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JINJ 6905 No. of Pages 12

ARTICLE IN PRESS

Injury, Int. J. Care Injured xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Injury

journal homepage: www.elsevier.com/locate/injury

Review

Infection after fracture fixation: Current surgical and microbiological concepts

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ARTICLE INFO

Keywords:
Infection after fracture fixation
Implant-related infection
Infected non-union
Complications
Biofilm
Antibiotic therapy

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.

Contents

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http://dx.doi.org/10.1016/j.injury.2016.09.019

Please cite this article in press as: W.J. Metsemakers, et al., Infection after fracture fixation: Current surgical and microbiological concepts, Injury (2016), http://dx.doi.org/10.1016/j.injury.2016.09.019

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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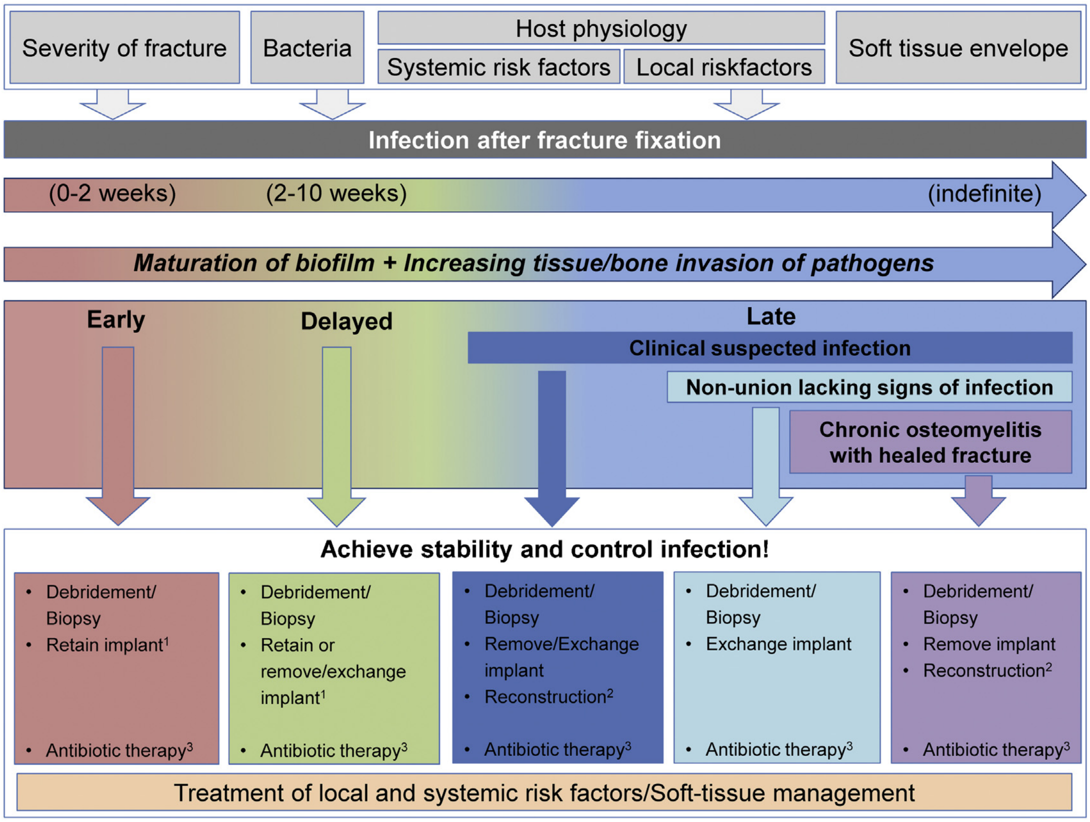

Fig. 1. Pathophysiology, classification and treatment algorithm of IAFF.
[1] See Table 4: Factors favoring implant removal and exchange
[2] Reconstruction can be carried out in a single step (with implant exchange) or in multiple stages; after resection of necrotic soft-tissue and bone a multidisciplinary 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 novel 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.

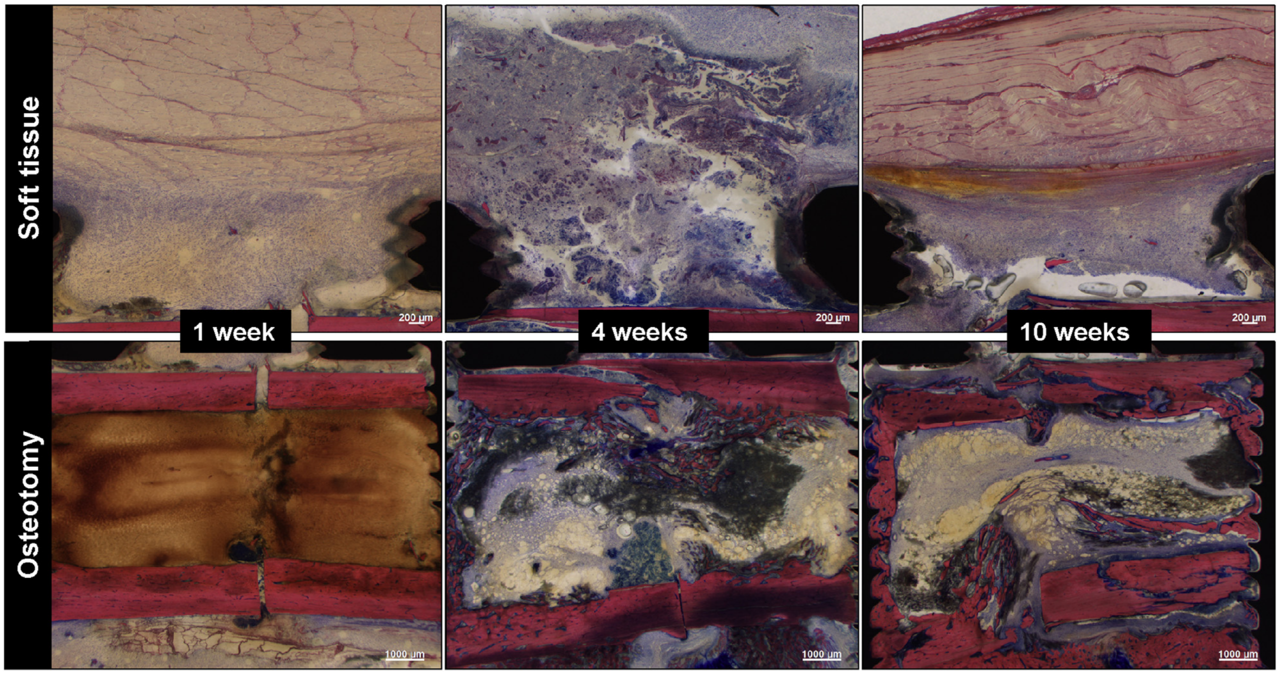

Fig. 2. Histological sections revealing the time-dependent changes in an artificially contaminated (*S. aureus*) osteotomy of the rabbit humerus. Upper panel, from left to right shows the changes in the soft tissues overlying an LCP from the early post-operative phase (left) where some early signs of 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].

Microbiology

IAFF 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 IAFF 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 IAFF, 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 (99mTc) 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 IAFF [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]. 18F-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 IAFF still remains inconclusive and has to be determined.

Treatment

General considerations

The central aims of treating IAFF are shown in Table 1. Remember that every case of IAFF 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

Table 1
Central aims of treating IAFF.

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?[a]

[a] 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.

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. sequesters, 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 3) [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 *E. 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 carries 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 IAFF [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

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

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

[a] Measuring minimal inhibitory concentration (MIC) for penicillin recommended.
[b] Iv.- therapy if curative intention, for suppressive therapy consider e.g. amoxicillin 750–1000 mg every 8 h po.
[c] No Ceftazidime for Enterobacter spp. (even if measured susceptible), alternative: Ertapenem 1 g every 24 h.
[d] In infections with Pseudomonas: high dosage recommended.
[e] If penicillin allergy Type I (anaphylactic): Clindamycin 600–900 mg every 8 h iv.

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 megaprostheses [111].

Stage-dependent surgical treatment considerations

Treatment of early infection

Colonization of hardware can occur intraoperatively, and biofilm formation may proceeds 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 4. 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 (Fig. 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 4), 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 (Fig. 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 IAFF is a continuum (Fig. 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 (Fig. 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 sequesters 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 (sequesters) 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].

Table 4
Factors favoring implant removal and exchange.

1.	Nail osteosynthesis[a]
2.	Unstable osteosynthesis or insufficient fracture reduction[a]
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[b]

[a] Exchange/removal strongly recommended.
[b] 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.

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 IAFF, 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 IAFF.

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

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

Please cite this article in press as: W.J. Metsemakers, et al., Infection after fracture fixation: Current surgical and microbiological concepts, Injury (2016), http://dx.doi.org/10.1016/j.injury.2016.09.019

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 IAFF. 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.

Conflict of interest

All authors declare no conflict of interest with respect to the preparation and writing of this article.

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Please cite this article in press as: W.J. Metsemakers, et al., Infection after fracture fixation: Current surgical and microbiological concepts, Injury (2016), http://dx.doi.org/10.1016/j.injury.2016.09.019