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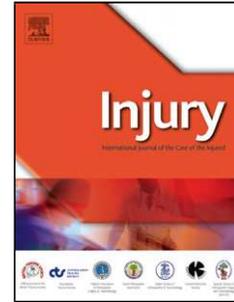


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Definition of infection after fracture fixation: A systematic review of randomized controlled trials to evaluate current practice.

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Abstract

Introduction One of the most challenging musculoskeletal complications in modern trauma surgery is infection after fracture fixation (IAFF). Although infections are clinically obvious in many cases, a clear definition of the term IAFF is crucial, not only for the evaluation of published research data but also for the establishment of uniform treatment concepts. The aim of this systematic review was to identify the definitions used in the scientific literature to describe infectious complications after internal fixation of fractures. The hypothesis of this study was that the majority of fracture-related literature do not define IAFF.

Material and methods A comprehensive search was performed in Embase, Cochrane, Google Scholar, Medline (OvidSP), PubMed publisher and Web-of-Science for randomized controlled trials (RCTs) on fracture fixation. Data were collected on the definition of infectious complications after fracture fixation used in each study. Study selection was accomplished through two phases. During the first phase, titles and abstracts were reviewed for relevance, and the full texts of relevant articles were obtained. During the second phase, full-text articles were reviewed. All definitions were literally extracted and collected in a database. Then, a classification was designed to rate the quality of the description of IAFF.

Results A total of 100 RCT's were identified in the search. Of 100 studies, only two (2%) cited a validated definition to describe IAFF. In 28 (28%) RCTs, the authors used a self-designed definition. In the other 70 RCTs, (70%) there was no description of a definition in the Methods section, although all of the articles described infections as an outcome parameter in the Results section.

Conclusion This systematic review shows that IAFF is not defined in a large majority of the fracture-related literature. To our knowledge, this is the first study conducted with the objective to explore this important issue. The lack of a consensus definition remains a problem in current orthopedic trauma research and treatment and this void should be addressed in the near future.

Key words: definition of infection after fracture fixation, infectious complications, internal fracture fixation, definition, infection after fracture fixation

Introduction

One of the most challenging musculoskeletal complications in orthopaedic trauma surgery is infection after fracture fixation (IAFF). This complication may result in permanent functional loss or even amputation of the affected limb in patients who may otherwise be expected to achieve uneventful healing. Accurately estimating the impact of this fracture related complication has been hampered by the lack of a clear definition [1-3].

In contrast to the situation for periprosthetic joint infection (PJI) [4, 5], there is currently no consensus definition for IAFF [6]. Many of the surgical and medical treatment concepts applied to IAFF have been adopted from PJI treatment algorithms. Specific concepts tailored towards the musculoskeletal trauma patient are comparatively scarce. Although, IAFF and PJI do indeed have similar clinical properties, there are important distinctions between the elective arthroplasty patient and the trauma patient in terms of infection susceptibility, diagnostic modalities and treatment options. The Centers for Disease Control (CDC) has published guidelines for surgical site infection (SSI), which distinguish between superficial incisional, deep incisional and organ/space infections [7-9]. However, neither the PJI nor the CDC-guidelines were specifically developed for fracture patients and critical parameters, including presence of the fracture and soft tissue damage, are not covered by these definitions. Probably for the above mentioned reasons, authors of IAFF publications have difficulties defining infection [3]. A definition of IAFF is urgently required to aid evaluation of routine clinical data, as well as aid in the evaluation of published novel research data and to establish uniform treatment concepts.

The aim of this systematic review was to identify the different definitions used to describe infectious complications after fracture fixation in randomized controlled trials (RCTs). The hypothesis was that the majority of fracture-related literature do not define IAFF. Furthermore, we searched for different parameters that were used to diagnose IAFF and could be useful for a possible future consensus definition.

Methods

All relevant aspects of the Cochrane Handbook for Interventional Systematic Reviews were followed and the study was written according to the Preferred

Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [10].

Literature search strategy

A comprehensive search was performed with the help of a biomedical information specialist on January 21st 2016 in Embase, Cochrane, Google Scholar, Medline (OvidSP), PubMed publisher and Web-of-Science. Search strings for each database are provided in Appendix 1. All references were screened by two reviewers (*names omitted for blinding*). In case of disagreement, a third reviewer (*name omitted for blinding*) would have been consulted, but consensus was reached for every case. Study selection was accomplished through two phases (Fig. 1). During the first phase, titles and abstracts were reviewed for relevance and relevant articles were obtained. Published meeting abstracts for which a full text was not yet published, were excluded in order to prevent bias. During the second phase, full-text articles were reviewed. Table 1 provides an overview of the inclusion and exclusion criteria.

Data extraction and critical appraisal

Data were collected on the definition of infectious complications used in the articles. This was again performed by two reviewers (*names omitted for blinding*). First, all definitions were literally extracted and collected in a database. Subsequently, the quality of the description/definition was classified according to:

- a. The authors used a validated definition for IAFF (Table 2)
- b. The authors used a self-designed definition for IAFF
- c. No description of any definition for IAFF was given by the authors

Table 2 shows the definitions that were considered to be validated definitions. The PJI related definitions were not developed for patients with the diagnosis of IAFF. Although, we are aware of the fact that diagnostic criteria for PJI are not optimal for diagnosis of IAFF because of important differences that exist between these two types of infectious complications, our hypothesis was that due to the lack of definitions for IAFF, authors would include PJI related definitions in their publications. Definitions regarding pin track infections were not included.

Results

A total of 100 RCTs were identified in the search (Fig. 1). Of these studies, only two (2%) cited a validated definition for IAFF (as listed in Table 2). Both of these studies described the CDC-guidelines in the Methods section of their paper [11, 12]. In 28 (28%) RCTs, the authors used a self-designed definition [13-39]. Table 3 describes different signs and parameters that the authors used in these self-designed definitions of IAFF. In Table 4 the different definitions are cited per author.

In the other 70 RCTs (70%) there was no description of a definition in the Methods section, although all of the articles described infections as an outcome parameter in the Results section [40-109].

When evaluating these papers it was noted that 30 RCTs (43%) used terms such as "superficial skin infection", "superficial wound infection", "infection in surgical margins" and "deep infection" [64-76, 78, 80, 82, 84-93, 102, 105-107]. Such terms may be suggestive of the CDC-guidelines, although this could not be confirmed in the text. It has to be stated that terms like superficial and deep infection already existed in the literature prior to the introduction by the CDC, proven by two articles included in this group [72, 80]. So overall the authors of 28 studies were contacted by email with a request for additional information regarding the exact definition of infection, and their perception of superficial infection, deep infection and other terms described in their papers. More specifically, they asked whether these definitions were based on the CDC-guidelines. The response rate was 25% (7/28). Only one of the authors stated that they used the CDC-guidelines, the others stated that they did not use any specific guideline to describe IAFF.

Discussion

Development of IAFF is one of the most serious complications in musculoskeletal trauma surgery. The consequences for patients and healthcare systems are severe [2, 110]. Accurately estimating the incidence and impact of this complication has been hampered by the lack of a clear definition. In 1996, Arens *et al.* [3], stated: *'It is astonishing that in all papers in which infection is mentioned, the term 'infection' is not defined'*. The problem becomes clear when reviewing the clinical literature as presented here.

The goal of this systematic review was to perform an exploratory analysis regarding the use of definitions for IAFF in RCTs. The hypothesis was that the majority of included fracture-related RCT's do not clearly define IAFF. We believed that it was not realistic to include every publication regarding fracture care. Consequently, we aimed at high quality publications with an optimal study design, i.e. RCTs. We believed that if these studies did not use a definition, others (i.e. retrospective, etc.) would be even less likely to do so. To our surprise, only 2% of the included RCTs used a validated definition, which in both cases were the CDC-guidelines.

As already mentioned, the CDC-guidelines [9] are currently the only standard definition available for musculoskeletal trauma surgeons [6]. The fact that they are not used routinely in fracture-related studies suggests that they are probably not very suitable in these cases. The CDC divides SSIs into superficial incisional, deep incisional and organ/space infections.

Different objections to the use of the CDC-guidelines in IAFF are offered. First, the CDC defines time-limits for the diagnosis of SSIs: within 30 days after the operation if there is no implant, and within 1 year if there is an implant in place, according to the 1992 guidelines [7]. The recently updated CDC-guidelines define a deep incisional or organ/space SSI after fracture fixation as one occurring within 90 days after the operation [9]. The CDC definitions are used for surveillance and, for practical purposes, limit diagnosis of infection to specific time frames to avoid the burden of additional data collection with potentially low yield. However, in IAFF, some infections will occur outside these time frames (i.e. late-onset infections) [111]; as such the CDC-guidelines do not cover these infections. In general the presence of time frames pose a serious problem from a definition point of view.

A second challenge in IAFF when following the CDC-guidelines emerges in the case of superficial incisional infection. Bonneville *et al.* already stated that the term 'superficial infection' is at best arbitrary [2]. The depth of bacterial colonization can only be assessed by tissue samples taken under the subcutaneous tissue layer, which means that every wound must be opened because superficial swabs are no longer acceptable for diagnosis [2]. An illustration of this problem is an IAFF of the ankle, where there is minimal subcutaneous tissue. Superficial cultures would require the surgeon to open the surgical wound and both the implant and the fracture site would become visible; this defines a deep infection. Therefore, is it actually possible

in all clinical settings to differentiate between these three types of infection (superficial, deep and organ space) and does this change or even influence the clinical treatment algorithm for a patient with IAFF?

In this systematic review none of the included RCTs used the standard definitions for PJI [4, 5]. As already mentioned, there are important differences between PJI and IAFF. A first difference is the initial damage to soft tissues overlying the surgical site. An open fracture may for example lead to wound contamination and massive crush injuries can cause a disturbed vascularization with concomitant skin necrosis, both will therefore have an increased susceptibility for infection. A second difference is the presence of a fracture and the need for biomechanical stability in order to heal both – the fracture and the soft tissue. Clinical guidelines highlight the fact that bone and soft tissue stability are important not only for prevention, but also for treatment of IAFF [111-113]. These are both examples of why the use of PJI definitions does not directly translate to cases of IAFF, and expectedly results in a lack of acceptance of PJI definitions for IAFF.

In 28% of the RCTs, the authors used a self-designed definition. Table 3 shows the different parameters that were included in these definitions. The results are interesting and potentially useful, since a consensus definition should be developed in the future and such parameters are likely highly relevant. Most authors included purulent drainage or discharge and positive cultures as parameters for the diagnosis of IAFF. Furthermore, although describing their own definition, multiple authors included terms as osteomyelitis, superficial septic complications and deep bone infection. If a consensus definition is desired, a more uniform description of terminology seems critical.

Our study furthermore shows that 70% of the RCTs did not give a definition at all. These are staggering numbers and suggest an urgent need for the introduction of a consensus definition of IAFF [6]. A better understanding and description of the definition of IAFF is a crucial first step towards improving scientific reporting, evaluation of routine clinical data, as well as evaluation of novel prevention and treatment strategies [1].

Conflict of interest

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

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Figure Legends

Figure 1. Outline of the search and selection process including exclusions and final count of acceptable manuscripts. RCT: Randomized Controlled Trial

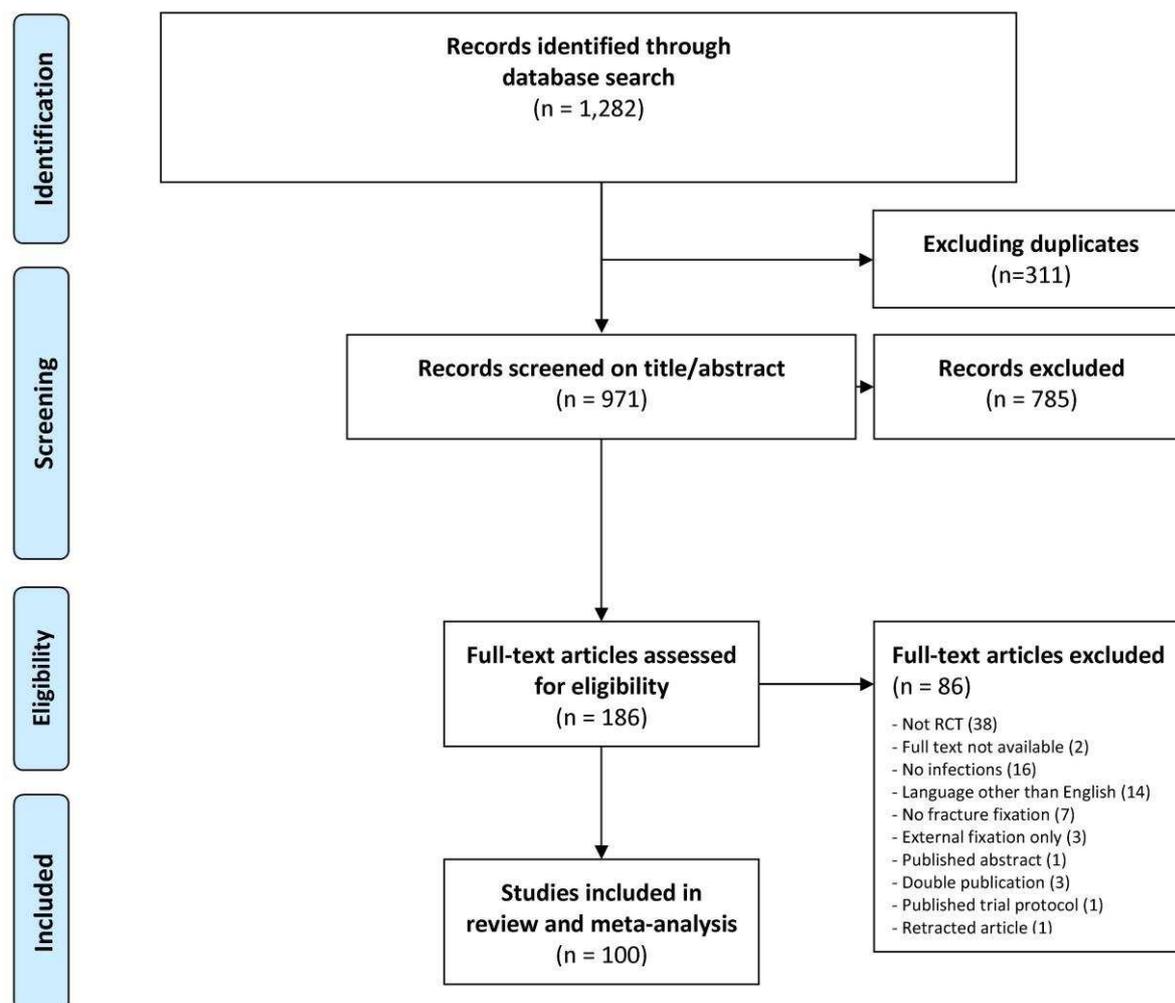


Table 1. Inclusion and exclusion criteria used during study selection.

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none"> • RCT • Fracture fixation <ul style="list-style-type: none"> - Internal fixation versus external fixation - Internal fixation versus other internal fixation - Internal fixation versus non-operative management • Infections / Infectious complications • Full text written in English • Published between January 1st 1985 and December 31st 2015 	<ul style="list-style-type: none"> • Study design other than RCT • External fixation only • Infections not mentioned as outcome measure or as a detected complication

RCT: Randomized Controlled Trial

Table 2. List of definitions considered as "validated".

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- CDC-guidelines (superficial incisional, deep incisional and organ/space surgical site infection) [7-9]
 - IDSA-guidelines for PJI [5]
 - New Definition for PJI: From the Workgroup of the Musculoskeletal Infection Society [4]

CDC: Centers for Disease Control; IDSA Infectious Disease Society of America; PJI: Prosthetic Joint Infection

Table 3. Parameters used to diagnose and/or define IAFF.

Parameters associated with IAFF	N	References
• Positive cultures	15	[13, 15, 17-23, 27, 30, 31, 33, 37, 38]
• Clinical signs unspecified	4	[18, 25, 30, 34]
• Purulent drainage (or discharge)	16	[13-17, 19, 20, 22, 23, 25, 27, 30, 33, 34, 37, 38]
• Fever	3	[17, 22, 38]
• Rubor (redness)	5	[15, 16, 37-39]
• Calor (warmth)	4	[15, 16, 38, 39]
• Tumor (swelling)	4	[15, 16, 33, 39]
• Dolor (pain)	2	[16, 39]
• Wound dehiscence/breakdown	5	[13, 14, 27, 32, 37]
• Need for surgical debridement	5	[23, 29, 31, 32, 39]
• Treatment with oral antibiotics	6	[13, 24, 26, 29, 32, 33]
• Need for implant removal	4	[22, 26, 28, 39]
• Radiological (X-ray) evidence	2	[34, 38]
• CRP	1	[18]

CRP: C-reactive protein

Table 4. Definition for IAFF cited per author.

Self-designed definitions for infection after fracture fixation	References
"Wound infection was defined as spontaneous drainage of pus after suture removal or in association with overt wound dehiscence. If a wound infection was identified in the postoperative period, a swab specimen of the exudate was sent for microscopy, culture, and sensitivity testing to guide subsequent antibiotic therapy."	[13]
"Wound infection was defined as spontaneous drainage of pus after suture removal or in association with overt wound dehiscence."	[14]
"The infections were graded as local or systemic, according to specific criteria. Purulent drainage at the operative site, with positive cultures, represented major infection. Erythema with edema and warmth adjacent to the incision indicated the presence of minor infection."	[15]
"Wound infection was defined as one or more of the classic signs and symptoms of inflammation (rubor, calor, tumor, dolor) together with pus at the operation site. Wound infections were classified as superficial or deep. Infections of the skin and subcutaneous tissue, not communicating with the site of bone operation, were judged as superficial. Deep infections were defined as infections, that by physical examination, reached bone or material inserted for osteosynthesis."	[16]
"Evidence of infection was defined as presence of discharge and constitutional symptoms (fever, malaise and nausea) documented post operatively and confirmed with a wound swab."	[17]
"Clinical signs, CRP, and cultures from the intramedullary canal or tissue adjacent to the bone and deep to the superficial fascia were positive."	[18]
"An infection was considered to be present, whether or not the culture was positive, when pus drained spontaneously from the wound or when the surgeon released purulent material from an inflamed wound."	[19]
"An infection was diagnosed when the wound drained pus spontaneously or was inflamed to the point that it had to be opened by the surgeon and then drained purulent material. A diagnosis of infection was recorded whether or not the culture was positive. A wound with a hematoma or one that drained serous material was considered to be infected only when the culture was positive. In all of the deep infections bone or metal was exposed, and in several a deep tract was demonstrated on a sinogram."	[20]
"Infections were conservatively defined as any suspected or confirmed superficial or deep bone or soft-tissue infection, with or without bacteriological confirmation."	[21]
"Deep infection: Septic fever concomitant to purulent infection affecting the osteosynthesis area eventually necessitating a removal of the foreign material. Superficial infection: purulent discharge with or without a positive culture. Serous discharge with a concomitant positive culture."	[22]
"A soft-tissue infection was defined as the presence of purulent discharge from the wound with positive bacteriological findings. Deep infection was diagnosed if operative exploration with osseous debridement was needed to eradicate the infection."	[23]
"We defined a mild infection as a superficial infection that did not involve the bone, joint or implants, and was successfully treated on an outpatient basis with oral antibiotics."	[24]
"Surgical wound infection was defined as one or more of classic signs and symptoms of inflammation together with pus at the operation site. The classification of surgical wound infections was done as per standard definitions."	[25]
"Deep wound infection (defined as established infection beneath the fascia requiring surgical revision), superficial wound infection (defined as cutaneous/subcutaneous infection requiring antibiotic therapy)."	[26]
"Infection was defined as persistent drainage that was on culture, from an open fracture site or wound that had broken down, regardless of size."	[27]

- "Deep infection was defined as infection requiring implant removal." [28]
- "Superficial wound infection requiring only antibiotic therapy was classified as a Grade II complication. Deep infection requiring operative debridement under anesthesia and antibiotic administration was classified as a Grade IIIb complication." [29]
- "Deep infection was defined as purulent drainage or osteomyelitis presenting after definitive wound healing and was diagnosed by the treating surgeon based on clinical suspicion and subsequent cultures." [30]
- "Wound infection was based on positive bacterial organisms obtained from operative debridement of the wound or fracture region." [31]
- "Superficial infection was treated with organism-specific antibiotics. Deep infection was defined as wound breakdown requiring debridement and organism-specific antibiotics." [32]
- "Superficial infection was defined as local erythema or swelling, which resolves with antibiotic therapy. Deep infection was defined as continuing wound drainage of pus or a positive bacteriological culture. Infection was also categorized according to time of occurrence: early surgical infection site, delayed union, non-union and mal-union." [33]
- "Wound infection could be considered when there are signs and symptoms of infection around the wound. The diagnosis of chronic osteomyelitis was based on the presence of chronic drainage from sinuses, fistulas, ulcers, or X-ray evidence." [34]
- "Complications deep into the investing muscular fascia were called deep septic complications, whereas those deep into the dermal or subcutaneous tissues only were called superficial septic complications." [35]
- "Deep infections were defined as those below the deep investing muscular fascia. Superficial infections were clinically confined to the dermal and subcutaneous tissue." [36]
- "Superficial infection: superficial to the deep fascia, discharge, erythema, bacteriological culture, no delay in wound healing. Deep infection: extending to the deep fascia, persistent wound discharge, bacteriological cultures, delay in wound healing." [37]
- "The authors were suspicious of infection when patients were febrile (temperature > 37.5°C); their wounds were erythematous, warm, or draining purulent material; there were radiographic signs of infection; or there was a nonunion. Patients with possible infection were taken to the operating room for debridement or hardware removal. In the operating room, deep culture specimens were obtained. If these specimens grew organisms, these patients were deemed to have infection." [38]
- Wound infection was defined as one or more of the classic signs and symptoms of inflammation (rubor, calor, tumor, dolor) together with pus at the operation site. Wound infections were classified as superficial and deep. Infections of the skin and subcutaneous tissue, not communicating under the fasciae were judged superficial. Deep infections were defined as infections that were located under the fascia and diagnosed by opening of the wound. [39]
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