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Diagnostic challenges and future perspectives in fracture-related infection

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ABSTRACT

Fracture-related infection (FRI) is one of the most challenging complications in orthopaedic trauma surgery. It has severe consequences for patients and an important socio-economic impact. FRI has distinct properties and needs to be addressed interdisciplinary. Since criteria for the diagnosis of FRI are not standardized, an expert panel recently proposed a definition for FRI. In this review the current diagnostic modalities and an interdisciplinary diagnostic algorithm based on this recently published definition, are presented and future diagnostic techniques discussed. Since to date, there is no single universal diagnostic test available that gives the clinician the definitive diagnosis of FRI, it is mandatory to follow a standardized diagnostic algorithm to correctly diagnose FRI.

Introduction

The risk of developing a fracture-related infection (FRI) depends on the location and severity of the injury, the extent of concomitant injuries, as well as on the host's physiology [1]. The incidence of FRI ranges from 1% after closed low energy fractures to more than 15% after complex open limb fractures, which are often associated with considerable bone damage including periosteal stripping, extensive soft-tissue trauma and severe contamination [2,3]. FRI is acquired almost exclusively exogenously, primarily due to the initial trauma mechanism (e.g. open fractures) or surgery [4,5]. Once bacteria have breached the skin barrier they are able to grow in communities in protected biofilms on non-living surfaces, such as implants or dead bone fragments, and possess the ability to hide in extra- and intracellular niches. These localized grouped bacteria are often metabolic quiescent, able to evade the host's immune responses and resist antimicrobial therapy. This makes them not only difficult to identify but also very challenging to treat [1,2,6]. Therefore, FRI is the most feared complication after fracture fixation with a significant socio-economic impact. Due to an incidence of approximately 100,000 FRIs annually in the US (2004) and median treatment costs of over 15,000 USD per infection, the estimated overall costs have been calculated to be four times higher than that of prosthetic joint infection (PJI) [7,8]. Recent data on infections in operatively treated tibia fractures showed even higher numbers than previously published [9].

To overcome this challenge, not only prevention but also standardized interdisciplinary diagnostic and treatment approaches are mandatory. In contrast to PJI, these standardized protocols tailored to infection in patients after musculoskeletal trauma are scarce [1,2]. Important differences can be found between FRI and PJI regarding pathophysiology, diagnosis and treatment. The most obvious is the presence of a fracture in FRI, which needs stability to achieve bone consolidation and to allow successful treatment of the accompanying infection [1]. Furthermore, FRIs are more heterogeneous due to various localizations, the unpredictable contamination of open wounds as well as the heterogeneity of soft tissue trauma and bone damage. Preoperative identification of the infecting pathogen is normally not possible in FRI, while joint puncture may already identify the pathogen in PJI prior to surgical intervention. The clinical picture of FRI can range from acute, pus draining, surgical site infections to infected non-unions, which might even miss obvious clinical signs of infection.

In this review the current diagnostic modalities and an interdisciplinary diagnostic algorithm, based on the recently published definition on FRI [10], are presented and future diagnostic techniques discussed.

Definition

Despite its tremendous impact, until recently no uniform definition of FRI was developed [1]. Therefore, to date, objective

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Table 1
Definition of fracture-related infection (FRI)

Confirmatory criteria	Suggestive criteria
Fistula – Sinus – Wound breakdown	Local and systemic signs of infection
Purulent drainage or presence of pus	Radiological signs
Presence of microorganisms in deep tissue specimens confirmed by histopathological examination[a]	New onset joint effusion
	Elevated serum inflammatory makers
Phenotypically indistinguishable pathogens identified by culture from at least two separate deep tissue/ implant specimen	Persistent, increased or new onset wound discharge
	Pathogenic organism identified by culture from a single deep tissue/ implant specimen

The presence of at least one confirmatory criterion defines FRI. The presence of a suggestive criterion requires further investigations in order to look for confirmatory criteria [10]. [a] The presence of microorganisms is confirmed by using specific staining techniques for bacteria or fungi.

estimation of the impact of FRI in clinical studies has been largely impossible. The problem was confirmed by a recent systematic review, which showed that only a minority of randomized controlled trials in fracture care uses any kind of standardized definition of FRI [11]. For PJI the situation was similar many years ago, which however, has improved significantly with consensus definitions emerging over the last decade [12]. In response to this conclusion, a survey on the need of a FRI definition was distributed amongst an international cohort of orthopaedic surgeons. Approximately 90% agreed that a definition of FRI was required [10]. In order to address this issue, an international expert group represented by delegates of various scientific organizations and disciplines was recently convened to develop such a consensus definition [10]. The expert panel defined two levels of certainty around diagnostic features. The criteria could be confirmatory (infection definitely present) or suggestive (Table 1).

This definition should support clinicians in their daily clinical and scientific practice to diagnose and define FRI.

Classification and clinical presentation

Over the past decades, different classifications have been proposed each focusing on another aspect of FRI. According to the time interval between osteosynthesis and manifestation of infection Willenegger and Roth classified FRIs into three groups: early (≤2 weeks), delayed (between weeks 3 and 10), and late (>10 weeks) infections [13]. This classification was widely adopted by orthopaedic trauma surgeons and infectious disease specialists over the last three decades, as it considers both the pathophysiological changes and their derived treatment strategies [1,5]. In a previous article, the authors have discussed the time dependent pathophysiological changes with maturation of biofilm, establishment of infection and its influence on treatment strategies [1]. Early infections can present with impaired wound healing, as well as with local (rubor, calor, dolor et tumor) and systemic signs of infection (e.g. fever). They are mainly caused by highly virulent pathogens, such as *Staphylococcus aureus*, group A streptococci and Gram-negative bacilli [1,5]. Delayed infections represent a diagnostic grey zone. They may derive from a virulent pathogen with deferred manifestation due to previous antibiotic treatment (e.g. pre-emptive antibiotics in open trauma), or from a low-virulent pathogen requiring more time until manifesting symptoms. Therefore, delayed infections can present with symptoms of either early or late infections. Late infections mostly manifest as chronic infections. These have to be considered in patients with persistent clinical signs of infection, as well as in patients with non-unions lacking any other clinical sign of infection. Therefore, they can present either with local signs of infection (e.g. swelling, erythema, draining sinus tract), or just with subtle symptoms such as compromised functionality and stress-dependent pain or pain at night. Chronic infections are primarily induced by low-virulent pathogens such as coagulase-negative staphylococci, whereas in case of a draining fistula any microorganism may be found [1, 5].

Importantly, haematogenous seeding during bacteraemia can occur at any time after fracture fixation. These acute haematogenous infections occur after an asymptomatic period and develop within a short interval acute systemic and/ or local signs of infection. Highly virulent pathogens, such as *S. aureus*, *E. coli* and beta-haemolytic streptococci are mainly responsible for the acute nature of infection.

Diagnostic algorithm

To date, there is no single universal diagnostic test available that gives the clinician the definitive diagnosis of FRI. A combination of tests is needed and therefore it seems advisable to create a standardized diagnostic algorithm for FRI. The above-mentioned definition is the backbone of the proposed interdisciplinary diagnostic algorithm, which also serves as a fundament for a standardized treatment protocol (Fig. 1).

After diagnostic assessment, a surgical and antimicrobial treatment plan has to be set up. In addition to the diagnostic criteria, classification and clinical presentation, the further considerations [14], listed in Fig. 1, should be taken into account to conduct the optimal treatment protocol.

Clinical examination and patient history

Patients presenting with a suspected FRI have to undergo detailed clinical examination for documentation of local and systemic signs of infection, evaluation of other infectious foci, and determination of the host`s comorbidities and possible impairment of the immune system. Above-mentioned confirmatory and suggestive criteria for FRI diagnosis have to be assessed during the clinical examination (Table 1) [10]. The surgical wound and the soft tissue envelope overlying the suspected site of infection have to be evaluated critically, photographically documented and presented to the plastic surgeons, if problems with sufficient wound closure may arise. In addition, other disciplines (infectious disease specialists, internal medicine, vascular surgery, dermatology etc.) have to be consulted pre-operatively to optimize the local and systemic host's physiology.

Besides information on allergies (e.g. antibiotics), medication (e.g. antibiotics and anticoagulants) and overall medical condition (i.e. host`s physiology, risk factors) the medical history concerning the suspected FRI has to be obtained carefully. This includes information on: the initial trauma (mono- or polytrauma), initial fracture pattern with accompanied soft tissue injury (including nerve and vascular injuries), fracture fixation and other surgeries, postoperative wound healing disorders or history of previous FRIs with prior results from microbiology.

Laboratory examination

In suspected FRI, peripheral blood tests are part of a general diagnostic evaluation to monitor the host's inflammatory response to a possible infection. Although unspecific and typically influenced by many other pathophysiological changes and surgery-related stress, they should be included in a diagnostic algorithm. White blood cell (WBC) count has a low sensitivity and moderate specificity for diagnosing FRI. Persistent elevation or a secondary rise in C-reactive protein (CRP) can be an indicator for FRI, whereas low CRP levels do not exclude low-grade infections [1].

There is a lack of studies analysing other serum inflammatory markers in FRI. In PJI serum markers such as interleukin-6 or pro-