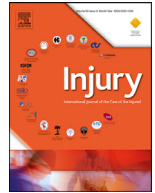




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Fracture-related infection: Prevalence and application of the new consensus definition in a cohort of 1004 surgically treated ankle fractures

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ABSTRACT

Background: Surgical treatment of ankle fractures comes with a substantial risk of complications, including infection. An unambiguously definition of fracture-related infections (FRI) has been missing. Recently, FRI has been defined by a consensus group with a diagnostic algorithm containing suggestive and confirmatory criteria. The aim of the current study was to report the prevalence of FRI in patients operated for ankle fractures and to assess the applicability of the diagnostic algorithm from the consensus group.

Patients and methods: Records of all patients with surgically treated ankle fractures from 2015 to 2019 were retrospectively reviewed for signs of postoperative infections. Patients with suspected infection were stratified according to *confirmatory* or *suggestive criteria* of FRI. Rate of FRI among patients with *confirmatory* and *suggestive criteria* were calculated.

Results: Suspected infection was found in 104 (10%) out of 1004 patients. Among those patients, *confirmatory criteria* were met in 76/104 (73%) patients and *suggestive criteria* were met in 28/104 (27%) at first evaluation. Patients with clinical confirmatory criteria ($N = 76$) were diagnosed with FRI. Patients with suggestive criteria were further examined with either bacterial sampling at the outpatient clinic, revision surgery including bacterial sampling, or a wait-and-see approach. Eleven (39%) of the 28 patients had positive cultures and were therefore diagnosed as having FRI at second evaluation. In total 87 (9%) patients were diagnosed with FRI according to the consensus definition. Only 73 (70%) of the 104 patients with suspected FRI had adequate bacterial sampling.

Conclusion: The prevalence of FRI, applying the FRI-consensus criteria, for patients with surgically treated ankle fractures was 9%. Twenty-two percent of patients who met the *confirmatory criteria* had negative bacterial cultures. The current study shows that we did not have a systematic approach to patients with suspected FRI as recommended by the consensus group. A systematic approach to adequate bacterial sampling when FRI is suspected is paramount. The consensus definition of FRI and its diagnostic algorithm facilitates such an approach.

Level of evidence: Level III – retrospective cohort study

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Introduction

Ankle fractures constitute 9% of all fractures and have an incidence of 107–187 per 100,000 persons per year [1,2]. Operative treatment comes with a substantial risk of complications, including wound healing problems and postoperative infection. After ankle

fracture surgery the incidence of infection and wound dehiscence reportedly varies from 2.6% to 17.6% [3–5]. Until recently, except the more general Center for Disease Control and Prevention (CDC) definition of postoperative surgical site infection (SSI), the lack of a standardized definition of infection after fracture surgery has precluded comparisons across studies [6–8].

A consensus group of orthopedic surgeons, radiologists, microbiologists, pharmacists, and infection disease specialists proposed a new definition denoted *fracture-related infection* (FRI) in 2017 [9]. The definition was updated in 2020 [10]. This consensus distin-

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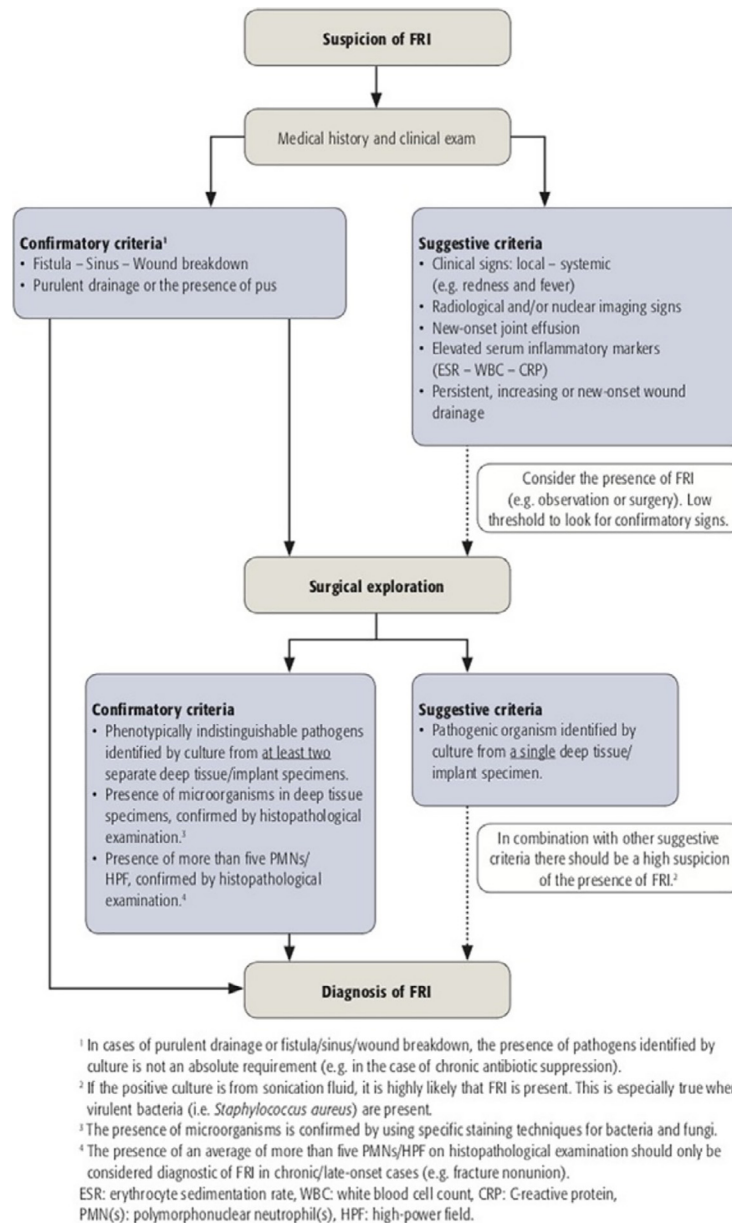


Fig. 1. Definition and flow-chart for diagnosis of Fracture-related infection. Figure from “Diagnosing Fracture-related Infection: Current Concepts and Recommendations”, Govaert GAM, Kuehl R, Atkins BL, Trampuz A, Morgenstern M, Obremesky WT, Verhofstad MHJ, McNally MA, Metsemakers WJ; Fracture-Related Infection (FRI) Consensus Group. J Orthop Trauma. 2020 Jan;34(1):8–17.

The figure is adapted from: Fracture-related infection: A consensus on definition from an international expert group. Metsemakers WJ, Morgenstern M, McNally MA, Moriarty TF, McFadyen I, Scarborough M, Athanasou NA, Ochsner PE, Kuehl R, Raschke M, Borens O, Xie Z, Velkes S, Hungerer S, Kates SL, Zalavras C, Giannoudis PV, Richards RG, Verhofstad MHJ. Injury. 2018 Mar;49(3):505–510.

guishes between *confirmatory* and *suggestive* criteria of FRI (Fig. 1). *Confirmatory criteria* are the presence of fistulas, sinus formation, or wound breakdown with communication to bone or implant. Presence of purulent drainage or pus also confirms an infection. These clinical signs are considered pathognomonic of FRI [11]. Further *confirmatory criteria* include phenotypically indistinguishable pathogens identified by culture from at least two separate deep tissue/implant specimens - and the presence of microorganisms in deep tissue specimens, confirmed by histopathological examination. In the updated definition from 2020 the presence of ≥ 5 polymorphonuclear neutrophils per high-power-field (PMN/HPF) was also included as a confirmatory sign for late-onset cases [10].

Suggestive criteria include clinical signs of infection (redness, swelling, warmth, pain, and fever), radiological signs, new-onset

joint effusion, elevated serum inflammatory markers (white blood cell count (WBC), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR)), and persistent, increasing or new-onset wound drainage. The *suggestive criteria* require a surgical exploration for the confirmation of FRI. A positive culture from a single deep tissue/implant specimen is also considered a suggestive criterion which, in combination with other *suggestive criteria*, should give a high suspicion of FRI [9]. Positive findings on nuclear imaging such as 3-phase bone scan, fluorodeoxyglucose positron emission tomography (FDG-PET), and white blood cell (WBC) scintigraphy were included as suggestive criteria in 2020 [10].

Currently there are only a few studies reporting the rate of postoperative infection after ankle fracture surgery, applying the FRI definition [9,10,12].

The aim of the current study was to report the prevalence of FRI in patients operated for ankle fractures and to assess the applicability of the diagnostic algorithm from the consensus group at a level 1 trauma hospital in Bergen, Norway.

Patients and methods

Patient records of all patients with ankle fractures operated at Haukeland University Hospital in the period January 2015 through December 2019 were retrospectively assessed for indications of postoperative infection. Patients < 18 years of age at the time of primary surgery, those with bilateral injuries, and patients with follow-up at other hospitals were excluded.

Patients were identified by a selective search through the operation planning system, Orbit version 5.11.2 (Tieto Evry, Kristianstad, Sweden), based on Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical Procedures (NCSP) codes for uni-, bi- and trimalleolar fractures and infection complication diagnoses. Records were examined for information concerning clinical, radiological, biochemical, and microbiological signs of postoperative infection and wound problems, as well as for classification of fractures. Sectra software version 22.1 (Sectra AB, Linköping, Sweden) was used for radiograph examination.

Information indicating wound problems such as prolonged healing or dehiscence as well as clinical signs of infection, drainage or puss resulted in suspicion of infection. These patients were stratified to either have *confirmatory criteria* or *suggestive criteria* of FRI. Following the diagnostic algorithm published by FRI consensus group patients were considered to have FRI when meeting either of the *confirmatory criteria* (Fig. 1) [9,10]. Culture status (negative/positive) was evaluated thereafter. Patients meeting the *suggestive criteria* were classified as having an FRI if they had one positive culture with virulent pathogens (*Staphylococcus aureus* (*S. aureus*), *Staphylococcus lugdunensis* (*S. lugdunensis*), *Streptococci species*, or *gram-negative species*), or phenotypically equal bacterial cultures in two or more bacterial samples. Although it is a coagulase negative staphylococcus, *S. lugdunensis*, was included as a virulent bacterium due to similarities to *S. aureus* in causing infection [13,14]. Those who had *suggestive criteria*, but negative cultures, were classified as not having an FRI. Also, patients without bacterial sampling, not having received any antibiotic treatment and who did not develop any *confirmatory criteria* of FRI, were defined as not having had FRI. Patients with *suggestive clinical signs* of FRI treated without revision surgery were considered to have a good treatment outcome if the infection or soft tissue problems resolved and they were infection free 12 months after the initial treatment.

Revision surgery of patients with suspected FRI was performed by the surgeon on call. Both swab and tissue sampling were performed. We accepted two or more samples as adequate in the current study. A single swab sample in the outpatient clinic or the operating room was considered inadequate.

Depending on the samples taken, the Department of microbiology at the study hospital use different agars for cultivation. Direct PCR is performed in cases with high suspicion of infection but negative cultures. Standard incubation time for swabs is two days. In suspected FRI, the incubation time was five days early in the study period but later extended to 10 days for peroperatively taken bacterial samples, to identify slow growing bacteria with affinity for implants.

Results

Patient journal examination was concluded by 1st of July 2022 giving a mean follow-up period of 59 (Standard deviation (SD) 17) months. The search rendered 1064 operations for ankle fractures in 1057 patients. Patients with bilateral injuries (seven patients)

Table 1

Fracture characteristics for the 104 patients with suspected fracture-related infection (FRI).

		n (%)
AO classification	44A3.3	1 (1)
	44B1	17 (16)
	44B2	7 (7)
	44B3	43 (41)
	44C1	12 (12)
	44C2	18 (17)
	44C3	6 (6)
Dislocation fracture		32 (31)
Open fracture		4 (4)
Multitrauma		1 (1)
High energy trauma		7 (7)

Fracture characteristics for the 104 patients with suspected Fracture-related infection (FRI). Number of patients (n) with percentages in parenthesis.

and patients with follow-up elsewhere (46 patients) were excluded from the study. A total of 1004 patients (60% women, 40% men) were eligible for inclusion in the study (Fig. 2). The patients' mean age at time of primary fracture surgery was 52 (SD = 18) years and the mean body mass index (BMI) was 27.5 (SD = 4.8). Eight-hundred and ninety-one (89%) patients were American Society of Anesthesiologist (ASA) class 1 or 2, 109 (11%) were ASA 3 and four (0.4%) patients were ASA class 4.

FRI was suspected in 104 (10%) of the 1004 patients. Among the suspected FRIs, *confirmatory criteria* were met in 76/104 (73%) and *suggestive criteria* in 28/104 (27%) of cases at first evaluation. AO 44B was the most common fracture type (67 (64%) of 104 patients, Table 1) among patients with suspected FRI.

Prevalence of fracture-related infection

Eighty-seven of 1004 (9%) patients were finally diagnosed with FRI after second evaluation (Fig. 2). One of the patients with FRI underwent below the knee amputation for infection control.

Confirmatory criteria

Fistula, sinus tract or wound breakdown were the most common *confirmatory criteria* (Table 2). Seventy-one (93%) of 76 patients with *confirmatory criteria* developed the clinical signs of FRI after the primary fracture surgery, while in 5 (7%) patients the wound problems occurred after a reoperation.

All 76 patients who met the *confirmatory criteria* had bacterial samples taken (Table 3), but only in 64 (84%) patients the samples were adequately taken. Fifty of the 64 patients had bacterial sampling without prior antibiotic treatment. Among them, 36 (72%) patients had two or more positive cultures, 2 had one positive culture, 1 had one positive culture with a non-virulent pathogen, and 11 patients (22%) had negative cultures.

Revision surgery due to suspected FRI was performed in 67 (88%) of 76 patients who met the *confirmatory criteria*. Seventy (92%) of the 76 patients received treatment for FRI. Six patients did not receive any further antimicrobial treatment after evaluation of bacterial cultures and did not develop further signs of FRI.

Suggestive criteria

Twenty-eight patients presented with clinical *suggestive criteria*. All wound problems suspicious of FRI for these patients occurred after the primary fracture surgery. Wound drainage was the most common clinical sign of infection among patients with *suggestive criteria* (Table 2). Radiographic signs suggesting infection

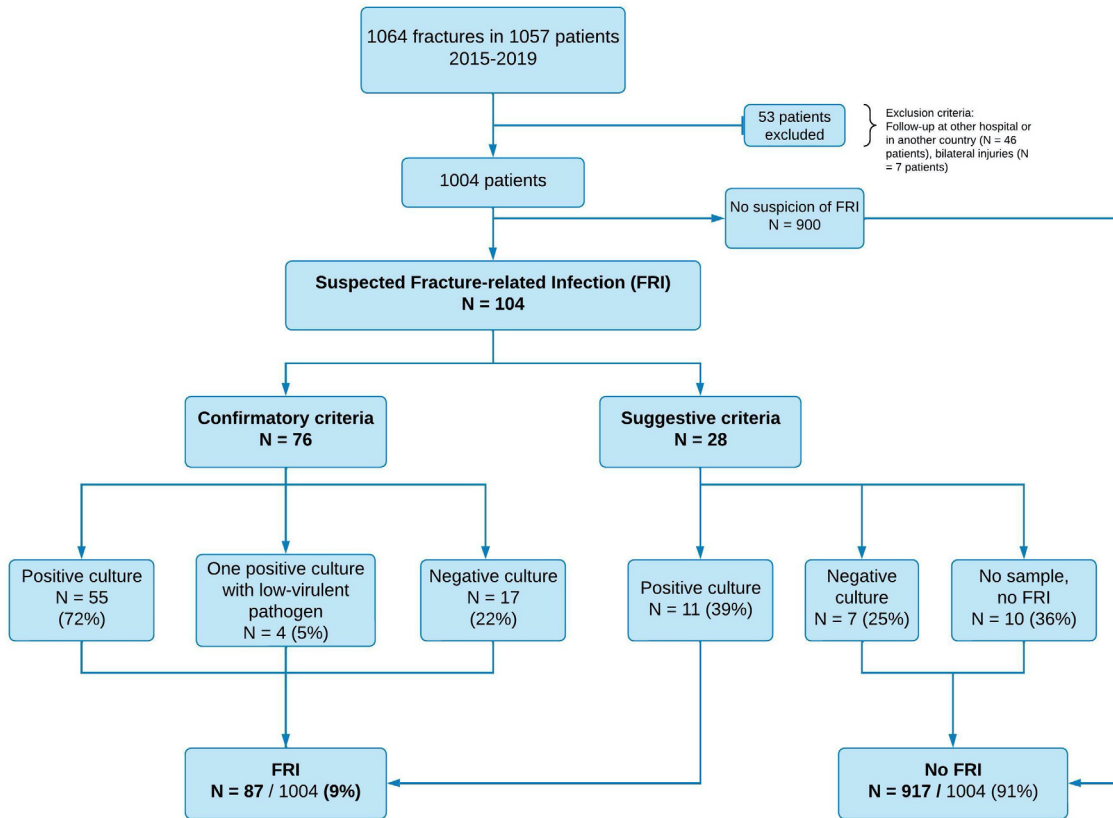


Fig. 2. Patient inclusion flow-chart. N – Number of patients. FRI – Fracture-related Infection.

Table 2

Distribution of confirmatory and suggestive criteria among the 104 patients with suspected Fracture-related Infection.

	n (%)
<i>Patients with confirmatory criteria, clinical signs, n = 76*</i>	
Fistula, sinus, wound breakdown	55 (72)
Purulent drainage, pus	21 (28)
Clinical signs of infection**	46 (61)
<i>Patients with suggestive criteria, n = 28*</i>	
Local clinical signs	7 (25)
Systemic clinical signs (fever)	n.a.
Other clinical signs	n.a.
	New-onset joint effusion
	Wound drainage
	0
Histopathology	0
Radiographic signs	1 (4)
Serum inflammatory markers#	Erythrocyte Sedimentation Rate (ESR) 2 (7)
	Leukocyte particle count (LPC) 0
	Neutrophile count 0
	C-reactive protein (CRP) 4 (14)

Distribution of confirmatory (clinical) and suggestive criteria among the 104 patients suspected of FRI. N.a. = not applicable.

* A patient may have more than one confirmatory or suggestive criteria.

** Clinical signs of infection: redness, warmth, swelling and pain.

For the serum inflammatory markers the number of patients with abnormal values are presented with percentages in parenthesis. Normal values: ESR ≤ 20 , LPC $\leq 11 \times 10^9$, Neutrophile count $1-8.5 \times 10^9$, CRP < 5 .

was found in only one patient, but FRI was not confirmed in this patient. The 28 patients were further examined with either bacterial sampling at the outpatient clinic, revision surgery including bacterial sampling, or a wait-and-see approach. Eighteen (64%) of 28 patients had bacterial samples taken but only in 9 patients an adequate sample method was used (Table 3). Eleven (39%) of 28 patients had positive cultures. Bacterial sampling was not performed in 10 (36%) of 28 patients who met the suggestive criteria.

These 10 patients had close, subsequent follow-up by an orthopedic surgeon until the wound problem and suspicion of infection was resolved.

Revision surgery was performed in 10 (36%) of 28 patients with suggestive criteria. Even though only 11 of 28 patients were diagnosed with FRI, 16 patients with suggestive criteria were treated for a suspected infection including 11 with positive cultures, 4 patients with negative cultures, and one patient in which bacterial sampling

Table 3
Bacterial sampling and culture results.

		Confirmatory criteria of FRI (n = 76)	Suggestive criteria of FRI (n = 28)
		n (%)	n (%)
Patients with bacterial sampling	Yes	76 (100)	18 (64)
	No	0	10 (36)
Quantity of bacterial samples	Swab only	10 (13)	9 (32)
	One sample	2 (3)	0
	2 or more samples	64 (84)	9 (32)
Antibiotics prior to sampling	Yes	19 (25)	0
	No	57 (75)	28 (100)
Bacterial findings	No bacterial culture	0	10 (36)
	Negative culture	17 (22)	7 (25)
	1 culture low-virulent	4 (5)	0
	1 culture virulent	7 (9)	5 (18)
	2 or more positive cultures	48 (63)	6 (21)

Bacterial sampling and culture results. Number of patients (n) with percentages in parenthesis.

was not performed. All 28 patients who met the *suggestive criteria* were infection free one year after treatment of the wound problems and FRI.

The number of samples taken per patient are presented in Table 3.

No histopathology was performed.

Discussion

In this study, FRI was suspected in 104 out of 1004 patients with surgically treated ankle fractures and a FRI, as defined by the consensus group, was subsequently confirmed in 87 of 1004 (9%) patients.

Fracture-related infection

While the prevalence of FRI in the current study was 9%, the prevalence of infection after ankle fracture surgery varies in the literature, from 2.6% to 8.4% depending on the definition of infection in the given study and the duration of follow-up [3,8,15]. The criteria from CDC for defining SSI is commonly used [8,16]. Sun et al. and Sato et al. found an SSI-rate of 3.7% and 5.7%, respectively, both lower than the current study [8,17]. However, the follow-up period in these studies was only 12-weeks as opposed to nearly 5 years in our study, allowing us to identify late infections in addition to the early ones. The use of FRI has been shown to capture more patients with postoperative infection than using the SSI definition [18]. Cooke et al. reported a 15% FRI-rate in patients with open ankle fractures [12]. To our knowledge the current study is one of the first to report the prevalence of FRI applying the diagnostic criteria and algorithm suggested by the FRI consensus group in patients operated for ankle fractures [9,10,12,19].

Confirmatory criteria

Seventy-three percent of the patients with suspected infection in the current cohort met the *confirmatory criteria* of FRI, compared to 97.5% in the study by Onsea et al. which however comprised other injuries in addition to ankle fractures, possibly explaining the different findings between the studies [11].

Three percent of patients with *confirmatory criteria* of FRI in the current study had only one positive culture after adequate bacterial sampling. Still, Onsea highlights that a single positive culture with a virulent pathogen should raise a high suspicion of infection and reported a low sensitivity but a specificity of 100% for a single positive culture.

All patients who met the *confirmatory criteria* in the current study had clinical *confirmatory signs* of FRI. However, 22% were culture negative, suggesting culture negative infections or no infection at all. In the study by Onsea 8.5% of patients with FRI were culture negative.

Bacterial samples were collected in a total of 96 patients having *confirmatory* or *suggestive criteria*. Negative bacterial culture results were found in 29 (31%) of these 96 patients. Culture negative infections may be assumed, particularly in patients with *confirmatory criteria*. Due to the potential dire consequences of an FRI, patients with clinical findings of *confirmatory criteria* should be treated with revision surgery. Swift surgery facilitates adequate bacterial sampling and restores the soft tissue envelope around implants and fracture.

Suggestive criteria

Few patients in the current study were reported to have local signs of inflammation (local redness, swelling or warmth). As pain is not registered in a satisfactory manner in the patient's records, data regarding pain were not included in our study. However, pain has been shown to have a weak association with FRI as it might be due to several causes [11]. Fever was also not systematically reported in the current study, but Onsea found a specificity of 98.7% and argues that if FRI is suspected, and the patient presents with fever, the diagnosis must be strongly considered [11].

Radiographic signs of infection appear late, and their value remain unclear. Contra-intuitively Onsea et al. found a higher rate of radiographic suggestive signs among patients without FRI [11]. Comparatively, only one patient in our study had radiographic findings suggesting infection. This patient, however, did not have a confirmation of the FRI diagnosis. X-ray findings of FRI, such as osteolysis, may appear several weeks after infection onset at which time the FRI in most cases will already have been diagnosed and treated.

Few patients who met the *suggestive criteria* and were confirmed to have an FRI in the current study, had blood samples taken as part of the diagnostics. This suggests the need for improved routines for diagnosing FRI at the study hospital. However, given the low levels of WBC, CRP, and ESR among the patients with clinical *suggestive criteria* in the current study, these tests seemed to add little value in the search of the FRI diagnosis in ankle fractures. Wound drainage, however, was reported in all patients diagnosed with FRI in the current study. This result contrasts those of Onsea et al. where only a few patients had wound drainage [11].

Increased leucocyte (WBC) level or prolonged or recurrent wound drainage in combination with local clinical signs of inflammation is reported to have a high sensitivity for FRI [11].

The majority of the study period was prior to the publication of the FRI definition (2018) and the tissue sampling was consequently not undertaken according to the requirements described by Hellebrekers et al. [20]. Later, the practice has changed to comply with sampling routines similar to periprosthetic joint infections (PJI) with a minimum of five samples taken with separate, non-contaminated, instruments.

A swab was used for bacterial sampling in half of the patients who met the *suggestive criteria* of FRI and who had bacterial samples taken. Inadequate sampling is challenging when a culture returns negative or positive with a low-virulent pathogen. One may wonder if the result is due to contamination or an infection. In such cases further assessment through revision surgery and adequate bacterial sampling is needed. Finding a single positive culture with a virulent pathogen has a sensitivity of 100% for the diagnosis of FRI and PJI [11,21]. Therefore, adequate, and meticulous tissue sampling and wound assessment must be performed. Patients presenting *suggestive criteria* should be thoroughly investigated and followed.

All bacterial samples taken in patients with *suggestive criteria* were collected without prior antibiotic treatment. Orthopedic trauma is treated at public hospitals in Norway and the access as well as distance to secondary health care is generally easy. This allows a wait-and-see approach until results of bacterial cultures are available, and even a 14-day cessation of antibiotics prior to bacterial sampling, which is likely to reduce the number of false negative bacterial samples. In this period of expectancy, the wound problem may be closely observed by an orthopedic surgeon at the outpatient clinic at subsequent visits. In case of changes- or additional clinical signs of FRI, the patient may be admitted for further assessment, revision surgery and bacterial sampling. This is in line with the diagnostic algorithm of FRI by the consensus group [9,10].

Strengths

This study is a transparent report of FRI from a level 1 trauma hospital, with a high number of ankle fractures and consecutive complications. We had access to comprehensive data on patient demographics, fracture characteristics, type of surgery, samples, treatment, and clinical course. In this unselected cohort, the prevalence of FRI after ankle fracture surgery was calculated [11] and we believe the external validity is good. Another strength is the chronology for patient inclusion and application of the FRI algorithm [9]. Onsea et al. used intention-to-treat as recommended by a multidisciplinary team to select patients to a FRI group and a control group. The current study stratified patients to the *confirmatory* or *suggestive criteria* groups according to clinical signs presented either at the outpatient clinic or postoperatively while admitted, before culture results. Consequently, this study presents a recognizable setting for orthopedic surgeons including the clinical pathway for their patients and the applicability of the FRI algorithm as a diagnostic tool.

Limitations

The retrospective study design has inherent limitations. The FRI criteria were not in use when the patients were treated and for this reason data from the patient's records in some cases were imprecise or inadequate. None of the patients with *suggestive criteria* but a quarter of the patients with *confirmatory criteria* had antibiotic treatment prior to revision surgery and bacterial sampling, similar to the report by Onsea et al. [11]. Such use of antibiotics may result in false negative bacterial cultures. The bacterial

sampling method applied in this study, with at least two bacterial samples taken, is not in line with current recommendations, but was deemed adequate due to the practice during that time period. This sampling protocol is a limitation, but we believe it to be recognizable in other clinical settings. However, from 2018, after establishing an orthopedic infection ward with dedicated surgeons, the sampling routines have been changed in concordance with PJI and FRI recommendations. A culturing protocol including five or more separate deep tissue samples, each collected with individual sterile instruments, is now standard of care [10,22]. In retrospect, routines for infection diagnostics and sampling were unsatisfactory and not in accordance with the FRI algorithm. A more systematic and standardized sampling might have influenced the results regarding prevalence of FRI. A swab from the skin or wound secretion is considered an inadequate sampling method [20,23]. Adequate bacterial sampling was performed in a minority of patients with *suggestive criteria*, and in some cases no bacterial sampling were collected at all. More patients with clinical *suggestive signs* may have been classified as FRI with improved bacterial sampling [10,11]. Another challenge in retrospective classification of infections is the differentiation between the clinical confirmatory criteria "wound breakdown" and the clinical *suggestive criteria* "increasing or new onset wound drainage". A misclassification in some of these cases may therefore not be ruled out.

Conclusion

The prevalence of FRI, applying the FRI-consensus criteria, for patients with surgically treated ankle fractures was 9%. Twenty-two percent of patients who met the confirmatory criteria had negative bacterial cultures. The current study shows that we did not have a systematic approach to patients with suspected FRI as recommended by the consensus group. A systematic approach to adequate bacterial sampling when FRI is suspected is paramount. The consensus definition of FRI and its diagnostic algorithm facilitates such an approach.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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