**EFORT** *open reviews*

# Definition and diagnosis of fracture-related infection

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- Fracture-related infection (FRI) is common and often diagnosed late.

- Accurate diagnosis is the beginning of effective treatment.

- Diagnosis can be difficult, particularly when there are no outward signs of infection.

- The new FRI definition, together with clear protocols for nuclear imaging, microbiological culture and histological analysis, should allow much better study design and a clearer understanding of infected fractures.

- In recent years, there has been a new focus on defining FRI and avoiding non-specific, poorly targeted treatment. Previous studies on FRI have often failed to define infection precisely and so are of limited value. This review highlights the essential principles of making the diagnosis and how clinical signs, serum tests, imaging, microbiology, molecular biology and histology all contribute to the diagnostic pathway.

## Introduction

Successful treatment of a fracture is aimed at promoting bone healing and good functional recovery with the avoidance of complications which may impair function or prolong treatment. When an infection occurs, this can be a devastating event, with the need for unexpected surgery, increased hospital stay and much higher healthcare costs.[1,2] The effects on the patient extend far beyond the initial treatment of the infection or fracture. Patients may require support from healthcare providers and social services over a prolonged period.[2,3] It is even more stressful for patients if the diagnosis of an infection is delayed or missed. Failure to begin treatment promptly may convert a simple early fracture infection into a chronic persistent infected non-union which may be very difficult to eradicate.[4,5]

Considering the importance of diagnosing and treating an infected fracture, it is surprising that it is only very recently that an accepted definition of fracture-related infection (FRI) has been published. In 1996, Arens et al reported that in all studies they had reviewed, the term 'infection' was not defined.[6] This situation remained unchanged for 22 years when, in 2018, Metsemakers et al found that only 2% of randomized trials of fracture fixation used any definition of infection when reporting this complication.[7]

By contrast to prosthetic joint infection, the lack of a definition or diagnostic strategy for infection has hampered the development of treatment protocols with comparable studies and outcomes. This deficit has prompted many surgeons to use diagnostic criteria developed for prosthetic joint infection. However, this is not appropriate, as the patient populations are different (elective arthroplasty versus traumatized patients) and pre-operative diagnostic tests from joint puncture or biopsy are often not feasible.

This review aims to summarize the significant advances which have been made in recent years towards establishing good diagnostic pathways with validated investigations. These have been developed by several groups around Europe and have been brought together through the FRI Consensus Group,[8] the European Bone and Joint Infection Society (EBJIS), the AO Foundation, Pro-Implant and the Orthopaedic Trauma Association (OTA).
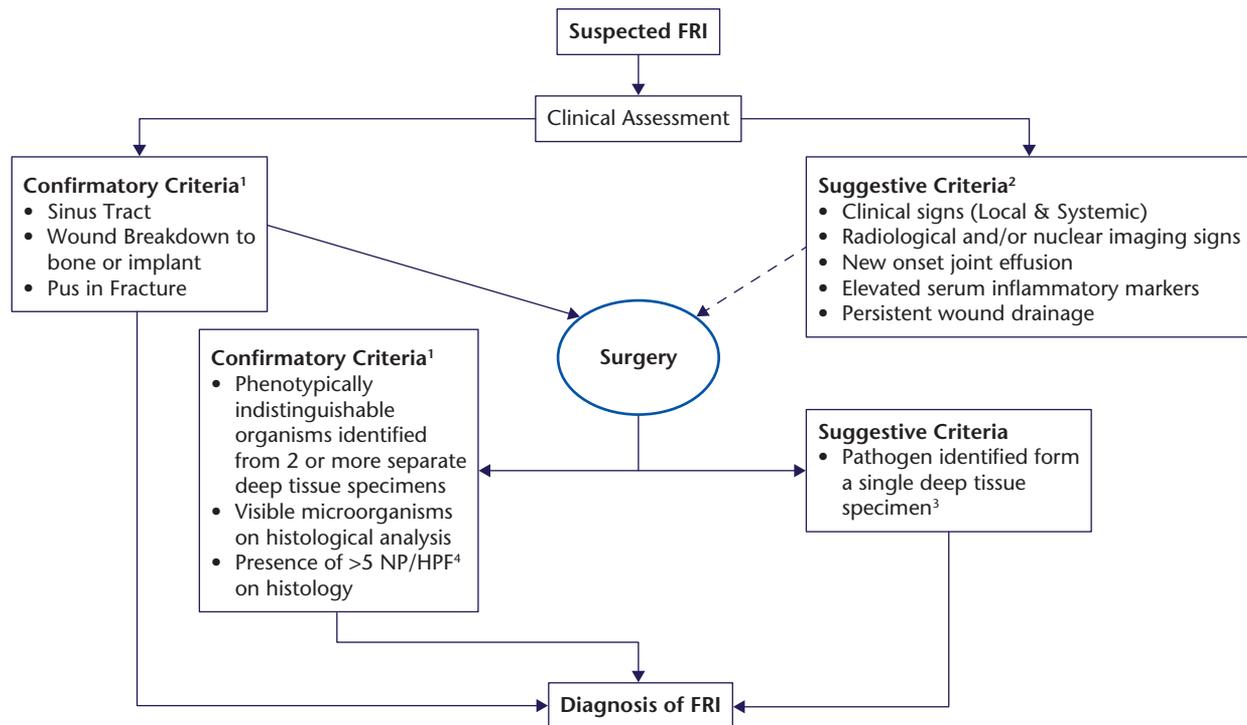
**Fig. 1** The diagnostic algorithm for a suspected fracture-related infection (FRI), using the updated definition criteria of the FRI Consensus Group.[28]

*Note.* NP/HPF, neutrophils per high-power field (x 400 magnification).
1. Any of these criteria will diagnose the presence of an infection independently. For instance, the presence of a draining sinus communicating with the fracture does not need microbiological culture for confirmation of infection.
2. Suggestive criteria should prompt the surgeon to consider further investigations which may lead to identifying possible confirmatory criteria.
3. A single positive culture from sonication fluid at >50 colony-forming units per ml, particularly from a virulent organism, such as *Staph. aureus*, is highly suggestive of infection and may be taken as confirmatory on an intention-to-treat basis.
4. >5NP/HPF is regarded as confirmatory of infection in cases more than 8 weeks after fracture.

# Terminology and definition of infection

Many terms have been used to describe the onset of infection after fracture. The use of words like osteomyelitis, osteitis or deep surgical site infection can be confusing and do not give specific indication of the relationship with a fracture. The FRI Consensus Group published the initial definition criteria in 2018[8] and the term 'fracture-related infection' was adopted to encompass all infections which occur in the presence of a fracture. This includes early infection around fracture implants, infected non-unions, haematogenous infections arising after fracture healing and infections in fractures with no internal fixation.

Review of the literature showed that there are some diagnostic tests which are highly specific for the presence of infection (confirmatory criteria). These included sinus tracks communicating with the fracture, microbiological culture of organisms and histological features of infection. Conversely, there were features which suggested the presence of infection but could not be diagnostic alone (suggestive criteria). These included some clinical signs, blood biomarkers and imaging tests. The FRI definition has recently been updated to include new data and is summarized in Fig. 1.

# Blood biomarkers

Common serum inflammatory markers such as leukocyte count, C-reactive protein and erythrocyte sedimentation rate have been evaluated in the diagnosis of FRI. All are non-specific and can be raised after trauma without infection and in many other inflammatory conditions. Also, they can be normal in many chronic or late infections. C-reactive protein (CRP) levels rise after injury to a maximum at day 2 and then reduce to normal over 1–2 weeks.[9] Systematic review of the literature reveals that CRP is perhaps the most useful marker, but with only moderate sensitivity and specificity.[10] In recent studies of infected fractures and non-unions, blood markers had very limited predictive value.[11,12] They cannot be used to confirm or exclude an infection.

## Imaging for FRI

Imaging is inextricably linked to fracture surgery. When a post-operative FRI is considered, there are three main indications to (re)image the affected limb:

1. To evaluate fracture consolidation and implant stability.
2. To determine if an infection is present.
3. To assess the extent of that infection with specific anatomical details (such as sinuses, sequestra and cloacae) for surgical planning.

The most commonly used imaging modalities are plain X-ray, computed tomography (CT), magnetic resonance imaging (MRI) and the nuclear imaging techniques of white blood cell (WBC) scintigraphy and fluorodeoxyglucose positron emission tomography (18FDG-PET). Three-phase bone scintigraphy (BS) is highly sensitive for detecting FRI (89–100%) but unfortunately has a very low specificity (0–10%).[13] BS is therefore almost obsolete for this indication.

In established FRI, for example in the presence of a draining sinus,[8] imaging should focus on determining fracture consolidation and implant stability. For this purpose, plain X-ray, possibly combined with a CT scan, is usually sufficient. If the presence of an infection or the extent of the infection is the issue, more advanced imaging techniques such as MRI or nuclear imaging are required. MRI has many advantages: it is familiar, relatively cheap and widely available. Also it can distinguish anatomical details in the bone and adjacent soft tissues and has excellent sensitivity for detecting FRI (82–100%).[13] With artifact reduction techniques the interference of metal implants can be reduced to a minimum.[14] The downside of MRI is that, probably due to its inability to differentiate between sterile inflammation, normal bone healing and infected tissue, its specificity is reduced (43–60%).[13]

Nuclear imaging is far more accurate in cases where it is important to distinguish infected from non-infected tissues. It has been shown that both WBC scintigraphy and 18FDG-PET are highly accurate for diagnosing FRI shortly after surgery.[15,16] More recently, the use of hybrid camera systems which combine nuclear imaging with CT (single photon emission computed tomography (SPECT) (SPECT/CT, PET/CT or PET/MRI) has led to increased accuracy and better anatomical details.[13,17–19] Large retrospective studies show a sensitivity and specificity of WBC scintigraphy with SPECT/CT for diagnosing FRI, of 79–100% and 97% respectively.[15,20] For 18FDG-PET, sensitivity is 88–89% and specificity is 76–80%.[16,21] This means that WBC scintigraphy + SPECT/CT is slightly more accurate than 18FDG-PET/CT, but one has to bear in mind that all these studies were hampered by their retrospective study designs. Secondly, although less accurate, 18FDG-PET has major advantages over WBC scintigraphy in terms of lower complexity of the labelling procedure, the requirement for just one scan, rather than early and late phase scans (over 20 hours), and its higher spatial resolution (3–4 mm vs. 8 mm).[19]

For the diagnosis of FRI, every imaging modality has its advantages and disadvantages and most studies have methodical limitations. A prospective clinical trial has recently been launched that will hopefully provide more clarity about the optimal imaging strategy for FRI in terms of diagnostic accuracy, cost-effectiveness and how to solve logistic challenges.[22] While awaiting these results, the imaging modality of choice therefore mostly depends on the clinical question to be answered and local availability and experience with the imaging technique of choice.

## Microbiological diagnosis of FRI

Published evidence relating to the microbiological diagnosis of FRI should be considered with the caveat that the consensus definition of FRI is recent, and that many previous studies excluded patients on the basis of the duration, site, and other clinical features of infection.

The aims of microbiological diagnosis of FRI are two-fold:

1. To confirm fracture-related infection when it is suspected.
2. To identify the infecting pathogen(s) and assess antimicrobial susceptibility patterns, and to select a targeted and tolerable, preferably oral, antimicrobial treatment for the patient.

### Confirmation of infection

Accurate microbiological diagnosis requires the analysis of representative, uncontaminated samples of tissue or fluid from the fracture. Pre-operative diagnosis from superficial swabs, biopsies or aspirations is usually unhelpful as there is often poor concordance between biopsies and intra-operative sampling. A high proportion of FRIs are caused by bacteria that may be considered skin commensals. Detection of organisms such as coagulase-negative Staphylococci, Corynebacteria, and *Cutibacterium acnes* on a single biopsy specimen is thus very difficult to interpret. Also, up to one third of patients with FRI have polymicrobial infection, which is often missed in pre-operative biopsies.[23,24] If antimicrobial therapy is based on limited pre-operative cultures alone, it has been shown that poor outcomes will be achieved.[25]

Reliable microbiological information is obtained by culture of at least five uncontaminated samples, collected during surgery. Samples should be collected in a structured process, with separate instruments for each sample

and without touching the patient's skin with the sample or instrument.[24,26,27] A study of the implementation of a structured sampling protocol following the recommendations for the diagnosis of FRI, found a greater proportion of polymicrobial infections diagnosed after the implementation, compared with unstructured microbiological sampling prior to the implementation, despite no increase in the proportion of positive samples or suspected culture contamination.[24] Specimens should be transferred rapidly to the laboratory and handled in a standardized protocol.[28] Five operative specimens can be processed under aerobic and anaerobic conditions with selective and non-selective media for less than 55 Euros per patient.[29] Automated liquid culture may be even more cost-effective.[30,31]

Infections around implants or dead bone will frequently occur in the presence of biofilm. Methods which disrupt biofilm may enhance the isolation of organisms and improve diagnostic yield.[28] Sonication is a useful adjunct in the diagnosis of FRI where implants or cortical bone fragments are removed during operative debridement. The sensitivity of sonication alone in a series of 158 fractures, assessed against a clinical diagnosis of infection (sinus, purulence or histopathology findings consistent with infection) was 68%.[32] Prior studies reported sonication fluid sensitivity for FRI at between 65% and 95%, with specificity between 50% and 97%.[33] Sonication should be used together with deep tissue sampling for optimum diagnostic accuracy.[28,32]

Microbiological confirmation of FRI is obtained when phenotypically indistinguishable organisms are cultured from at least two separate deep tissue/implant specimens (including sonication fluid), collected and processed as above. A single positive culture is not confirmatory but is suggestive of infection and should be confirmed with other tests.[8,28]

*Identification of pathogens and antimicrobial susceptibilities*

FRI is caused by a very wide variety of bacteria and fungi. Additionally, polymicrobial infection is common and often includes Gram-negative organisms.[23,34] Clinical characteristics (open fracture, presence of metalwork, draining sinus, compromised host) do not discriminate sufficiently to anticipate who may be affected with polymicrobial or non-staphylococcal FRI.[23] The microbiological diagnosis of FRI must involve methods which determine antimicrobial susceptibility in individual microbial species, as antimicrobial sensitivity cannot be reliably predicted. Up to one third of classifiable organisms causing FRI may be multi-drug-resistant (MDR), even in countries with a low incidence of MDR infection.[23] The presence of these resistant bacteria adversely affects outcome.[35] Therefore, there is no place for empirical broad-spectrum therapy, particularly aimed at Gram-positive bacteria.

Antibiotic side-effects are frequent in the context of FRI treatment for at least six weeks, with around one in six patients affected, so the careful choice of antimicrobials for FRI must be justified by microbiological diagnosis.[36] The use of non-targeted, broad-spectrum agents is associated with subsequent multi-resistant infection for individual patients[37,38] and cannot be justified. Intravenous empirical therapy should only be used immediately after surgery, while microbiological diagnosis is awaited. Thus, antimicrobial susceptibility assessment must form an integral part of the microbiological diagnosis of FRI.

Molecular methods have now been investigated in the diagnosis of FRI. Whole genome sequencing[39] and multiplex polymerase chain reaction methods (PCR)[40] have shown initial encouraging results. PCR-based identification panels and 16s-PCR have low sensitivity for the detection of all infecting organisms and may not be able to detect fungal or unusual bacterial infection. An evaluation of sonication fluid PCR for the microbiological diagnosis of FRI found that *Candida spp.* and *Enterococcus spp.*, pathogens with particularly poor treatment outcomes in the context of orthopaedic infection, were especially likely to be missed.[40] Currently, molecular techniques cannot give useful information on antimicrobial susceptibility.

## Histopathology

The presence of visible microorganisms in deep tissue, as confirmed by histopathological examination using specific staining techniques for bacteria (e.g. Gram stain, Ziehl-Neelsen stain for tuberculosis or Grocott methenamine silver stain for fungi), is regarded as a confirmatory sign of FRI.[8] In prosthetic joint infection (PJI), the presence of $\geq$ 5 polymorphonuclear neutrophils per high-power field (PMN/HPF) in five high-power fields observed in histological sections, at x 400 magnification, is considered to be an important intra-operative criterion for PJI.[41] In contrast to the definition for PJI, the FRI Consensus Group did not include the presence of an acute inflammatory cell infiltrate on histopathological examination (i.e. PMN count) in the first version of the FRI definition.[8] The reason for this was the lack of clear scientific evidence and, more specifically, agreement on a cut-off value above which FRI can be reliably diagnosed.[8,33]

However, a large study on the value of quantitative histopathology for the diagnosis of chronic/late-onset FRI (at least two months after fracture) has now been published.[42] Morgenstern et al. proposed a novel bimodal approach to confirm or exclude infection in unhealed fractures. The complete absence of PMNs had a very high correlation with aseptic non-union (specificity 98%, positive predictive value (PPV) 98%). Conversely, the presence of >5 PMN/HPF only occurred with infection (specificity 100%; PPV 100%). The combination of clinical signs, $\geq$ 2

microbiological cultures and bimodal histopathological analysis (absent NPs vs. >5 PMN/HPF) improved diagnostic accuracy in up to 96.8% of cases. Due to increasing evidence, the presence of >5 PMN/HPF in fractures more than 8 weeks after injury (e.g. fracture non-union) was added by the expert panel in the second consensus meeting as the fifth confirmatory sign of FRI.[28] (Fig. 1).

## Conclusions

Interest in the definition and diagnosis of FRI is a recent development. There are now good studies which give clear definition criteria and some evidence around the effectiveness of diagnostic methods. Pre-operative diagnosis with serum markers, superficial swabs or percutaneous biopsies is not accurate. Diagnosis depends on the interpretation of deep tissue specimens for microbiological culture and histological analysis. The improvements in imaging, particularly with nuclear medicine combined with localizing scans ($^{18}$FDG-PET/CT or SPECT/CT), offer new possibilities for the diagnosis of infection and for planning of surgical procedures.

There is now no place for empirical treatment of suspected infection, in the hope of a miraculous cure. Careful attention to establishing the diagnosis allows better surgical planning and pathogen-specific antimicrobial therapy, designed to improve outcomes in FRI.

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