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What is the diagnostic value of the Centers for Disease Control and Prevention criteria for surgical site infection in fracture-related infection?

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ABSTRACT

Background: Fracture-related infection (FRI) remains one of the most challenging complications in orthopaedic trauma surgery. An early diagnosis is of paramount importance to guide treatment. The primary aim of this study was to compare the Centers for Disease Control and Prevention (CDC) criteria for the diagnosis of organ/space surgical site infection (SSI) to the recently developed diagnostic criteria of the FRI consensus definition in operatively treated fracture patients.
Methods: This international multicenter retrospective cohort study evaluated 257 patients with 261 infections after operative fracture treatment. All patients included in this study were considered to have an FRI and treated accordingly ('intention to treat'). The minimum follow-up was one year. Infections were scored according to the CDC criteria for organ/space SSI and the diagnostic criteria of the FRI consensus definition.
Results: Overall, 130 (49.8%) FRIs were captured when applying the CDC criteria for organ/space SSI, whereas 258 (98.9%) FRIs were captured when applying the FRI consensus criteria. Patients could not be classified as having an infection according to the CDC criteria mainly due to a lack of symptoms within 90 days after the surgical procedure ($n = 96$; 36.8%) and due to the fact that the surgery was performed at an anatomical localization not listed in the National Healthcare Safety Network (NHSN) operative procedure code mapping ($n = 37$; 14.2%).
Conclusion: This study confirms the importance of standardization with respect to the diagnosis of FRI. The results endorse the recently developed FRI consensus definition. When applying these diagnostic criteria, 98.9% of the infections that occured after operative fracture treatment could be captured. The CDC criteria for organ/space SSI captured less than half of the patients with an FRI requiring treatment, and seemed to have less diagnostic value in this patient population.

Introduction

Fracture-related infection (FRI) remains one of the most challenging complications in orthopaedic trauma surgery. If not recognized and treated at an early stage it can lead to permanent loss of function or even amputation of the affected limb. Therefore, early

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diagnosis and appropriate treatment are of paramount importance [1–4].

To standardize clinical reports and optimize the diagnostic pathway for FRI, a consensus definition was recently introduced [5,6]. Although this definition is gaining popularity [7], its added value is not yet generally accepted. Historically, publications related to orthopaedic trauma did not define FRI based on diagnostic criteria, and when specified authors often used self-invented definitions or the more generic Centers for Disease Control and Prevention (CDC) criteria for surgical site infection (SSI) [8]. An important issue regarding the CDC criteria is that, although they are a widely accepted tool to define SSI in a variety of surgical specialties, only a minority of the high-quality orthopaedic trauma studies use these criteria to define infection after fracture fixation indicating that they may be difficult to apply in FRI patients [8]. This was confirmed by an international survey among 2327 orthopaedic trauma surgeons of whom only one third believed that the CDC guidelines are applicable to FRI [9].

The primary aim of this study was to compare the CDC criteria for the diagnosis of organ/space SSI to the diagnostic criteria of the FRI consensus definition in operatively treated fracture patients. Within this scope we tried to answer the following questions: (1) Are the CDC criteria for organ/space SSI applicable to the diagnosis of FRI? (2) What are the most important differences between the CDC criteria for organ/space SSI and the criteria of the FRI consensus definition?

Patients and methods

Study design and setting

This international retrospective cohort study evaluated data of patients with an FRI that were treated between January 1st 2015 and November 24th 2019 at the University Hospitals Leuven (Belgium) and the University Medical Center Groningen (the Netherlands). During this time period, diagnostic procedures (e.g. culture procurement) were performed according to standardized guidelines [6,10–12].

Patients and study population

All fracture patients included in this study were considered to have an FRI and treated accordingly ('*intention to treat*'), based on recommendations from a multidisciplinary team. The multidisciplinary team consisted of surgeons, microbiologists, clinical pharmacists, radiologists/nuclear medicine physicians and clinical infectious disease specialists. The minimum follow-up was at least one year after cessation of FRI treatment. Exclusion criteria were patients with an FRI diagnosed outside the study period, patients younger than 18 years of age, pathological fractures, fractures of the skull and fractures of the cervical, thoracic and lumbar spine. Although all patients in this cohort were treated surgically, conservative treatment was not a reason for exclusion.

Variables, outcome measures, data sources and bias

The CDC criteria can be used for surveillance of SSI following a National Healthcare Safety Network (NHSN) operative procedure. The included procedures are listed in the International Classification of Diseases 10th Revision Procedure Coding System (ICD-10-PCS) and the Current Procedural Terminology (CPT) NHSN operative procedure code mapping (supplementary material: appendix 1 and 2). For this study, only the ŕX - open reduction of fracture´procedures were relevant. This means that open reduction of a fracture must have taken place within any of the following anatomical regions: humerus, ulna, radius, femur, tibia or fibula. Other NHSN operative procedure requirements include that at least one incision through the skin must have been made, the procedure must have taken place in an operating room and the otherwise eligible procedures must be assigned an American Society of Anesthesiologists (ASA) score of less than 6. Furthermore, the surveillance period for open reduction of fracture procedures is 90 days. This means that to be able to classify patients according to the CDC criteria, the first symptoms of infection must have occurred within 90 days after surgery. Finally, the CDC criteria for SSI are divided into superficial incisional infection, deep incisional infection and organ/space infection [13]. In this study, the organ/space SSI criteria (Table 1) were used as they relate to bone infection in the CDC criteria (BONE-osteomyelitis) [7,8,14].

If the above mentioned conditions are not fulfilled the CDC criteria for SSI cannot be applied and as a result these patients cannot be classified as having a SSI. There is no chronological order in which the criteria need to be scored. However, a patient has to meet all the organ/space criteria to be classified as having a SSI. Most criteria consist of multiple scoring items of which at least one, or a combination of items, must have been met to fulfill a criterion (Table 1).

The FRI consensus criteria define infection related to a fracture and consist of two levels of certainty: there are confirmatory criteria (infection definitely present) and suggestive criteria (suspicion of infection and further investigation should be performed) [5,6]. This means that an infection can only be definitively diagnosed in case of the presence of at least one confirmatory sign. The FRI consensus criteria are shown in Table 2.

The medical records of all patients were thoroughly reviewed. Data regarding gender, age, Body Mass Index (BMI), ASA physical status classification, fracture characteristics (open or closed and anatomical location) and time from injury to onset of FRI was collected. Furthermore, all the CDC organ/space SSI and FRI criteria were scored as separate variables by four reviewers (JS, JO, FIJ, WJM). When there was disagreement, a fifth independent reviewer was consulted (CZ).

Statistical analysis

Data was collected and analyzed using SPSS (version 23, IBM Inc, Armonk, NY, USA). The data were reported using standard descriptive statistics, including mean and standard deviation (SD) for continuous variables and median and interquartile range (IQR) for categorical variables. Counts and percentages are used to report proportions.

Ethical approval

The protocol was approved by Ethical Committee of the University Hospitals Leuven (Ethics Committee Research UZ/KU Leuven; S62394).

Results

Within the mentioned timeline, 257 patients, with 261 FRIs were included. The patient cohort consisted of 174 (67.7%) male and 83 (32.3%) female patients with a mean age of 53.6 years (range 18 – 89). The median number of days from initial fracture fixation until the onset of symptoms was 44 (IQR; 15.5–220.0) days. Sixty-six (25.3%) patients had an open fracture. Table 3 summarizes the baseline patient characteristics.

In all patients, an FRI involved a body region deeper than the fascia or muscle layers. In total, 10 patients (3.9%) were initially treated for a superficial incisional SSI with antibiotics only. All these patients returned after a median of six (IQR; 4.0–27.5) days

Table 1
The CDC organ/space SSI criteria ($n = 261$) (13,14).

Criterion	Organ/space surgical site infection scoring items	Number of cases that meet the corresponding scoring item n (%)	Number of cases that meet a required combination of scoring items n (%)	Number of cases that meet the corresponding criterion n (%)
Condition to use CDC organ/space criteria	Date of event occurs within 90 days after operative fracture fixation procedure (where day 1 = the procedure date)	165 (63.2)	.	165 (63.2)
Condition to use CDC organ/space criteria	An NHSN procedure was performed (open reduction of humerus, ulna, radius, femur, tibia or fibula fracture)	224 (85.8)	.	224 (85.8)
	AND			
1	Involves any part of the body deeper than the fascia or muscle layers that is opened or manipulated during the operative procedure	261 (100)	.	261(100)
	AND patient has at least *one* of the following:			
2	a. purulent drainage from a drain that is placed into the organ/space (for example, closed suction drainage system, open drain, T-tube drain, CT-guided drainage)[1]	0 (0) Not applicable	.	257 (98.5)
	b organism(s) identified from fluid or tissue in the organ/space by a culture or non-culture based microbiologic testing method which is performed for purposes of clinical diagnosis or treatment (for example, not Active Surveillance Culture/Testing (ASC/AST)).[2]	252 (96.6)	.	.
	c. an abscess or other evidence of infection involving the organ/space that is detected on gross anatomical or histopathologic exam, or imaging test evidence suggestive of infection.[3,4]	187 (71.6)	.	.
	AND meets at least *one* criterion for a specific organ/space infection site, BONE - osteomyelitis			
3	Osteomyelitis must meet at least *one* of the following criteria:			254 (97.3)
	Patient has organism(s) identified from bone by culture or non-culture based microbiologic testing method which is performed for purposes of clinical diagnosis and treatment, for example, not Active Surveillance Culture/Testing (ASC/AST).[2]	252 (96.6)	.	.
	Patient has evidence of osteomyelitis on gross anatomic or histopathologic exam[5]	7 (2.7)	.	.
	Patient has at least two of the following localized signs or symptoms: fever (>38.0 °C), swelling [6], pain or tenderness [6], heat [6], or drainage [6]	107 (41.0)	37 (14.2)	.
	AND at least *one* of the following:			
	a. organism(s) identified from blood by culture or non-culture based microbiologic testing method which is performed for purposes of clinical diagnosis and treatment, for example, not Active Surveillance Culture/Testing (ASC/AST).[7]	2 (0.7)	.	.
	AND			
	imaging test evidence suggestive of infection (for example, x-ray, CT scan, MRI, radiolabel scan [gallium, technetium, etc.]), which if equivocal is supported by clinical correlation, specifically, physician documentation of antimicrobial treatment for osteomyelitis.[4]	96 (36.8)	.	.
	b. imaging test evidence suggestive of infection (for example, x-ray, CT scan, MRI, radiolabel scan [gallium, technetium, etc.]), which if equivocal is supported by clinical correlation, specifically, physician documentation of antimicrobial treatment for osteomyelitis.[4]	96 (36.8)	.	.

In all cases: (1) at least one incisionthrough the skin has been made
(2) procedures have taken place in anoperating room, (3) patients had an ASA-scoreless than 6.

[1] No drains were placed after surgery in this cohort. It is not common practice to place a drain after fracture fixation.

[2] Based on cultures. Non-culture based testing is not common in trauma surgery. Non-culture based testing was performed in six patients, the only one which was positive also had positive cultures.

[3] Scored solely as abscess, unclear what to score as 'other evidence'.

[4] Unclear what 'evidence suggestive of infection' is. Scored as in FRI; any one of: bone lysis, implant loosening, sequestration, failure of progression of bone healing, presence of periosteal bone formation, implant breakout or abscess.

[5] Histopathology was performed in ten cases. Seven cases were positive, in three of which, the sample was taken less than 3 weeks after primary surgery.

[6] With no other recognized cause.

[7] Blood cultures were taken in 15 patients, only 2 were positive. Taking blood cultures is not considered common care in orthopedic trauma patients. It is only done when a patients presents with a fever without a focus, to rule out sepsis, not to diagnose hematogenous osteomyelitis

showing worsening of the symptoms, requiring surgical debridement of the bone and soft tissues, after which an FRI was confirmed.

In our cohort, 130 (49.8%) FRIs were captured when applying the CDC criteria. Overall, 131 (50.2%) FRIs could not be captured due to the following reasons: (1) 96 cases (36.8%) did not show signs or symptoms of SSI within 90 days after operative fracture fixation; (2) 37 cases (14.2%) had surgery performed in an anatomical location not listed as an NHSN operative procedure (Table 1); 3) four cases (1.5%) remained unclassified because they did not have a drain, a positive culture, purulent discharge from the wound or imaging suggestive of infection; (4) seven cases (2.7%) remained

Table 2
The FRI consensus criteria (n = 261) (5,6).

	n (%)
Confirmatory criteria	
Fistula, sinus or wound breakdown (with communication to the bone or the implant).	125 (47.9)
Purulent drainage from the wound or presence during surgery	121 (46.4)
Indistinguishable pathogens identified by culture from at least two separate deep tissue/implant samples	246 (94.3)
Presence of microorganisms in deep tissue taken during an operative intervention, as confirmed by histopathological examination using specific staining techniques for bacteria or fungi.	7 (2.7)
Presence of more than five PMNs/HPF, confirmed by histopathological examination*	1 (0.3)
Total number of patients having at least one confirmatory sign	258 (98.9)
Suggestive criteria	
Local clinical signs, any one of: Pain (without weight bearing, increasing over time, new-onset): local redness, local swelling increased local temperature, fever (single oral temperature measurement of ≥38.3°C (101°F))	220 (84.3)
Radiological and/or nuclear imaging signs, any one of: bone lysis (at the fracture site, around the implant), implant loosening, sequestration (occurring over time), failure of progression of bone healing (i.e. non-union), presence of periosteal bone formation	96 (36.8)
A pathogenic organism identified by culture from a single deep tissue/implant specimen taken during an operative intervention	6 (2.3)
Elevated serum inflammatory markers (ESR, WBC, CRP)	186 (70.7)
Persistent, increasing or new-onset wound drainage, beyond the first few days postoperatively, without solid alternative explanation	78 (29.9)
New-onset of joint effusion in fracture patients	19 (7.3)
Total number of patients having at least one suggestive sign	259 (99.2)

PMN(s): polymorphonuclear neutrophil(s), HPF: high-power field, ESR: erythrocyte sedimentation rate, WBC: white blood cell count, CRP: C-reactive protein (CRP)
* Only diagnostic in later infections, ≥8 weeks after injury (i.e. fracture nonunion)

Table 3
Baseline patient characteristics (n = 257).

	***n* (%)**
Gender	
Male	174 (67.7)
Female	83 (32.3)
Age mean ± SD	53.6 ± 16.8
BMI mean ± SD	27.1 ± 5.9
ASA Classification	
I	43 (16.7)
II	137 (53.3)
III	71 (27.6)
IV	6 (2.4)
Fractures*	
Closed	195 (74.7)
Open	66 (25.3)
Fracture location*	
Tibia	74 (28.4)
Femur	48 (18.4)
Ankle (tibia + fibula)	37 (14.2)
Humerus	28 (10.7)
Forearm	19 (7.3)
Fibula	18 (6.9)
Clavicle	14 (5.4)
Pelvis	9 (3.4)
Calcaneus	6 (2.3)
Patella	5 (1.9)
Midfoot/forefoot	1 (0.4)
Sternum	1 (0.4)
Scapula	1 (0.4)
Days from primary fixation until onset of symptoms Median (IQR)	44.0 (15.5–220.0)

* Total adds up to 261 because four patients suffered from two FRIs at different anatomical localizations.SD: standard deviation, IQR: interquartile range.

unclassified as they failed to meet the BONE-osteomyelitis criteria mentioned in the CDC criteria for organ/space SSI (Table 1).

When applying the FRI consensus criteria, 258 (98.9%) FRIs were captured. In total, three patients (1.1%) were treated for an FRI, based on recommendation of the multidisciplinary team, although no confirmatory criteria were present. These patients were under systemic antibiotic treatment at time of culture procurement. Yet, they all had one positive culture with a high virulent organism (i.e., *Staphylococcus aureus, Staphylococcus lugdunensis* and *Citrobacter koseri*), suggesting but not confirming infection. In none of these three patients histopathology was performed. Fig. 1 shows a flow diagram of the scoring process.

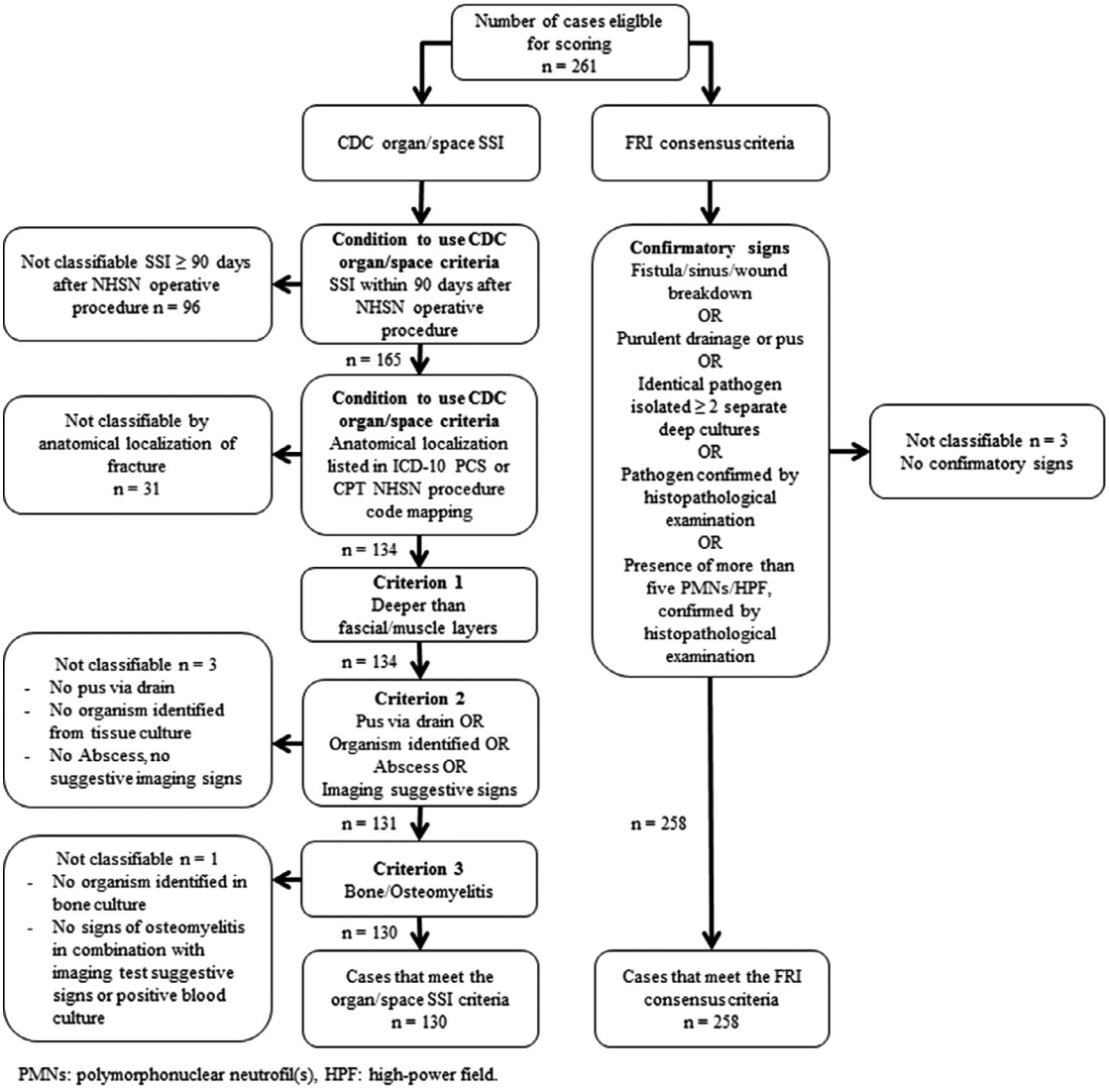

Fig. 1. Flow diagram of the scoring process of the CDC organ/space criteria and the FRI consensus criteria.

Regarding the presence or absence of the confirmatory criteria of the FRI consensus definition there was no observer-related disagreement. Regarding the CDC criteria for organ/space SSI there was no observer-related disagreement regarding the exclusion of patients due to follow up or anatomical location. For the remaining 134 cases, in approximately one out of five (20%) reevaluation by the whole group of reviewers was done for clarification of the CDC criteria and consensus was reached in all cases.

The number of eligible cases that could be scored in the CDC group would increase from 165 (63.2%) to 216 (82.8%) when the follow-up is extended from 90 days to one year. The number of cases classified as having a SSI thereby increases from 130 (49.8%) to 174 (66.7%).

Discussion

The aim of this study was to compare the CDC criteria for the diagnosis of organ/space SSI to the diagnostic criteria of the FRI consensus definition in operatively treated fracture patients. The results showed that only 49.8% of the FRIs were captured when using the CDC criteria for organ/space SSI, whereas 98.9% of the FRIs were captured when using the diagnostic criteria of the FRI consensus definition. Multiple reasons can be stated for the fact that the CDC criteria have limited value in defining infection in operatively treated fracture patients.

Time to onset of infection

Zalavras et al. recently reported that the 90-day follow-up period used by the CDC is not sufficient for many cases of FRI [15]. The authors reported that a surveillance period of 90 days after management of an open long-bone fracture only captured 64% of infections. In our patient cohort, 165 cases (63.2%) were captured when using the CDC criteria for organ/space SSI given that they were diagnosed with an FRI within 90 days after initial fracture fixation (Fig. 1). When follow-up would be extended to one year, the number of eligible cases that could be scored in the CDC group increases by 19.6%, from 165 to 216, and the number of cases classified as having a SSI increases by 16.9%, from 130 to 174.

The CDC criteria for the diagnosis of organ/space SSI are used for surveillance and, for practical purposes (i.e. cost), limit diagnosis of infection to specific time frames to avoid the burden of additional data collection with potentially low yield [8]. However, in case of FRI this can pose a serious problem as infections will also occur outside the surveillance period of 90 days [15]. For this

reason, the FRI consensus definition does not state any time limit [5].

Anatomical localization

Currently, within the CDC guidelines, the ICD-10-PCS and CPT open reduction of fracture NHSN Operative Procedure Code Mapping only include the humerus, radius, ulna, femur, tibia and fibula, as anatomical locations. Therefore, in our study, another 37 cases (14.2%) could not be captured by the CDC guidelines (Fig. 1). It should be stated that FRI is an entity which can occur within almost any anatomical location. Although infections at the level of the skull and spine have historically evolved as separate entities – probably due to their close relationship to the nervous system – diagnostic features of FRI can be extrapolated to any other anatomical area of the body. The wider use of internal fixation of pelvic, sacrum and rib fractures made this limitation more important in recent years.

Another challenge emerges regarding the location of infection within the surgical site or wound and includes superficial and deep incisional SSIs [5,8]. The CDC guidelines distinguish between superficial incisional, deep incisional and organ/space infections [13]. Bonnevialle et al. stated that the term '*superficial infection*' is at best arbitrary and poses challenging problems with respect to the diagnosis of FRI [16]. An important reason is that the depth of bacterial colonization can only be assessed by tissue samples taken under the subcutaneous tissue layer. This means that superficial swabs are not acceptable for diagnosis and every wound must be opened to take appropriate samples. The distinction between a superficial and deep infection cannot reliably be made on simple observation of a wound. Additionally, also in a substantial number of procedures no distinction between superficial and deep can be made (e.g. ankle fractures where there is minimal subcutaneous tissue). In FRI, this would require the surgeon to open the surgical wound and expose both the implant and the fracture site in many, if not all cases [8]. If the cultures are positive, this defines an organ/space infection (*not* a deep incisional SSI). For the above mentioned reasons, in clinical studies on FRI, these terms (e.g. superficial incisional and deep incisional SSI) are often used inaccurately or inappropriately [8]. Moreover, the CDC seems to advise to use the diagnostic criteria of organ/space SSI – instead of the criteria for superficial and deep incisional SSI – as these include infections of the bone. Interestingly this is often not known among scientists and till today even high-quality studies not only still use the CDC criteria to define FRI but authors keep using the superficial and/or deep incisional SSI criteria [17–19]. This lack of a standardized approach to adequately diagnose FRI not only greatly impacts our clinical practice but also influences the quality of our everyday studies.

In summary, this means that the presence of confirmatory signs of an infection should be sufficient to alert clinicians of the need for treatment [5,6]. When these are not present, the physician should still suspect infection and closely monitor the patient. In our patient cohort, for example, 10 patients were initially treated as a 'superficial incisional SSI' with oral antibiotics only. Within the following days to weeks, all these patients returned showing worsening of the symptoms and in need of surgical debridement after which an FRI was confirmed.

Type of treatment

As previously stated, the CDC criteria can by definition only be used for surveillance of SSI following an NHSN operative procedure. Although this study focused on operative fracture treatment, and patients were not excluded if treated non-operatively beforehand, it should be recognized that many fractures are still treated conservatively. Open fractures can also be complicated with infection after non-operative management, e.g. in low-income countries [20]. This should be taken into account when developing diagnostic guidelines for FRI that are available on a worldwide scale. The FRI consensus definition includes both operatively and non-operatively treated patients, for this specific reason.

Diagnostic criteria

Even though the majority of patients were excluded based on the time to onset of symptoms and anatomical localization, other issues regarding the diagnostic criteria of the CDC guidelines need to be addressed: (1) the placement of drains was not performed in our patient cohort and is often not considered necessary after fracture fixation; (2) the CDC guidelines state: ́patient has organism(s) identified from …´implying that a single positive culture would be sufficient to meet this item. However, no distinction is made between single cultured pathogens, which can be contaminants, and multiple cultured micro-organisms resulting in an overestimation of this criterion; (3) to our knowledge the CDC guidelines do not define specific features that should be considered as evidence suggestive of infection on imaging tests. This creates room for interpretation and complicates the scoring of this item; (4) one of the *Bone – osteomyelitis criteria* states: Ṕatient has evidence of osteomyelitis on gross anatomic or histopathologic exam. Osteomyelitis however cannot be based on gross anatomical examination because it is a diagnosis made through histopathological examination [21,22]. Moreover, as previously published, osteomyelitis is often not present within the first weeks that an FRI develops [21]. This confusion between osteomyelitis and FRI is not helpful as the classical features of osteomyelitis (e.g. sequestration, involucrum formation, cortical cloacae, systemic upset) are not commonly found in FRI [23]; (5) another item of the *Bone – osteomyelitis criteria* states: Órganism(s) identified from blood by culture…. Blood culture is routine in acute osteomyelitis but is not considered common practice in orthopedic trauma patients suspected of an FRI and is only done when a patient presents with a fever.

Limitations

This study has a number of limitations. The retrospective nature of this study meant that the scoring of all criteria had to be done with the information available in the medical records. This might have led to an underestimation of clinical signs that were present but not documented, which could have resulted in patients not meeting a certain criterion. Furthermore, retrospective scoring may be subjective for some features and notes could be ambiguous, therefore multiple reviewers scored the diagnostic criteria. The CDC criteria themselves could lead to an information bias because they leave significant room for interpretation. This complicated the scoring process. For example, it is unclear what is considered an ímaging test with evidence suggestive of infection. To clarify this, we decided to use the same scoring criteria stated by the FRI consensus criteria (e.g. bone lysis, implant loosening, failure of progression of bone healing) [5,6]. PCR was considered the only non-culture based microbiologic test method, since no other methods are applied in FRI. Another limitation is the fact that one of the confirmatory criteria, histopathological examination, was only performed in ten patients. Another limitation is the involvement of some authors in both the multidisciplinary team (evaluating patients for treatment) and the expert group that developed the FRI consensus definition, which in theory could bias the results of our study. This said, the majority of the FRI cases in our study were diagnosed prior to the development of the FRI consensus definition. Finally, we acknowledge that patient inclusion based on an '*intention to treat*', recommended by the multidisciplinary team, is

potentially biased. Clinicians may over diagnose cases in order to avoid the harmful effects of missing a serious bone infection. However, the study showed that the large majority of cases had objective evidence of infection (i.e. positive microbiological cultures or draining sinuses).

Conclusions

This study confirms the importance of standardization with respect to the diagnosis of FRI. The results endorse the recently developed FRI consensus definition. When applying these diagnostic criteria, 98.9% of the infections that occured after operative fracture treatment could be captured. The CDC criteria for organ/space SSI captured less than half of the patients with an FRI requiring treatment, and seemed to have less diagnostic value in this patient population.

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Declaration of Competing Interest

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

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.injury.2021.08.009.

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