reduction by surgery and antibiotic therapy has occurred, all drains are drawn and the wound is dry [82, 83]. For staphylococci, quinolones such as ciprofloxacin or levofloxacin are the best-studied and effective oral antibiotic partners to rifampicin [76]. Other combinations have been successfully used in orthopedic implant infections but are less widely studied (see options in Table 3) [84]. If bacteria are resistant to the mentioned biofilm-active antibiotics, they are classified as difficult to treat and generally cannot be eradicated by the available alternative antibiotics as long as the implants are retained [85]. In these cases, the surgeon should strongly consider implant removal.

#### Local antibiotic therapy

Local application of antimicrobials at the site of infection through different carriers has gained increasing attraction. Especially in the light of impaired blood flow to the site of infection and necrotic bone tissue, the advantage of achieving very high local concentration of antimicrobials with low systemic exposure is compelling [87].

Furthermore, their carriers can be an important treatment option for 'dead-space management'. Nowadays, the mostly used antimicrobials are gentamicin, tobramycin, vancomycin and cephalosporins [88]. As a carrier, one can differentiate between resorbable versus non-resorbable materials. Commonly, an antibiotic loaded non-resorbable polymethylmethacrylate (PMMA) bone cement is applied, which can be introduced as beads on a string or simultaneously be used for mechanical stabilization as a rod or for temporary filling of large bone defects [89]. Nevertheless, cement may also serve as an additional surface for bacteria to attach to, particularly after antibiotics have been eluted. This can promote ongoing infection or even induce antibiotic resistance [90-93]. Another negative aspect of PMMA is that it needs to be removed during follow-up surgery, as it is non-resorbable. Furthermore, studies on the elution kinetics have shown that less than 10% of incorporated antibiotics will normally be released from PMMA [94]. Increasing the porosity of the material or mixing e.g. vancomycin with tobramycin can produce higher eluted doses [95, 96].

Resorbable materials such as calcium sulfate, which can carry a wider range of antibiotics than PMMA and do not necessarily need re-surgery for removal, have shown good first results [97-100]. As a side effect, a serous fluid pocket or prolonged wound secretion can develop [101]. Other degradable materials are bioactive glass, calcium phosphates and collagen implants. It needs to be stated that for all these materials data from large clinical trials is lacking.

To date, there is no clear evidence of advantage of the addition of local antibiotic to systemic therapy in randomized clinical trials and no clear advantage of degradable versus non-degradable materials in the treatment of IFF [102-104]. Despite this, local antibiotics seem to lower infection rates in open fractures [105]. The antibiotics generally exert low local and systemic toxicity [106, 107]. Nevertheless, there are rare case reports of acute renal failure attributable to locally applied gentamicin [108] or tobramycin [109].

Exploring the effect of coating osteosynthetic materials with an antimicrobial is a matter of ongoing research. Only few have made it so far onto the market. Among these are a gentamicin-coated intramedullary tibia nail [16, 110] and silver-coated megaprotheses [111].

### **Stage-dependent surgical treatment considerations**

### Treatment of early infection

Colonization of hardware can occur intraoperatively, and biofilm formation may proceed within days, with the implant thus serving as the nidus for infection and complicating healing/treatment [3, 112-114]. In this early stage, biofilm formation seems in an immature stage, and fulminant osteomyelitis is often not yet present [29, 115]. Only in very rare clinical situations, such as severely contaminated open fractures, will osteomyelitis (i.e. histological signs of inflammation of the bone/bone marrow) occur in this timeframe. This is why retention of the fracture fixation device is common practice and treatment involves antibiotic therapy and tissue debridement. Experimental studies in the rat have shown that callus formation could be observed despite retention of the implant [32]. Retaining an implant in early stages is tempting because hardware removal would complicate the management of an unhealed fracture, especially in complex articular fractures. However, retention of the implant is only reasonable if sufficient irrigation and debridement of the implant/surgical site can be carried out, if the osteosynthesis construct is stable, and antibiotic therapy is appropriate [72, 116]. The importance of implant stability was already outlined by earlier research from Rittmann and Perren in experimental studies in sheep, which showed the positive effects of stability on fracture healing in infection [9]. Furthermore, stability has a much more profound influence than that of the chosen implant material (i.e. different metal alloys) [117, 118]

In early infections, consolidation can be achieved despite the presence of an infection, as long as the osteosynthesis construct remains stable [9, 119]. If stability is not granted and the implant cannot be debrided properly, e.g. in intramedullary nails, hardware exchange should be considered [36]. Debridement also includes careful revision of hematomas, since they are a suitable growth medium for bacteria [26]. Subsequently, a 12-week course of antibiotic therapy with retained implants or up to 6 weeks after implant removal should follow the debridement [26, 78, 120]. Since debridement reduces the bacterial load and may clear an immature biofilm, additive systemic antibiotics will treat the remainder of the infection. Once the fracture has healed, it is strongly recommended to remove the implant to reduce the risk of a recurrent infection [119]. Berkes *et al.* investigated osseous union in patients who developed an infection within 6 weeks after the operative fracture fixation and that were treated with debridement, antibiotics and hardware retention. Fracture healing could only be achieved in 71% of the patients, whereas an open fracture and

the presence of an intramedullary nail were predictors for treatment failure [3]. Rightmire *et al.* performed a similar approach in infections within 16 weeks after osteosynthesis and reported successful union in 68%, although in 38% of the patients with successful bone healing, hardware had to be removed for persistent infection after union and therefore only 49% of the original study group achieved healing and was free of infection after six months [119]. These findings support the fact that the approach of debridement and retention is only promising in an early time frame after fracture fixation to achieve union and long term absence of infection.

In the majority of early infections retention and antibiotic therapy is the best option [26], but there are indications where exchanging the implant should be taken into account [26, 39, 119]. The factors are listed in Table IV. These factors should be interpreted as suggestions, rather than as definite decision criteria.

#### Treatment of delayed infection

Delayed infections, ranging from 3 to 10 weeks are a grey area in which decision making regarding the right treatment option is more difficult than in early or late onset infections. It is important to understand that the classification we use (Figure 1) is a continuum, which means that in the early stages of this phase, implant retention could still be considered, whilst at the later stages, this would be more clearly contraindicated.

In the presence of above-mentioned criteria (Table IV), and with increasing duration of symptoms or delay in diagnosis, the decision should tend towards implant exchange. As explained above, the biofilm develops (matures) over time and signs of osteomyelitis are increasingly observed (Figure 2), which means that treating these types of infection often demands for radical debridement and implant exchange. An important consideration in delayed infection is the evaluation of fracture consolidation by imaging studies and during surgery. If callus formation is visible and bone healing has progressed sufficiently to provide stability, debridement and implant removal can be the best choice.

The main principles of debridement and implant removal/exchange in one or multiple stages are outlined in the subsection “Late infections”.

#### Treatment of late infection

In the following section we summarize three different scenarios: clinically suspected infection with full bone consolidation, clinically suspected infection without full bone

consolidation, and non-union lacking clinical signs of infection. The first two scenarios will be discussed together.

*Clinically suspected infection with and without full consolidation*

As mentioned previously this classification of IFF is a continuum (Figure 1). Although this means that there is no red line separating late and delayed infections, it has to be taken into account that after 10 weeks (Figure 1), inflammation, fibrous encapsulation and osteolysis often lead to instability of the osteosynthetic construct, potentially resulting in delayed or non-union [29]. Furthermore, fibrous encapsulation of the infected area acts as a barrier around sequestrae and devitalized bone.

Clinically suspected late infection necessitates an extensive debridement with possible creation of bone and soft-tissue defects. The surgical treatment concept therefore has to include a multidisciplinary approach (trauma and plastic surgeon). Staged procedures may often be required, depending upon the extent of infection, the degree of stability, and the condition of the patient (host physiology).

The most important considerations in late infections with, and without, consolidation of the fracture are: removal of the remaining fracture fixation devices/foreign bodies; radical debridement of all involved bone (sequestrae) and soft tissue; long-term antimicrobial therapy (normally 6 weeks of antibiotics and up to 12 weeks if a lot of necrosis is present) and reconstruction of the soft tissue envelope [121].

In both clinical scenarios, preoperative imaging studies, such as CT, MRI and nuclear imaging modalities are helpful to plan the resection margins including safety zones. The operating surgeon should be aware that resection lines should be re-evaluated during surgery, since transition from necrotic to vital bone is not always obvious from preoperative imaging. Necrotic, non-bleeding bone is removed with a chisel or high-speed burr and represents one of the most critical steps in surgery. Intramedullary infection manifestations require debridement of the intramedullary canal using a classic reamer or a Reamer – Irrigator – Aspirator (RIA, DepuySynthes; Johnson & Johnson Co. Inc., New Brunswick, NJ, USA) system [121, 122].

If possible, stability of the bone should be preserved, although in certain cases where extensive debridement leads to instability, especially when fracture consolidation did not take place, external fixation and later reconstruction are necessary. External fixation can be a temporary or even definitive solution (i.e. bone transport). As



mentioned before, the use of spacers can be important in these cases, not only for dead-space management but also for local antibiotic therapy.

#### *Non-union lacking clinical signs of infection*

In this section it will not be our goal to discuss the treatment of non-union in general. It seems appropriate although to start with an issue similar to the one we described for IFF, namely that the definition of non-union is still arbitrary [123]. It has to be stated that recent literature starts to accept the US Food and Drug Administration (FDA) guidelines, which defines non-union as a fractured bone that has not completely healed within 9 months of injury and that has not shown progression toward healing over the past 3 consecutive months on serial radiographs [124].

Infected non-union is an underestimated problem. Gille *et al.* examined culture negative samples of 23 patients with non-union and reported the presence of bacterial RNA following analysis with PCR in two patients (8.7%) [125]. Palmer *et al.* analyzed 34 samples obtained from patients with non-union [126]. Although eight samples had a positive conventional culture, only four of 34 cases were negative following analysis of bacterial DNA using a combination of Ibis molecular diagnostics and fluorescence *in situ* hybridization techniques. The benefit of utilizing molecular based techniques could be very important, as distinguishing between septic and aseptic non-union is essential for determining the course of treatment [127]. In case of a longstanding therapy-resistant non-union, an infection should be suspected. If cultures are negative in these patients, as mentioned earlier, PCR could be a future solution.

The problem with this type of infection is that the diagnosis often follows the surgical intervention. It is clear that if there is a suspicion during surgery, an extensive surgical debridement should be performed, as for the previously mentioned late-onset infections. Planning a second stage procedure with removal of all internal fixation material (for sonication) and awaiting the results from cultures, should be considered. Furthermore, the use of spacers with local antibiotics (i.e. PMMA) is often a good additive treatment if there is a suspicion of infection during surgery. Solely exchanging the implant doesn't have good results in cases of infection as was recently described by Tsang *et al.* for infected non-union of the tibia [128].

In a second stage, when the infection has been treated, bone grafting (i.e. Masquelet or induced-membrane technique) could for example be considered. In case of a

Masquelet procedure, the surgeon should be sure that there is no remaining infection, as a recent experimental study by Seebach *et al.* showed this can be worsened by the introduction of mesenchymal stromal stem cells [129]. Of course, definitive treatment with external fixation (i.e. bone transport) can also be considered [128].

Table 5 summarizes the considerations a surgeon should make when treating an infected non-union.

## Future directives

Infection complicates a significant minority of patients after osteosynthesis, and so improvements in both prevention and treatment will be required to achieve better patient care in the coming decades. Such improvements may range from better-defined and controlled peri-operative antibiotic prophylaxis, to more rapid and specific diagnostics of even sub-acute infection, to increased availability of antimicrobial functionalized medical devices or bone void fillers and graft material.

Preclinical studies occupy an important junction in the assessment of such novel interventions, as this is the stage where new or improved interventions are assessed in a controlled environment prior to patient trials and full clinical implementation [130, 131]. Numerous *in vivo* models of infection have been described in the literature, however, those that model the clinical situation as closely as possible are considered to provide the most robust evaluation of efficacy [132]. In the case of infection after osteosynthesis, models that incorporate bone infection associated with a functioning implant (i.e. actually fixing a surgically induced fracture/osteotomy) achieve this goal [29].

Research and development has focused more on preventative rather than treatment strategies, as preventative strategies are considered more likely to have greater overall impact on healthcare costs and patient outcomes. New approaches to improve prevention of infection after osteosynthesis have primarily focused on local delivery of antibacterial compounds from specialized biomaterials formulated as coatings on devices [14, 16] or as additives in bone void fillers such as bone cement [133] or bacteriostatic bone substitute materials [134].

Currently, there is to our knowledge, only one antibiotic coated trauma implant that was available on the market, which has been found to effectively prevent infection in even complicated cases with high risk of infection [14, 16]. In future, more antibacterial functionalized implants are likely to come to market, offering competing, though ultimately quite similar technologies (release of conventional antibiotics or silver). Development and clinical implementation of antimicrobial devices in trauma surgery is both a scientific and economic challenge due to the complexities of the cost benefit equation for clinical studies and subsequent clinical uptake. For this reason, in the future, good cost analyses are necessary to further emphasize the problem of IFF.

Looking further ahead to a scenario where antibiotic resistance in commonly encountered pathogens may increase, antibiotic loaded devices may become contraindicated, at least in hospitals with high endemic rates of pathogens resistant to the antibiotics within the implants. In this regard, silver has maintained its position as an antimicrobial for medical devices due to low resistance rates in clinical isolates. Antimicrobial peptides (AMP's) are also emerging as possible antimicrobials that do not induce resistance within pathogens after exposure [135]. At the present time, AMPs have been limited to topical applications, though research strategies for implant functionalization have continued to emerge [136], and may yet prove a critical support in the face of antibiotic resistance.

Finally, hydrogels have recently emerged as promising vehicles for antibiotic delivery into trauma wounds [88]. Recently, early phase clinical studies have been described whereby antibiotic loaded hydrogels have been applied to patients during osteosynthesis [137]. These hydrogels offer the benefit of ease of application to potentially complex wounds and may cover both the implant surface and the surrounding tissues. Coatings or bone void fillers, in contrast, may leach antibiotics from the surface to the surrounding tissues, but the surgical field may extend significantly beyond the peri-implant space. Hydrogels, on the other hand, can be applied through the wound site due to their viscous yet flowing nature [138]. It remains to be seen if such hydrogels progress to routine clinical implementation, but at the current time, they offer an attractive option for antibacterial delivery to trauma wounds.

## Summary

One of the most challenging complications in trauma surgery is the development of IFF. The consequences for patients and healthcare systems regarding this complication are severe. Despite modern advances, implant-related infection remains a problem in fracture care. This article gives an overview of current standpoints regarding diagnosis and treatment of this serious complication. Further clinical and translational research is necessary to improve the outcome of this specific patient population.

## References

- [1] Darouiche RO. Treatment of infections associated with surgical implants. *The New England journal of medicine*. 2004;350:1422-9.
- [2] Thakore RV, Greenberg SE, Shi H, Foxx AM, Francois EL, Prablek MA, et al. Surgical site infection in orthopedic trauma: A case-control study evaluating risk factors and cost. *J Clin Orthop Trauma*. 2015;6:220-6.
- [3] Berkes M, Obremsky WT, Scannell B, Ellington JK, Hymes RA, Bosse M, et al. Maintenance of hardware after early postoperative infection following fracture internal fixation. *J Bone Joint Surg Am*. 2010;92:823-8.
- [4] Tschudin-Sutter S, Frei R, Dangel M, Jakob M, Balmelli C, Schaefer DJ, et al. Validation of a treatment algorithm for orthopedic implant-related infections with device-retention - results from a prospective observational cohort study. *Clin Microbiol Infect*. 2016.
- [5] Patzakis MJ, Wilkins J. Factors influencing infection rate in open fracture wounds. *Clinical orthopaedics and related research*. 1989:36-40.
- [6] Boxma H, Broekhuizen T, Patka P, Oosting H. Randomised controlled trial of single-dose antibiotic prophylaxis in surgical treatment of closed fractures: the Dutch Trauma Trial. *Lancet*. 1996;347:1133-7.
- [7] Metsemakers WJ, Handojo K, Reynders P, Sermon A, Vanderschot P, Nijs S. Individual risk factors for deep infection and compromised fracture healing after intramedullary nailing of tibial shaft fractures: a single centre experience of 480 patients. *Injury*. 2015;46:740-5.

- [8] Ktistakis I, Giannoudi M, Giannoudis PV. Infection rates after open tibial fractures: are they decreasing? *Injury*. 2014;45:1025-7.
- [9] Rittmann W, Perren S. Cortical bone healing after internal fixation and infection. Berlin, Heidelberg, New York: Springer; 1974.
- [10] Worlock P, Slack R, Harvey L, Mawhinney R. The prevention of infection in open fractures: an experimental study of the effect of fracture stability. *Injury*. 1994;25:31-8.
- [11] Metsemakers WJ, Emanuel N, Cohen O, Reichart M, Potapova I, Schmid T, et al. A doxycycline-loaded polymer-lipid encapsulation matrix coating for the prevention of implant-related osteomyelitis due to doxycycline-resistant methicillin-resistant *Staphylococcus aureus*. *J Control Release*. 2015;209:47-56.
- [12] Rochford ET, Sabate Bresco M, Zeiter S, Kluge K, Poulsson A, Ziegler M, et al. Monitoring immune responses in a mouse model of fracture fixation with and without *Staphylococcus aureus* osteomyelitis. *Bone*. 2016;83:82-92.
- [13] Rand BC, Penn-Barwell JG, Wenke JC. Combined local and systemic antibiotic delivery improves eradication of wound contamination: An animal experimental model of contaminated fracture. *Bone Joint J*. 2015;97-B:1423-7.
- [14] Fuchs T, Stange R, Schmidmaier G, Raschke MJ. The use of gentamicin-coated nails in the tibia: preliminary results of a prospective study. *Archives of orthopaedic and trauma surgery*. 2011;131:1419-25.
- [15] Schmidmaier G, Lucke M, Wildemann B, Haas NP, Raschke M. Prophylaxis and treatment of implant-related infections by antibiotic-coated implants: a review. *Injury*. 2006;37 Suppl 2:S105-12.
- [16] Metsemakers WJ, Reul M, Nijs S. The use of gentamicin-coated nails in complex open tibia fracture and revision cases: A retrospective analysis of a single centre case series and review of the literature. *Injury*. 2015;46:2433-7.
- [17] Osmon DR, Berbari EF, Berendt AR, Lew D, Zimmerli W, Steckelberg JM, et al. Diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis*. 2013;56:e1-e25.
- [18] Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Guideline for Prevention of Surgical Site Infection, 1999. Centers for Disease Control and Prevention (CDC) Hospital Infection Control Practices Advisory Committee. *Am J Infect Control*. 1999;27:97-132; quiz 3-4; discussion 96.

- [19] Lin S, Mauffrey C, Hammerberg EM, Stahel PF, Hak DJ. Surgical site infection after open reduction and internal fixation of tibial plateau fractures. *Eur J Orthop Surg Traumatol.* 2014;24:797-803.
- [20] Bachoura A, Guitton TG, Smith RM, Vrahas MS, Zurakowski D, Ring D. Infirmity and injury complexity are risk factors for surgical-site infection after operative fracture care. *Clin Orthop Relat Res.* 2011;469:2621-30.
- [21] Claessen FM, Braun Y, van Leeuwen WF, Dyer GS, van den Bekerom MP, Ring D. What Factors are Associated With a Surgical Site Infection After Operative Treatment of an Elbow Fracture? *Clin Orthop Relat Res.* 2015.
- [22] Meena RC, Meena UK, Gupta GL, Gahlot N, Gaba S. Intramedullary nailing versus proximal plating in the management of closed extra-articular proximal tibial fracture: a randomized controlled trial. *J Orthop Traumatol.* 2015;16:203-8.
- [23] Large TM, Alton TB, Patton DJ, Beingessner D. Does perioperative systemic infection or fever increase surgical infection risks after internal fixation of femur and tibia fractures in an intensive care polytrauma unit? *J Trauma Acute Care Surg.* 2013;75:664-8.
- [24] Arens S, Hansis M, Schlegel U, Eijer H, Printzen G, Ziegler WJ, et al. Infection after open reduction and internal fixation with dynamic compression plates--clinical and experimental data. *Injury.* 1996;27 Suppl 3:SC27-33.
- [25] Metssemakers WJ. Long bone fractures in (poly)trauma patients: risk analyses of musculoskeletal complications and strategies to prevent them. [Thesis]. Leuven: Catholic University Leuven; 2015.
- [26] Trampuz A, Zimmerli W. Diagnosis and treatment of infections associated with fracture-fixation devices. *Injury.* 2006;37 Suppl 2:S59-66.
- [27] Willenegger H, Roth B. [Treatment tactics and late results in early infection following osteosynthesis]. *Unfallchirurgie.* 1986;12:241-6.
- [28] Ruedi TP, Buckley RE, Moran CG, Ito K, Perren SM, Richards RG, et al. *AO Principles of Fracture Management - Volume 1 - Principles - Second expanded edition.* 2. ed: Thieme; 2007.
- [29] Arens D, Wilke M, Calabro L, Hackl S, Zeiter S, Zderic I, et al. A rabbit humerus model of plating and nailing osteosynthesis with and without *Staphylococcus aureus* osteomyelitis. *Eur Cell Mater.* 2015.
- [30] Rahn BA. Bone healing: histologic and physiologic concepts. In: Sumner-Smith G, editor. *Bone in clinical orthopedics.* Second ed. Dübendorf: AO Publishing; 2002.

- [31] Lovati AB, Romano CL, Bottagisio M, Monti L, De Vecchi E, Previdi S, et al. Modeling Staphylococcus epidermidis-Induced Non-Unions: Subclinical and Clinical Evidence in Rats. *PLoS One*. 2016;11:e0147447.
- [32] Bilgili F, Balci HI, Karaytug K, Sariyilmaz K, Atalar AC, Bozdog E, et al. Can Normal Fracture Healing Be Achieved When the Implant Is Retained on the Basis of Infection? An Experimental Animal Model. *Clin Orthop Relat Res*. 2015;473:3190-6.
- [33] Patzakis MJ, Zalavras CG. Chronic posttraumatic osteomyelitis and infected nonunion of the tibia: current management concepts. *The Journal of the American Academy of Orthopaedic Surgeons*. 2005;13:417-27.
- [34] Marsh JL, Watson PA, Crouch CA. Septic arthritis caused by chronic osteomyelitis. *Iowa Orthop J*. 1997;17:90-5.
- [35] Ruedi TP, Buckley RE, Moran CG, Ito K, Perren SM, Richards RG, et al. *AO Principles of Fracture Management - Volume 2 - Principles - Second expanded edition*. 2. ed: Thieme; 2007.
- [36] Willey M, Karam M. Impact of Infection on Fracture Fixation. *Orthop Clin North Am*. 2016;47:357-64.
- [37] Cierny G, 3rd, Mader JT, Penninck JJ. A clinical staging system for adult osteomyelitis. *Clinical orthopaedics and related research*. 2003:7-24.
- [38] DeWall M, Henderson CE, McKinley TO, Phelps T, Dolan L, Marsh JL. Percutaneous reduction and fixation of displaced intra-articular calcaneus fractures. *Journal of orthopaedic trauma*. 2010;24:466-72.
- [39] Kleber C, Schaser KD, Trampuz A. [Complication management of infected osteosynthesis: Therapy algorithm for peri-implant infections]. *Chirurg*. 2015;86:925-34.
- [40] Neumaier M, Scherer MA. C-reactive protein levels for early detection of postoperative infection after fracture surgery in 787 patients. *Acta orthopaedica*. 2008;79:428-32.
- [41] Greidanus NV, Masri BA, Garbuz DS, Wilson SD, McAlinden MG, Xu M, et al. Use of erythrocyte sedimentation rate and C-reactive protein level to diagnose infection before revision total knee arthroplasty. A prospective evaluation. *The Journal of bone and joint surgery American volume*. 2007;89:1409-16.
- [42] Costerton JW, Post JC, Ehrlich GD, Hu FZ, Kreft R, Nistico L, et al. New methods for the detection of orthopedic and other biofilm infections. *Fems Immunol Med Mic*. 2011;61:133-40.

- [43] Veeh RH, Shirliff ME, Petik JR, Flood JA, Davis CC, Seymour JL, et al. Detection of *Staphylococcus aureus* biofilm on tampons and menses components. *Journal of Infectious Diseases*. 2003;188:519-30.
- [44] Post JC, Preston RA, Aul JJ, Larkinspettigrew M, Rydquistwhite J, Anderson KW, et al. Molecular Analysis of Bacterial Pathogens in Otitis-Media with Effusion. *Jama-J Am Med Assoc*. 1995;273:1598-604.
- [45] Burns TC, Stinner DJ, Mack AW, Potter BK, Beer R, Eckel TT, et al. Microbiology and injury characteristics in severe open tibia fractures from combat. *J Trauma Acute Care Surg*. 2012;72:1062-7.
- [46] Valenziano CP, Chattar-Cora D, O'Neill A, Hubli EH, Cudjoe EA. Efficacy of primary wound cultures in long bone open extremity fractures: are they of any value? *Arch Orthop Trauma Surg*. 2002;122:259-61.
- [47] Aggarwal VK, Higuera C, Deirmengian G, Parvizi J, Austin MS. Swab cultures are not as effective as tissue cultures for diagnosis of periprosthetic joint infection. *Clinical orthopaedics and related research*. 2013;471:3196-203.
- [48] Zuluaga AF, Galvis W, Jaimes F, Vesga O. Lack of microbiological concordance between bone and non-bone specimens in chronic osteomyelitis: an observational study. *BMC infectious diseases*. 2002;2.
- [49] Pasquaroli S, Zandri G, Vignaroli C, Vuotto C, Donelli G, Biavasco F. Antibiotic pressure can induce the viable but non-culturable state in *Staphylococcus aureus* growing in biofilms. *J Antimicrob Chemother*. 2013;68:1812-7.
- [50] Malekzadeh D, Osmon DR, Lahr BD, Hanssen AD, Berbari EF. Prior Use of Antimicrobial Therapy is a Risk Factor for Culture-negative Prosthetic Joint Infection. *Clinical orthopaedics and related research*. 2010;468:2039-45.
- [51] Schwotzer N, Wahl P, Fracheboud D, Gautier E, Chuard C. Optimal Culture Incubation Time in Orthopedic Device-Associated Infections: a Retrospective Analysis of Prolonged 14-Day Incubation. *Journal of clinical microbiology*. 2014;52:61-6.
- [52] Schafer P, Fink B, Sandow D, Margull A, Berger I, Frommelt L. Prolonged Bacterial Culture to Identify Late Periprosthetic Joint Infection: A Promising Strategy. *Clinical Infectious Diseases*. 2008;47:1403-9.
- [53] Trampuz A, Piper KE, Jacobson MJ, Hanssen AD, Unni KK, Osmon DR, et al. Sonication of removed hip and knee prostheses for diagnosis of infection. *New Engl J Med*. 2007;357:654-63.



- [54] Puig-Verdie L, Alentorn-Geli E, Gonzalez-Cuevas A, Sorli L, Salvado M, Alier A, et al. Implant sonication increases the diagnostic accuracy of infection in patients with delayed, but not early, orthopaedic implant failure. *Bone Joint J.* 2013;95B:244-9.
- [55] Yano MH, Klautau GB, da Silva CB, Nigro S, Avanzi O, Mercadante MT, et al. Improved Diagnosis of Infection Associated with Osteosynthesis by Use of Sonication of Fracture Fixation Implants. *Journal of clinical microbiology.* 2014;52:4176-82.
- [56] Dapunt U, Spranger O, Gantz S, Burckhardt I, Zimmermann S, Schmidmaier G, et al. Are atrophic long-bone nonunions associated with low-grade infections? *Therapeutics and clinical risk management.* 2015;11:1843-52.
- [57] Bergin PF, Doppelt JD, Hamilton WG, Mirick GE, Jones AE, Sritulanondha S, et al. Detection of Periprosthetic Infections With Use of Ribosomal RNA-Based Polymerase Chain Reaction. *Journal of Bone and Joint Surgery-American Volume.* 2010;92A:654-63.
- [58] Gomez E, Cazanave C, Cunningham SA, Greenwood-Quaintance KE, Steckelberg JM, Uhl JR, et al. Prosthetic Joint Infection Diagnosis Using Broad-Range PCR of Biofilms Dislodged from Knee and Hip Arthroplasty Surfaces Using Sonication. *Journal of clinical microbiology.* 2012;50:3501-8.
- [59] Greenwood-Quaintance KE, Uhl JR, Hanssen AD, Sampath R, Mandrekar JN, Patel R. Diagnosis of Prosthetic Joint Infection by Use of PCR-Electrospray Ionization Mass Spectrometry. *Journal of clinical microbiology.* 2014;52:642-9.
- [60] Clarke MT, Roberts CP, Lee PT, Gray J, Keene GS, Rushton N. Polymerase chain reaction can detect bacterial DNA in aseptically loose total hip arthroplasties. *Clinical orthopaedics and related research.* 2004:132-7.
- [61] Panousis K, Grigoris P, Butcher I, Rana B, Reilly JH, Hamblen DL. Poor predictive value of broad-range PCR for the detection of arthroplasty infection in 92 cases. *Acta orthopaedica.* 2005;76:341-6.
- [62] Tsuru A, Setoguchi T, Kawabata N, Hirotsu M, Yamamoto T, Nagano S, et al. Enrichment of bacteria samples by centrifugation improves the diagnosis of orthopaedics-related infections via real-time PCR amplification of the bacterial methicillin-resistance gene. *BMC research notes.* 2015;8:288.
- [63] Ochsner PE, Hailemariam S. Histology of osteosynthesis associated bone infection. *Injury.* 2006;37 Suppl 2:S49-58.

- [64] Wenter V, Muller JP, Albert NL, Lehner S, Fendler WP, Bartenstein P, et al. The diagnostic value of [(18)F]FDG PET for the detection of chronic osteomyelitis and implant-associated infection. *Eur J Nucl Med Mol Imaging*. 2016;43:749-61.
- [65] Tumei SS, Aliabadi P, Weissman BN, McNeil BJ. Disease activity in osteomyelitis: role of radiography. *Radiology*. 1987;165:781-4.
- [66] Gross T, Kaim AH, Regazzoni P, Widmer AF. Current concepts in posttraumatic osteomyelitis: a diagnostic challenge with new imaging options. *The Journal of trauma*. 2002;52:1210-9.
- [67] Steinhausen E, Glombitza M, Bohm HJ, Hax PM, Rixen D. [Non-unions. From diagnosis to healing]. *Unfallchirurg*. 2013;116:633-47; quiz 48-9.
- [68] Ledermann HP, Kaim A, Bongartz G, Steinbrich W. Pitfalls and limitations of magnetic resonance imaging in chronic posttraumatic osteomyelitis. *Eur Radiol*. 2000;10:1815-23.
- [69] Hsu W, Hearty TM. Radionuclide imaging in the diagnosis and management of orthopaedic disease. *The Journal of the American Academy of Orthopaedic Surgeons*. 2012;20:151-9.
- [70] Love C, Palestro CJ. Nuclear medicine imaging of bone infections. *Clin Radiol*. 2016.
- [71] Zimmerli W. Clinical presentation and treatment of orthopaedic implant-associated infection. *J Intern Med*. 2014;276:111-9.
- [72] Schmidt AH, Swiontkowski MF. Pathophysiology of infections after internal fixation of fractures. *The Journal of the American Academy of Orthopaedic Surgeons*. 2000;8:285-91.
- [73] Spellberg B, Lipsky BA. Systemic antibiotic therapy for chronic osteomyelitis in adults. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2012;54:393-407.
- [74] Rod-Fleury T, Dunkel N, Assal M, Rohner P, Tahintzi P, Bernard L, et al. Duration of post-surgical antibiotic therapy for adult chronic osteomyelitis: a single-centre experience. *International orthopaedics*. 2011;35:1725-31.
- [75] Daver NG, Shelburne SA, Atmar RL, Giordano TP, Stager CE, Reitman CA, et al. Oral step-down therapy is comparable to intravenous therapy for *Staphylococcus aureus* osteomyelitis. *The Journal of infection*. 2007;54:539-44.
- [76] Senneville E, Joulie D, Legout L, Valette M, Dezeque H, Beltrand E, et al. Outcome and predictors of treatment failure in total hip/knee prosthetic joint

infections due to *Staphylococcus aureus*. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2011;53:334-40.

[77] Widmer AF, Gaechter A, Ochsner PE, Zimmerli W. Antimicrobial treatment of orthopedic implant-related infections with rifampin combinations. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 1992;14:1251-3.

[78] Zimmerli W, Widmer AF, Blatter M, Frei R, Ochsner PE. Role of rifampin for treatment of orthopedic implant-related staphylococcal infections: a randomized controlled trial. Foreign-Body Infection (FBI) Study Group. *JAMA*. 1998;279:1537-41.

[79] Hsieh PH, Lee MS, Hsu KY, Chang YH, Shih HN, Ueng SW. Gram-negative prosthetic joint infections: risk factors and outcome of treatment. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2009;49:1036-43.

[80] Aboltins CA, Dowsey MM, Buising KL, Peel TN, Daffy JR, Choong PF, et al. Gram-negative prosthetic joint infection treated with debridement, prosthesis retention and antibiotic regimens including a fluoroquinolone. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases*. 2011;17:862-7.

[81] Martinez-Pastor JC, Munoz-Mahamud E, Vilchez F, Garcia-Ramiro S, Bori G, Sierra J, et al. Outcome of acute prosthetic joint infections due to gram-negative bacilli treated with open debridement and retention of the prosthesis. *Antimicrobial agents and chemotherapy*. 2009;53:4772-7.

[82] Sendi P, Zimmerli W. Antimicrobial treatment concepts for orthopaedic device-related infection. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases*. 2012;18:1176-84.

[83] Achermann Y, Eigenmann K, Ledergerber B, Derksen L, Rafeiner P, Clauss M, et al. Factors associated with rifampin resistance in staphylococcal periprosthetic joint infections (PJI): a matched case-control study. *Infection*. 2013;41:431-7.

[84] Coiffier G, Albert JD, Arvieux C, Guggenbuhl P. Optimizing combination rifampin therapy for staphylococcal osteoarticular infections. *Joint Bone Spine*. 2013;80:11-7.

[85] Zimmerli W, Trampuz A, Ochsner PE. Current concepts: Prosthetic-joint infections. *New Engl J Med*. 2004;351:1645-54.

[86] Zimmerli W. *Orthopedic Implant-Associated Infections* 2015.

- [87] Gogia JS, Meehan JP, Di Cesare PE, Jamali AA. Local antibiotic therapy in osteomyelitis. *Seminars in plastic surgery*. 2009;23:100-7.
- [88] ter Boo GJ, Grijpma DW, Moriarty TF, Richards RG, Eglin D. Antimicrobial delivery systems for local infection prophylaxis in orthopedic- and trauma surgery. *Biomaterials*. 2015;52:113-25.
- [89] Hake ME, Young H, Hak DJ, Stahel PF, Hammerberg EM, Mauffrey C. Local antibiotic therapy strategies in orthopaedic trauma: Practical tips and tricks and review of the literature. *Injury*. 2015;46:1447-56.
- [90] Neut D, van de Belt H, Stokroos I, van Horn JR, van der Mei HC, Busscher HJ. Biomaterial-associated infection of gentamicin-loaded PMMA beads in orthopaedic revision surgery. *The Journal of antimicrobial chemotherapy*. 2001;47:885-91.
- [91] Anagnostakos K, Hitzler P, Pape D, Kohn D, Kelm J. Persistence of bacterial growth on antibiotic-loaded beads: is it actually a problem? *Acta orthopaedica*. 2008;79:302-7.
- [92] Schmolders J, Hischebeth GT, Friedrich MJ, Randau TM, Wimmer MD, Kohlhof H, et al. Evidence of MRSE on a gentamicin and vancomycin impregnated polymethyl-methacrylate (PMMA) bone cement spacer after two-stage exchange arthroplasty due to periprosthetic joint infection of the knee. *BMC infectious diseases*. 2014;14:144.
- [93] Stoodley P, Nistico L, Johnson S, Lasko LA, Baratz M, Gahlot V, et al. Direct demonstration of viable *Staphylococcus aureus* biofilms in an infected total joint arthroplasty. A case report. *The Journal of bone and joint surgery American volume*. 2008;90:1751-8.
- [94] van de Belt H, Neut D, Schenk W, van Horn JR, van der Mei HC, Busscher HJ. Gentamicin release from polymethylmethacrylate bone cements and *Staphylococcus aureus* biofilm formation. *Acta Orthop Scand*. 2000;71:625-9.
- [95] Moojen DJ, Hentenaar B, Charles Vogely H, Verbout AJ, Castelein RM, Dhert WJ. In vitro release of antibiotics from commercial PMMA beads and articulating hip spacers. *The Journal of arthroplasty*. 2008;23:1152-6.
- [96] Penner MJ, Masri BA, Duncan CP. Elution characteristics of vancomycin and tobramycin combined in acrylic bone-cement. *The Journal of arthroplasty*. 1996;11:939-44.
- [97] Ferguson JY, Dudareva M, Riley ND, Stubbs D, Atkins BL, McNally MA. The use of a biodegradable antibiotic-loaded calcium sulphate carrier containing tobramycin

for the treatment of chronic osteomyelitis A SERIES OF 195 CASES. *Bone Joint J.* 2014;96B:829-36.

[98] Inzana JA, Schwarz EM, Kates SL, Awad HA. Biomaterials approaches to treating implant-associated osteomyelitis. *Biomaterials.* 2016;81:58-71.

[99] Beuerlein MJ, McKee MD. Calcium sulfates: what is the evidence? *Journal of orthopaedic trauma.* 2010;24 Suppl 1:S46-51.

[100] McKee MD, Wild LM, Schemitsch EH, Waddell JP. The use of an antibiotic-impregnated, osteoconductive, bioabsorbable bone substitute in the treatment of infected long bone defects: early results of a prospective trial. *Journal of orthopaedic trauma.* 2002;16:622-7.

[101] Ferguson JY, Dudareva M, Riley ND, Stubbs D, Atkins BL, McNally MA. The use of a biodegradable antibiotic-loaded calcium sulphate carrier containing tobramycin for the treatment of chronic osteomyelitis: a series of 195 cases. *Bone Joint J.* 2014;96-B:829-36.

[102] Calhoun JH, Henry SL, Anger DM, Cobos JA, Mader JT. The treatment of infected nonunions with gentamicin-polymethylmethacrylate antibiotic beads. *Clinical orthopaedics and related research.* 1993:23-7.

[103] Wasko MK, Kaminski R. Custom-Made Antibiotic Cement Nails in Orthopaedic Trauma: Review of Outcomes, New Approaches, and Perspectives. *BioMed research international.* 2015;2015:387186.

[104] Anagnostakos K, Schroder K. Antibiotic-impregnated bone grafts in orthopaedic and trauma surgery: a systematic review of the literature. *Int J Biomater.* 2012;2012:538061.

[105] Ostermann PA, Seligson D, Henry SL. Local antibiotic therapy for severe open fractures. A review of 1085 consecutive cases. *J Bone Joint Surg Br.* 1995;77:93-7.

[106] Walenkamp GH, Vree TB, van Rens TJ. Gentamicin-PMMA beads. Pharmacokinetic and nephrotoxicological study. *Clinical orthopaedics and related research.* 1986:171-83.

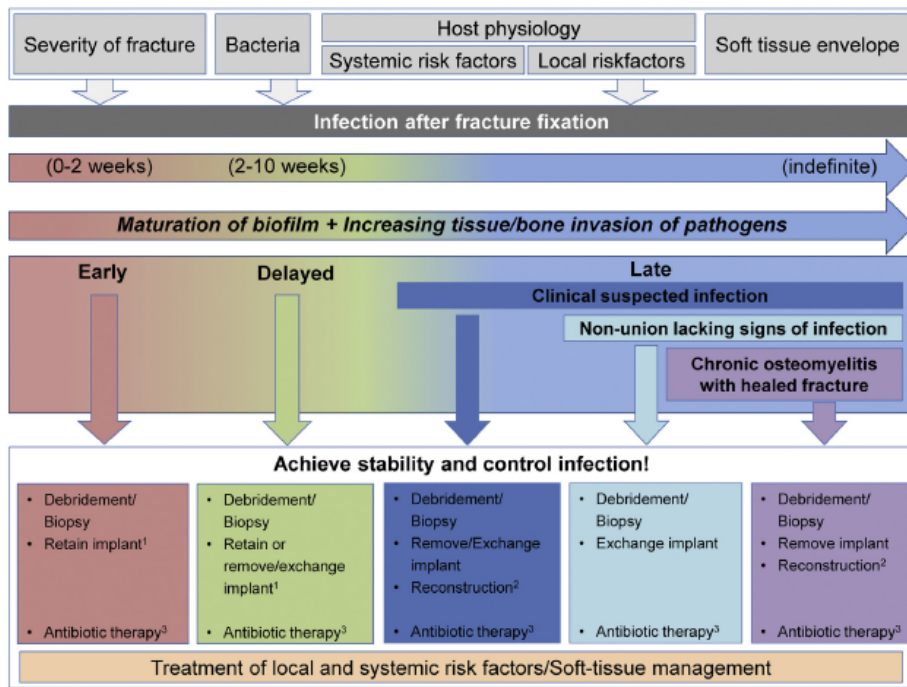
[107] Springer BD, Lee GC, Osmon D, Haidukewych GJ, Hanssen AD, Jacofsky DJ. Systemic safety of high-dose antibiotic-loaded cement spacers after resection of an infected total knee arthroplasty. *Clinical orthopaedics and related research.* 2004:47-51.

- [108] van Raaij TM, Visser LE, Vulto AG, Verhaar JA. Acute renal failure after local gentamicin treatment in an infected total knee arthroplasty. *The Journal of arthroplasty*. 2002;17:948-50.
- [109] Patrick BN, Rivey MP, Allington DR. Acute renal failure associated with vancomycin- and tobramycin-laden cement in total hip arthroplasty. *The Annals of pharmacotherapy*. 2006;40:2037-42.
- [110] Fuchs T, Stange R, Schmidmaier G, Raschke MJ. The use of gentamicin-coated nails in the tibia: preliminary results of a prospective study. *Archives of orthopaedic and trauma surgery*. 2011;131:1419-25.
- [111] Harges J, von Eiff C, Streitbuerger A, Balke M, Budny T, Henrichs MP, et al. Reduction of periprosthetic infection with silver-coated megaprotheses in patients with bone sarcoma. *Journal of surgical oncology*. 2010;101:389-95.
- [112] Petty W, Spanier S, Shuster JJ, Silverthorne C. The influence of skeletal implants on incidence of infection. Experiments in a canine model. *The Journal of bone and joint surgery American volume*. 1985;67:1236-44.
- [113] Costerton JW. Biofilm theory can guide the treatment of device-related orthopaedic infections. *Clinical orthopaedics and related research*. 2005:7-11.
- [114] Gristina AG, Naylor PT, Myrvik QN. Mechanisms of musculoskeletal sepsis. *Orthop Clin North Am*. 1991;22:363-71.
- [115] Nishitani K, Sutipornpalangkul W, de Mesy Bentley KL, Varrone JJ, Bello-Irizarry SN, Ito H, et al. Quantifying the natural history of biofilm formation in vivo during the establishment of chronic implant-associated *Staphylococcus aureus* osteomyelitis in mice to identify critical pathogen and host factors. *J Orthop Res*. 2015;33:1311-9.
- [116] Merritt K, Dowd JD. Role of internal fixation in infection of open fractures: studies with *Staphylococcus aureus* and *Proteus mirabilis*. *Journal of orthopaedic research : official publication of the Orthopaedic Research Society*. 1987;5:23-8.
- [117] Metsemakers WJ, Schmid T, Zeiter S, Ernst M, Keller I, Cosmelli N, et al. Titanium and steel fracture fixation plates with different surface topographies: Influence on infection rate in a rabbit fracture model. *Injury*. 2016;47:633-9.
- [118] Moriarty TF, Debeve L, Boure L, Campoccia D, Schlegel U, Richards RG. Influence of material and microtopography on the development of local infection in vivo: experimental investigation in rabbits. *The International journal of artificial organs*. 2009;32:663-70.

- [119] Rightmire E, Zurakowski D, Vrahas M. Acute infections after fracture repair: management with hardware in place. *Clin Orthop Relat Res.* 2008;466:466-72.
- [120] Trebse R, Pisot V, Trampuz A. Treatment of infected retained implants. *J Bone Joint Surg Br.* 2005;87:249-56.
- [121] Johnson E, Buckley R. Chronic infection and infected nonunion. In: Rüedi T, Buckley R, Moran C, editors. *AO Principles of Fracture Management*: Thieme; 2008. p. 543-55.
- [122] Lowe JA, Vosburg C, Murtha YM, Della Rocca GJ, Crist BD. A new technique for removing intramedullary cement. *Journal of orthopaedic trauma.* 2011;25:762-6.
- [123] Bhandari M, Guyatt GH, Swiontkowski MF, Tornetta P, 3rd, Sprague S, Schemitsch EH. A lack of consensus in the assessment of fracture healing among orthopaedic surgeons. *Journal of orthopaedic trauma.* 2002;16:562-6.
- [124] Brinker MR. Nonunions: Evaluation and treatment. In: Browner BD, Levine AM, Jupiter JB, Trafton PG, editors. *Skeletal Trauma: Basic Science, Management and Reconstruction.* 3 ed. Philadelphia: W.B. Saunders; 2003. p. 507–604.
- [125] Gille J, Wallstabe S, Schulz AP, Paech A, Gerlach U. Is non-union of tibial shaft fractures due to nonculturable bacterial pathogens? A clinical investigation using PCR and culture techniques. *J Orthop Surg Res.* 2012;7:20.
- [126] Palmer MP, Altman DT, Altman GT, Sewecke JJ, Ehrlich GD, Hu FZ, et al. Can we trust intraoperative culture results in nonunions? *Journal of orthopaedic trauma.* 2014;28:384-90.
- [127] Panteli M, Pountos I, Jones E, Giannoudis PV. Biological and molecular profile of fracture non-union tissue: current insights. *J Cell Mol Med.* 2015;19:685-713.
- [128] Tsang ST, Mills LA, Frantzias J, Baren JP, Keating JF, Simpson AH. Exchange nailing for nonunion of diaphyseal fractures of the tibia: our results and an analysis of the risk factors for failure. *Bone Joint J.* 2016;98-B:534-41.
- [129] Seebach E, Holschbach J, Buchta N, Bitsch RG, Kleinschmidt K, Richter W. Mesenchymal stromal cell implantation for stimulation of long bone healing aggravates *Staphylococcus aureus* induced osteomyelitis. *Acta Biomater.* 2015;21:165-77.
- [130] Grainger DW, van der Mei HC, Jutte PC, van den Dungen JJ, Schultz MJ, van der Laan BF, et al. Critical factors in the translation of improved antimicrobial strategies for medical implants and devices. *Biomaterials.* 2013;34:9237-43.

- [131] Moriarty TF, Grainger DW, Richards RG. Challenges in linking preclinical antimicrobial research strategies with clinical outcomes for device-associated infections. *Eur Cell Mater.* 2014;28:112-28; discussion 28.
- [132] Calabro L, Lutton C, Din AFSE, Richards RG, Moriarty TF. Animal Models of Orthopedic Implant-Related Infection. In: Moriarty FT, Zaat AJS, Busscher JH, editors. *Biomaterials Associated Infection: Immunological Aspects and Antimicrobial Strategies.* New York, NY: Springer New York; 2013. p. 273-304.
- [133] Buchholz HW, Engelbrecht H. [Depot effects of various antibiotics mixed with Palacos resins]. *Chirurg.* 1970;41:511-5.
- [134] van Gestel NA, Geurts J, Hulsen DJ, van Rietbergen B, Hofmann S, Arts JJ. Clinical Applications of S53P4 Bioactive Glass in Bone Healing and Osteomyelitic Treatment: A Literature Review. *BioMed research international.* 2015;2015:684826.
- [135] Zasloff M. Antimicrobial peptides of multicellular organisms. *Nature.* 2002;415:389-95.
- [136] de Breij A, Riool M, Kwakman PH, de Boer L, Cordfunke RA, Drijfhout JW, et al. Prevention of *Staphylococcus aureus* biomaterial-associated infections using a polymer-lipid coating containing the antimicrobial peptide OP-145. *J Control Release.* 2016;222:1-8.
- [137] Logoluso NM, K.; Blauth, M.; Danita, A.; Simon, K.; Romanò CL. Anti-bacterial hydrogel coating of osteosynthesis implants. Early clinical results from a multi-center prospective trial. *eCM XVI Bone and Implant Infection.* Davos, Switzerland 2015.
- [138] Ter Boo GA, Arens D, Metsemakers WJ, Zeiter S, Geoff Richards R, Grijpma DW, et al. Injectable gentamicin-loaded thermo-responsive hyaluronic acid derivative prevents infection in a rabbit model. *Acta Biomater.* 2016.



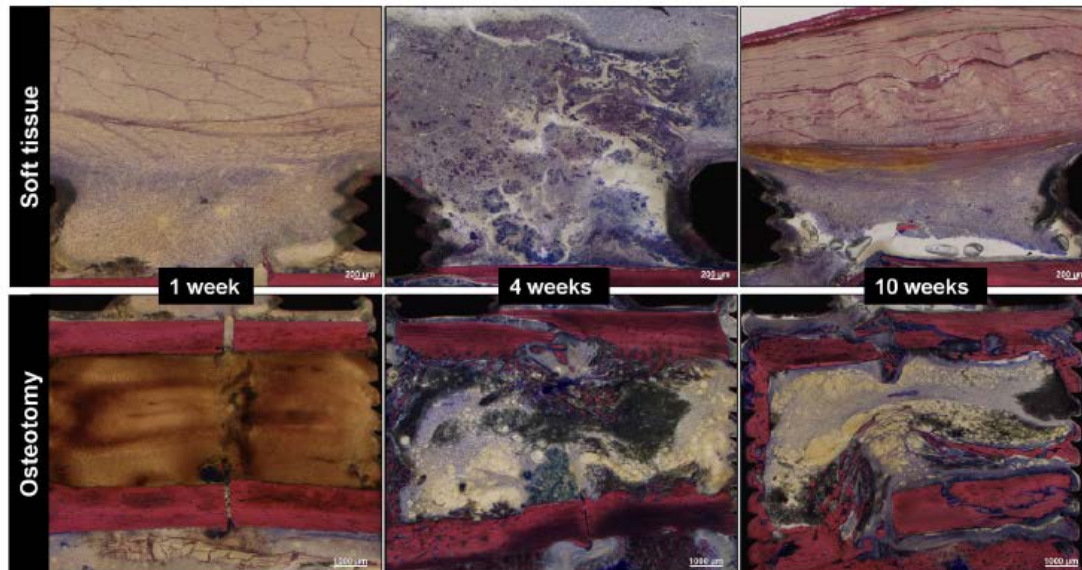


**Fig. 1.** Pathophysiology, classification and treatment algorithm of IAFF.

<sup>1</sup> See Table 4: Factors favoring implant removal and exchange

<sup>2</sup> Reconstruction can be carried out in a single step (with implant exchange) or in multiple stages; after resection of necrotic soft-tissue and bone a multidisciplinary approach will often be required

<sup>3</sup> Antibiotic therapy should be chosen in collaboration with an infectious disease specialist (especially in polymicrobial infections or proof of difficult to treat pathogens)



**Fig. 2.** Histological sections revealing the time-dependent changes in an artificially contaminated (*S. aureus*) osteotomy of the rabbit humerus. Upper panel, from left to right shows the changes in the soft tissues overlying an LCP from the early post-operative phase (left) where some early signs of inflammation are observed over the plate, to the position at 4 weeks, (center) where significant necrosis is observed. By ten weeks, the necrosis has resulted in a capsule formation surrounding the necrotic tissue adjacent to the LCP. Bone involvement lags behind the soft tissue involvement, which at 1 week (lower panel, left) is non-existent. By four weeks (center), the bone is showing signs of osteolysis and failure to heal, although this is more pronounced at ten weeks (right), at which time non-union is seen including sequestration of necrotic bone fragments. (Giemsa Eosin stained, upper panel scale bar 200 micrometers, lower panel, scale bar 1000 micrometers).

**Table 1**

Central aims of treating IAFF.

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1.	Fracture consolidation
2.	Eradication of infection or in certain cases suppression of infection until fracture consolidation is achieved
3.	Healing of the soft-tissue envelope
4.	Prevention of chronic osteomyelitis
5.	Restoration of functionality

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**Table 2**

Questions to tailor the appropriate treatment strategy.

- 
1. Onset of symptoms (classification): early–delayed–late onset of infection?
  2. Fracture healed or stable callus formed?
  3. Osteosynthetic construct: stable implant and satisfactory fracture reduction?
  4. Type of implant (e.g. plate, nail, external fixation)?
  5. Fracture localization (e.g. diaphyseal, articular)?
  6. Condition of soft-tissue envelope?
  7. Local and systemic host physiology?
  8. History of infection at site of interest?
  9. Difficult to treat pathogen?<sup>a</sup>
- 

<sup>a</sup> In general not available for the primary revision, since pre-operative pathogen identification is often not possible (in contrast to PJI, due to joint aspiration); microbiology results should be taken into account as soon as available.

**Table 3**  
Antibiotic treatment according to the pathogen (adapted from Zimmerli et al. [86]).

Pathogen	Antibiotic therapy	Dose (normal renal function)
<i>Staphylococcus</i> spp.	<b>2 weeks</b>	
Methicillin-susceptible	Flucloxacillin <b>plus</b> Rifampicin	2 g every 6 h. iv. 450 mg every 12 h iv./po.
Methicillin-resistant	<b>2 weeks</b> Vancomycin or Daptomycin <b>plus</b> Rifampicin	15 mg/kg every 12 h iv. 6–8 mg/kg every 24 h iv. 450 mg every 12 h iv./po.
all <i>Staphylococcus</i> spp.	<b>followed by</b> Rifampicin <b>plus</b>	450 mg every 12 h po.
	<b>1st choice</b> Ciprofloxacin or Levofloxacin or	750 mg every 12 h po. 500 mg every 12 h po.
	<b>2nd choice</b> Cotrimoxazole or Fusidic acid or	1 double strength tablet every 8 h po. 500 mg every 8 h po.
	<b>3rd choice</b> Clindamycin or Minocycline or Linezolid	600 mg every 8 h po. 100 mg every 12 h po. 600 mg every 12 h po.
<i>Streptococcus</i> spp. <sup>a</sup>	<b>4 weeks</b> Penicillin G or Ceftriaxon	5 Mio IU every 6 h iv. 2 g every 24 h iv.
	<b>followed by</b> Amoxicillin or Clindamycin	1000 mg every 8 h po. 600 mg every 8 h po.
<i>Enterococcus</i> spp.	<b>whole therapy</b> <sup>b</sup>	
Penicillin-susceptible	Amoxicillin or Penicillin G	2 g iv. every 6 h iv. 5 Mio IU every 6 h iv.
Penicillin-resistant	<b>whole therapy</b> Vancomycin or Daptomycin or Linezolid	15 mg/kg every 12 h iv. 6–8 mg/kg every 24 h iv. 600 mg every 12 h iv./po.
<i>Enterobacteriaceae</i>	<b>2 weeks</b> β-lactam antibiotic according to susceptibility	iv.
	<b>followed by</b> Ciprofloxacin	750 mg every 12 h po.
<i>Enterobacter</i> spp. and Nonfermenters (e.g. <i>P. aeruginosa</i> )	<b>2–4 weeks</b> Cefepime or Ceftazidime <sup>c</sup> or Meropenem	prolonged infusion (3 h): 1–2 g every 8 h iv. <sup>d</sup> 2 g every 8 h iv. 1–2 g every 8 h iv. <sup>d</sup> 750 mg every 12 h po.
	<b>followed by</b> Ciprofloxacin	
<i>Propionibacterium</i> spp.	<b>2–4 weeks</b> Penicillin G or Ceftriaxon <sup>e</sup>	5 Mio IU every 6 h iv. 2 g every 24 h iv.
	<b>followed by</b> Amoxicillin or Clindamycin	1000 mg every 8 h po. 600 mg every 8 h po.
<b>Gram-negative Anaerobes</b> (e.g. <i>Bacteroides</i> )	<b>whole therapy</b> Metronidazol	500 mg every 8 h iv./po.
<b>Mixed infections</b> (without methicillin-resistant <i>S. aureus</i> )	Individualized therapy according to susceptibility	

<sup>a</sup> Measuring minimal inhibitory concentration (MIC) for penicillin recommended.

<sup>b</sup> Iv.- therapy if curative intention, for suppressive therapy consider e.g. amoxicillin 750–1000 mg every 8 h po.

<sup>c</sup> No Ceftazidime for *Enterobacter* spp. (even if measured susceptible), alternative: Ertapenem 1 g every 24 h.

<sup>d</sup> In infections with *Pseudomonas*: high dosage recommended.

<sup>e</sup> If penicillin allergy Type I (anaphylactic): Clindamycin 600–900 mg every 8 h iv.

**Table 4**  
Factors favoring implant removal and exchange.

1.	Nail osteosynthesis <sup>a</sup>
2.	Unstable osteosynthesis or insufficient fracture reduction <sup>a</sup>
3.	Compromised soft-tissue envelope, which does not allow sufficient wound closure
4.	Compromised host physiology (alcoholism, diabetes, vascular insufficiency, smoking)
5.	Difficult to treat pathogen <sup>b</sup>

<sup>a</sup> Exchange/removal strongly recommended.

<sup>b</sup> In general not available for primary revision since pre-operative pathogen identification often not possible (like in PJI by joint aspiration), if in retention of implant was chosen and microbiology analysis detect postoperatively a difficult to treat pathogen, removal of the implant should strongly be considered.

**Table 5**  
Considerations when treating infected non-union.

1. Think about infection when treating a non-union (cultures)
2. Perform a good debridement of the non-union area
3. Implant exchange is not always enough and other fracture fixation methods should be considered (i.e. external fixation)
4. When in doubt perform a planned second, definitive, procedure