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 (IAFF), which can delay healing, lead to permanent functional loss, or even amputation of the affected limb.

Treating IAFF 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 IAFF 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 IAFF is completely effective despite best practice, and further improvements should be sought.

Much of the surgical and medical treatment concepts currently applied to IAFF have been adopted from prosthetic joint infection (PJI) treatment algorithms. Specific data, tailored towards the musculoskeletal trauma patient, is comparatively scarce. IAFF 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 IAFF 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 IAFF [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 IAFF, which can delay or complicate diagnosis of IAFF.

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 IAFF with an emphasis on the unique aspects of fracture care that distinguish IAFF from PJI. Furthermore, we summarize the latest preclinical and clinical research innovations regarding prevention and treatment of IAFF.

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 IAFF. 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

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Review

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 (IAFF). IAFF 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 IAFF. Although IAFF 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 IAFF has been of value to the trauma surgeon, but we should also be aware of the unique challenges posed by IAFF that may not be accounted for in the PJI literature.

This review summarizes the clinical approaches towards the diagnosis and treatment of IAFF with an emphasis on the unique aspects of fracture care that distinguish IAFF 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.

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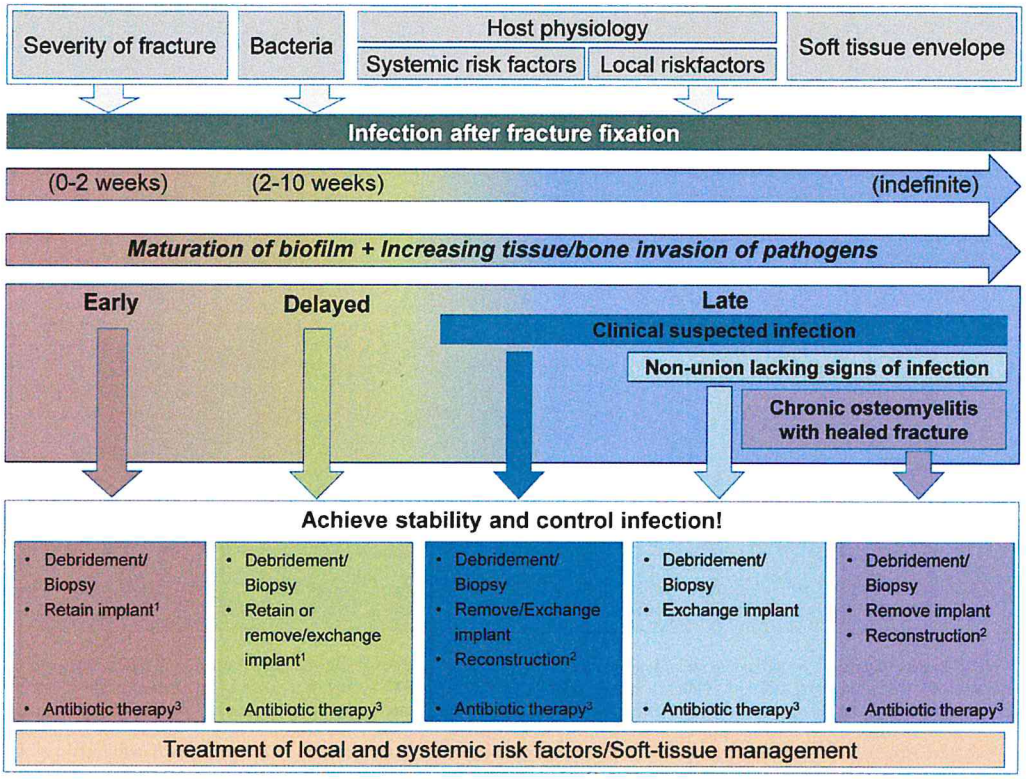

Fig. 1. Pathophysiology, classification and treatment algorithm of IAFF.
[1] See Table 4: Factors favoring implant removal and exchange
[2] Reconstruction can be carried out in a single step (with implant exchange) or in multiple stages; after resection of necrotic soft-tissue and bone a multidisciplinary approach will often be required
[3] Antibiotic therapy should be chosen in collaboration with an infectious disease specialist (especially in polymicrobial infections or proof of difficult to treat pathogens)

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 IAFF is therefore a needed first step towards improving scientific reporting and evaluation of routine clinical data, as well as aid in the evaluation of new prevention and treatment strategies [25].

Classification

Although there is a lack of clear definitions, there is a widely accepted classification scheme for IAFF [26,27]. Willeneger and Roth classified IAFF 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 IAFF, biofilm formation and, importantly for the trauma surgeon, fracture-healing status (Fig. 1).

Early infection (<2 weeks)

Early IAFFs 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 (Fig. 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.

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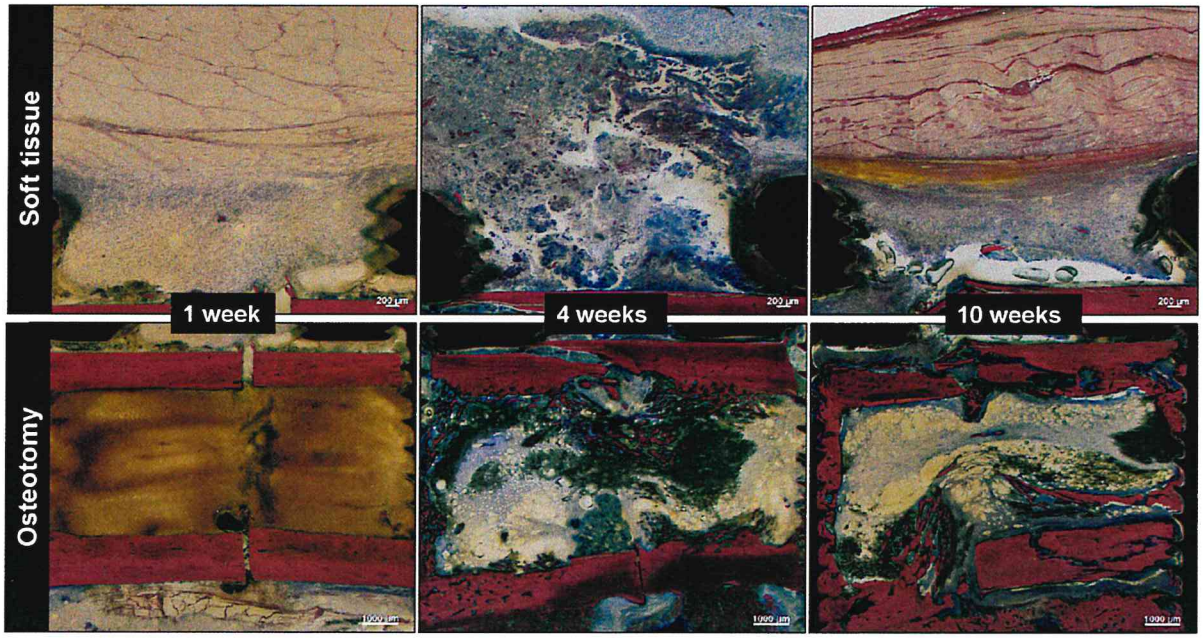

Fig. 2. Histological sections revealing the time-dependent changes in an artificially contaminated (*S. aureus*) osteotomy of the rabbit humerus. Upper panel, from left to right shows the changes in the soft tissues overlying an LCP from the early post-operative phase (left) where some early signs of 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 one fragments. (Giemsa Eosin stained, upper panel scale bar 200 micrometers, lower panel, scale bar 1000 micrometers).

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 and 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 IAFF 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 (Fig. 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, IAFF is primarily caused by micro-organisms 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 (Fig. 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 IAFF 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 IAFF 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 IAFF 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 IAFF [26,39]. Persistent elevation or a secondary rise in C-reactive protein (CRP) can be an indicator for IAFF [40,41].

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