

External Fixation

The infection rates reported with the use of external fixators are higher than with osteosynthesis with an incidence of infection of up to 71% [13]. However, there is also no clarity in regards to the diagnosis of SSI in external fixation. There are two classification systems, Checketts-Otterburn and Sims, neither of which have been validated [13,14]. The most commonly used is the Checketts-Otterburn schema, which describes clinical signs such as redness, discharge, pain, edema, radiological changes in the screw-bone interface and compromise in several levels [15].

In conclusion, there is a scarcity of scientific evidence regarding diagnostic criteria to define SSIs in orthopaedic trauma. The CDC published guidelines for SSIs, which distinguish between superficial incisional, deep incisional and organ/space infections, seem not suitable to define/diagnose infection in orthopaedic trauma patients. The recently published, and thereafter updated, international consensus definition seems an adequate replacement. This definition introduces, instead of SSI, the term FRI. Furthermore, two levels of certainty around the diagnostic features are defined. Criteria can be confirmatory (infection definitely present if a confirmatory criterion is met) or suggestive. This definition should be validated by prospective data in the future.

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QUESTION 3: What diagnostic criteria define infected non-union of long bone?

RECOMMENDATION: The lack of scientific evidence precludes the development of diagnostic criteria that are solely based on sound evidence. The combination of the consensus definition of fracture-related infection (FRI) with a nonunion is a reasonable starting place, however definitions of nonunion vary and both the FRI definition and any proposed criteria for long bone nonunion will need scientific validation.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 86%, Disagree: 9%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

Introduction

FRI is a feared musculoskeletal complication and one of the most challenging in trauma surgery. Currently, estimating the impact of FRI has been hampered by the lack of a clear definition [1,2]. Interestingly, this issue was previously raised in an Arbeitsgemeinschaft Osteosynthesefragen/Association for the Study of Internal Fixation (AO/ASIF) scientific supplement publication by Arens et al. in 1996, wherein the authors stated in a combined clinical and experimental study on FRI, “It is astonishing that in all papers in which infection is mentioned, the term ‘infection’ is not defined” [3]. In fact, this was confirmed by a recent systematic review, which showed that only a minority of randomized controlled trials (2%) in

fracture cares use any kind of standardized definition of FRI [4]. The lack of a clear definition of FRI mirrors the situation for prosthetic joint infection (PJI) identified many years ago [1–5]. The situation for PJI [6] and diabetic foot infection, for example [7], has improved with consensus definitions emerging in recent years. Orthopaedic trauma surgeons realized that neither the definition for PJI nor the Centers for Disease Control and Prevention (CDC) guidelines could be easily extrapolated to fracture cases and that a definition for FRI had to be developed.

This was recently confirmed by an international survey for registered AOTrauma users. In this survey, surgeons were asked about the need for a working definition of FRI and 90% of more than

2,000 surgeons who responded suggested that a definition of FRI is required [8]. Therefore, a special effort was made, with the support of the AO Foundation, to develop such a consensus definition. The process that was followed was comparable to the one described by Cats-Baril et al. for the new definition on PJI [9]. Finally, in 2016, a consensus meeting concerning this topic was held with an international expert panel. This resulted in the current consensus definition for FRI, which was recently published [10]. This resulted in the current consensus definition for FRI, which was recently published and adopted by the AO Foundation and the European Bone and Joint Infection Society (EBJIS).

Classifications

There are multiple classifications described in the literature that subdivide FRI into discrete groupings, such as acute and chronic infections, or early, delayed and late-onset infections [2,11–13]. The authors of the recently-published consensus definition stated that there should only be a single definition for FRI based on specific diagnostic criteria. Two primary reasons were proposed for this decision. First, a subdivision would make such a definition unnecessarily complex and difficult to use in daily practice. Second, although the available classifications are time-related, these time windows are not based on scientific evidence. This supports the view that they are poorly-defined for FRI (e.g., time since injury, or time since onset of symptoms) and somewhat arbitrary. All these concerns pose serious problems from a definition point of view [4]. The authors did agree that acute and chronic infections are different entities that may require different treatment strategies, however it should not affect the way clinicians define FRI [10].

Diagnostic Criteria

Recent systematic reviews, of which two are currently under submission, have been performed to analyze the value of specific diagnostic criteria for FRI. Below, three systematic reviews on diagnostic criteria are summarized.

Clinical Criteria

Studies specifically focusing on clinical criteria to diagnose FRI are currently scarce and validation studies are nonexistent. In two systematic reviews, clinical criteria used to define FRI were described. In a study by Metsemakers et al., the aim was to identify definitions used in the literature to describe infectious complications after internal fixation of fractures [4]. A total of 100 randomized control trials (RCTs) were identified in the search. Clinical signs used to diagnose FRI in the included studies were: purulent drainage (16 studies), wound dehiscence/breakdown (5 studies), rubor (redness) (5 studies), calor (warmth) (4 studies), tumor (swelling) (4 studies), unspecified signs (4 studies) and fever (3 studies). Other parameters that were used to diagnose FRI were positive cultures (15 studies), treatment with oral antibiotics (6 studies), need for surgical debridement (5 studies), need for implant removal (4 studies), radiological signs (2 studies) and C-reactive protein (CRP) levels (1 study). Most authors included purulent drainage or discharge and positive cultures as parameters for the diagnosis of FRI [4].

In an ongoing systematic review by Bezstarosti et al., the authors are aiming to provide an overview of the available diagnostic criteria, classifications, treatment protocols and patient-related outcome measures for surgically treated FRIs between 1990 and 2017. Clinical signs used in the 93 included studies were: purulent drainage or discharge (34 studies), pain (14 studies), tumor (swelling) (9 studies), calor (warmth) (8 studies), wound dehiscence/breakdown (7 studies), rubor (redness) (7 studies), fever (5 studies) and unspci-

fied signs (46 studies). It seems that swelling, pain and redness are often seen as signs of FRI, however, they are subject to interpretation and are difficult to measure. “Purulent drainage” and “wound dehiscence/breakdown” on the other hand, seem more appropriate as hard endpoints in the diagnosis of FRI.

Serum Inflammatory Markers

In an ongoing systematic review by van den Kieboom and Bosch et al., the diagnostic value of the serum inflammatory markers CRP, leukocyte count (LC) and erythrocyte sedimentation rate (ESR) in suspected FRI were assessed. A total of 8,280 articles were identified, of which 6 [14–19] were included in this review. CRP, reported in 6 studies, appeared to be the most useful serum inflammatory marker with a sensitivity ranging between 60.0 and 100% and specificity between 34.3 and 85.7%, which is in line with current clinical practice [20]. LC was reported in five studies. Sensitivity ranged from 22.9 to 72.6% and specificity from 73.5 to 85.7%. Five studies investigated ESR; sensitivity and specificity ranged from 37.1 to 100% and 59.0 to 85.0% respectively. For the meta-analysis, four CRP studies, four LC studies and three ESR studies could be pooled. Meta-analysis of pooled results demonstrated only limited diagnostic value of the individual markers. Four studies analyzed the value of combining markers and reported an increased diagnostic accuracy. However, these results should be interpreted with caution as this is based on limited data from heterogeneous studies. Indeed, the results of all serum markers vary greatly between studies. Another issue identified when analyzing these studies was that different measuring devices, lab protocols and/or thresholds were used across studies. The authors, therefore, concluded that the analyzed serum inflammatory markers (CRP, LC and ESR) appear to be unsuitable to rule out or diagnose FRI. When these markers are used in a diagnostic flow chart, they should be interpreted with caution [10]. Future research protocols using continuous serum inflammatory marker values and standardized lab protocols are required to assess their combined value in the diagnosis of FRI.

Tissue and Sonication Fluid Sampling

In an ongoing systematic review, Onsea et al. analyzed the available evidence on sonication of fluid sampling and tissue tests for the diagnosis of FRI. Out of 2,624 studies, ten [14,21–29] fulfilled the predefined inclusion criteria. Five studies [21–25] focused on sonication fluid culture, two on polymerase chain reaction (PCR) [14,26] and two on histopathology [27,28]. One additional histopathology study [29] was found after screening of reference lists. The review demonstrated that there is evidence that sonication fluid culture may be a useful adjunct to conventional tissue culture, but there is no strong evidence that it is superior or can replace tissue culture. Regarding molecular techniques and histopathology, the evidence is even less clear. Overall, studies had variable gold standard definition criteria for comparison and poorly-reported culture methods. By updating the review, one additional paper [30] was found that is currently in press. In this study by Morgenstern et al., including unhealed FRI cases more than four weeks from the occurrence of the fracture, a bimodal cut-off for the presence of polymorphonuclears (PMNs) provided encouraging results in reducing the number of cases in which the diagnosis was uncertain [29]. During a recent second consensus meeting (i.e. AO Foundation, OTA, EBJIS and PRO-Implant Foundation) it was decided that this cut-off for the presence of PMN's was included as a confirmatory sign for FRI.

Finally, in the systematic review by Onsea et al., the authors concluded it is imperative that lab protocols become standardized and that uniform diagnostic criteria, as recently published in a consensus definition, are implemented.

Imaging Modalities

In a recent systematic review by Govaert et al. [31], the recent literature (from 2000 to 2016) on imaging techniques for the diagnosis of post-traumatic osteomyelitis was analyzed. The literature search yielded 3,358 original records, of which 10 articles [32–41] were included. This review included seven studies on different nuclear imaging techniques, two studies on magnetic resonance imaging (MRI), one study on computed tomography (CT) with no studies identified regarding plain X-ray. The sensitivity for white blood cell (WBC) count or anti-granulocyte antibody (AGA) scintigraphy ranged between 50 and 100%, specificity ranged between 40 and 97%. For fluorodeoxyglucose positron emission tomography (FDG-PET), sensitivity and specificity ranged between 83 and 100% and between 51 and 100%, respectively.

WBC scintigraphy combined with hybrid imaging technique of single photon emission computed tomography combined with CT (SPECT/CT) was assessed by two studies. A higher diagnostic accuracy was reported in both studies that used this combination. Three studies investigated the combination of FDG-PET with PET-CT, which provided a significant increase in diagnostic accuracy. However, the studies that looked into these combinations provided only limited information. The authors concluded that, compared to other imaging techniques, either WBC or AGA scintigraphy combined with SPECT/CT and FDG-PET combined with CT demonstrates the highest diagnostic accuracy for the diagnosis of post-traumatic osteomyelitis when compared to other imaging techniques. It should, however, be taken into account that these results are based on a small number of studies and that imaging techniques and patient populations were heterogeneous across studies.

By updating the systematic review, two more studies from the past two years could be found. A study by Govaert et al. [42], aimed to establish the accuracy of 192 WBC scintigraphies for diagnosing FRIs, and investigate whether the duration of the time interval between surgery and WBC scintigraphy influences its accuracy. The authors concluded that WBC scintigraphy had a diagnostic accuracy of 92% for the detection of FRI in the peripheral skeleton. The duration of the interval between surgery and the WBC scintigraphy did not influence its diagnostic accuracy. The second study, by van Vliet et al. [43], evaluated the efficacy and diagnostic accuracy of a semi-quantitative measure, maximum standard uptake value (SUVmax), for the interpretation of FDG-PET/CT in the differentiation between aseptic and septic delayed union of the lower extremity. A total of 30 patients were included: 13 patients with aseptic delayed unions and 17 patients with septic delayed unions. Mean SUVmax in aseptic delayed union patients was 3.23 (SD $\pm$ 1.21). Mean SUVmax in septic delayed union patients was 4.77 (SD $\pm$ 1.87). A cut-off SUVmax set at 4.0 showed a diagnostic accuracy of 70% to differentiate between aseptic and septic delayed union. The authors concluded that the application of SUVmax for the interpretation of FDG-PET/CT imaging seems to be a promising tool for the discrimination between aseptic and septic delayed union. However, as this is based on a small number of patients, they acknowledge that larger, prospective trials are necessary to make a further statement regarding the role of FDG-PET/CT in the diagnosis of FRI.

Due to the current lack of high-quality evidence on the value of imaging techniques, which is similar to the other diagnostic criteria discussed above, imaging techniques seem not suitable to rule out or diagnose FRI and can only be considered a suggestive sign [10]. This was also included in the recently updated (i.e. AO Foundation, OTA, EBJIS and PRO-Implant Foundation) international consensus definition of FRI.

The definition for non-union is currently not standardized, which makes it difficult to introduce diagnostic criteria for infected non-

union. This said, overall there is little scientific evidence regarding the diagnostic criteria for FRI. With respect to serum inflammatory markers, tissue, sonication fluid sampling and imaging modalities, only a small number of studies are available. Validation studies on clinical parameters are nonexistent. This lack of scientific evidence precludes the development of diagnostic criteria that are solely based on sound evidence. Moreover, it seems that developing diagnostic criteria for *both* acute/early infections and chronic/late (e.g., infected nonunion) infections is arbitrary and complicates clinical decision-making. Finally, although the scientific evidence on diagnostic criteria to define FRI is scarce, the international Consensus definition of FRI that was recently updated seems an adequate start and offers clinicians the opportunity to standardize clinical reports and improve the quality of published literature. In our opinion, this definition should be validated by prospective data collection in the future.

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QUESTION 4: What differentiates acute from chronic osteomyelitis (OM)? Is it clinically important to distinguish one from the other?

RECOMMENDATION: Current literature is lacking consistent criteria for a distinct time point that differentiates the acute and chronic forms of infection. Differentiating between acute and chronic types may have practical implications on treatment plan and final prognosis.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 95%, Disagree: 5%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

To address this question an extensive search of the literature was conducted. Our search aim was to identify articles reporting on the diagnostic criteria for acute or chronic osteomyelitis. A clear definition of OM in terms of temporal evolution was considered mandatory. Furthermore, in order to investigate the potential practical significance of the temporal distinction of OM into acute or chronic types, we aimed to identify papers reporting on the outcome of antimicrobial therapy or combined treatment (antimicrobial plus

surgical intervention) of acute osteomyelitis. Our exclusion criteria included case reports, expert opinions, experimental studies, infections associated with prosthetic implants, diabetic ulcers and non-orthopaedic bone infections (facial, cranium, ribs).

We searched the Medline, Embase, Ovid, Cochrane and Google Scholar databases using the PubMed search engine. Our search strategy included the following Medical Subject Headings (MeSH) terms and Boolean operators: ("osteomyelitis"[MeSH Terms] OR