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Outcome and risk factors for recurrence of early onset fracture-related infections treated with debridement, antibiotics and implant retention: Results of a large retrospective multicentre cohort study

M.A.S. Buijs[a], J. van den Kieboom[a], J. Sliepen[b], K.L.H. Wever[a], J.M. van Breugel[a], F. Hietbrink[a], F.F.A. IJpma[b], G.A.M. Govaert[a,*]

[a] Department of Trauma Surgery, University Medical Centre Utrecht, University of Utrecht, Utrecht, The Netherlands
[b] Department of Trauma Surgery, University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands

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ABSTRACT

Introduction: Early Fracture-Related Infections (FRIs) are a common entity in hospitals treating trauma patients and are often treated with a Debridement, Antibiotics and Implant Retention (DAIR) procedure. Aims of this study were to 1) evaluate the recurrence rate after DAIR procedures for early onset FRI, 2) establish the number of surgical procedures to gain control of the initial infection and 3) identify independent predictors for recurrence in this cohort.

Methods: A retrospective multicentre cohort study was conducted in two level 1 trauma centres. Consecutive patients who underwent a DAIR procedure between January 1st 2015 and July 1st 2020 for confirmed FRI with an onset of <6 weeks after the latest osseous operation were included. Recorded data included patient demographics, treatment characteristics and follow-up. Univariate and multivariate logistic regression analyses were performed to assess predictors for recurrent FRI.

Results: A total of 141 patients with early FRI were included in this study with a median age of 54.0 years (interquartile range (IQR) 34.5–64.0). The recurrence rate of FRI was 13% (n = 19) at one year follow-up and 18% (n = 25) at 23.1 months (IQR 15.3–36.4) follow-up. Infection control was achieved in 94% (n = 127/135) of cases. In total, 73 patients (52%) underwent at least two surgical procedures to treat the ongoing initial episode of FRI, of whom 54 patients (74%) required two to three procedures and 17 patients (23%) four to five procedures. Predictors for recurrent FRI were use of an intramedullary nail during index operation (odds ratio (OR) 4.0 (95% confidence interval (CI) 1.1–13.8)), need for additional surgical procedures to treat ongoing infection during the treatment period following the first presentation of early FRI (OR 1.9 (95% CI 1.1–3.5)) and a decreased Injury Severity Score (ISS) (inverted OR 1.1 (95% CI 1.0–1.1)).

Conclusion: The recurrence rate after treatment of early onset FRI in patients treated with a DAIR procedure was 18% at 23.1 months follow-up. At least two surgical procedures to gain control of the initial infection were needed in 52% of patients. Independent predictors for recurrent FRI were the use of an intramedullary nail during index operation, need for additional surgical procedures and a decreased ISS.

Introduction

Fracture-Related Infections (FRIs) are amongst the most challenging complications in fracture care [1]. As the clinical presentations of FRI vary widely, the FRI Consensus Group proposed a consensus-based definition for this disease [2]. Classification methods, such as by infection location, duration or onset, were not included in this consensus definition. Historically however, based on the clinical differences, the presentation of FRI was related to the time of onset of infection after the initial surgery [3]. One approach was to divide FRIs in early (<6 weeks) and late onset (≥6 weeks) infections [4], another is to divide FRI in early (≤2 weeks), delayed (3 to 10 weeks) and late onset (>10 weeks) infections [5]. Even though these distinctions are arbitrary, they are still used in many protocols to guide treatment as challenges in terms of fracture and soft tissue management are thought to be important [3]. For example, due to the maturation of the biofilm over time and increasing

* Corresponding author at: University Medical Centre Utrecht (UMCU), Department of Trauma Surgery, P.O. Box 85500, Room # G.04.228, 3508 GA Utrecht, The Netherlands.
E-mail address: G.A.M.govaert@umcutrecht.nl (G.A.M. Govaert).

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osteolysis and necrosis of the affected bone, late onset FRIs are generally considered to be more difficult to eradicate compared to early onset FRIs [6].

In general, early onset FRIs occur at a time when fracture healing is still ongoing and therefore the stability of the fracture depends on the additional strength of an implant [7]. As a result, complete removal of the implant is often not an option in early FRI which forces the surgeon to decide whether the implant can be retained or should be exchanged for another fixation device [7]. Due to reduced maturation of the biofilm and generally healthier appearing bone and soft tissues in early FRIs, this results in a more frequent consideration of implant retention in cases with stable fracture fixation and good fracture reduction [7,8]. In these cases, an often challenging Open Reduction and Internal Fixation (ORIF) procedure is compromised by the chance of losing reduction and stability when an implant is (temporarily) removed. A so-called DAIR (Debridement, Antibiotics and Implant Retention) procedure, which is often performed for treatment of both early onset FRIs and Periprosthetic Joint Infections (PJIs) [9,10], is preferred in these cases. Besides stability of the fracture, other important factors such as vital soft tissues, the technical ability to perform a proper debridement, susceptibility of the pathogen and absence of major impairments regarding the host physiology determine whether a DAIR procedure can be performed [11,12].

Although recent literature has given more insight regarding the management of early onset FRI and the outcome of DAIR procedures for these patients [12], it remains challenging to accurately counsel patients about the expected course of their disease [2,4]. Therefore, the aims of this study were to 1) evaluate the recurrence rate after DAIR procedures for early onset FRI, 2) establish the number of surgical procedures needed to gain control of the initial infection in the same treatment period as the first FRI and 3) identify predictors for FRI recurrence in this cohort.

Patients and methods

Study design

A retrospective multicentre cohort study was performed. All consecutive patients diagnosed with FRI between January 1st 2015 to July 1st 2020 treated in either the University Medical Centre Utrecht (UMCU) or the University Medical Centre Groningen (UMCG), both level 1 trauma centres in The Netherlands, were eligible for inclusion in this study. A waiver was granted by the Medical Ethics Review Committee (METC-20-004/C) of the UMCU.

In- and exclusion criteria

Patients of at least 16-years of age with early onset FRI of <6 weeks after the latest osseous operation were eligible for inclusion. The latest osseous operation was defined as the intervention that most likely caused the FRI, which could therefore be the surgical fracture stabilisation procedure, but also a revision operation or removal of implants only. Solely patients who underwent a DAIR procedure for the (suspected) early onset FRI were included in this study. Additionally, during the first DAIR procedure, at least three separate intraoperative deep tissue cultures had to be obtained. FRI was defined according to the FRI consensus criteria and at least one confirmatory criterion had to be met (Table 1) [2,13–15]. Lastly, patients with spinal or skull fractures and fractures of the small bones of the hand or foot were not eligible for inclusion. All patients who did not meet these criteria were excluded. Moreover, patients with inadequate availability of data needed for this study were excluded, as well as patients who were lost to follow-up within <12 months after treatment of the initial FRI. Discharge from follow-up by the treating medical team, death or amputation within <12 months was not defined as loss to follow-up and these patients will therefore be included in this study. Patients discharged from follow-up were required to have complete fracture consolidation, absence of both confirmatory and suggestive criteria, and were instructed to contact the treating centre if recurrence of symptoms occurred.

Early FRI and DAIR treatment protocol

A treatment protocol for the management of patients with early onset FRI was used in both centres. All surgical interventions were performed or supervised by an experienced board-certified trauma surgeon. According to these protocols, the preferred treatment method in case of early onset FRI with a stable fracture fixation was a DAIR procedure [3,11]. Ensuring adequate soft tissue coverage was considered an essential part of the operative procedure [3]. Intravenous (IV) empiric antimicrobial therapy was started immediately after surgical debridement and tissue sampling for microbiological culturing [14]. Based on the definitive microbiological results, targeted antimicrobial treatment was initiated in consultation with Infectious Diseases specialists. Biofilm targeting antibiotic therapy such as Rifampicin was added if deemed appropriate. Antimicrobial treatment was continued for a duration of twelve weeks following any procedure where implants remained in situ [11].

Table 1
Confirmatory and suggestive FRI [1] consensus criteria.

Confirmatory and suggestive FRI consensus criteria	
Confirmatory criteria	**Suggestive criteria**
Fistula, sinus tract or wound breakdown	*Clinical signs (local & systemic)*[*]
Presence of pus in the fracture	*Radiological signs and/or nuclear imaging signs*[**]
Phenotypically indistinguishable organisms identified from two or more separate deep tissue specimens	*Pathogen identified from a single deep tissue specimen*
Visible microorganisms on histological analysis	*Elevated serum inflammatory markers:* *Erythrocyte sedimentation rate* *Leucocyte count* *C-reactive protein*
Presence of five or more neutrophils per high power field on histology [2]	*Persistent wound drainage* *New onset of joint effusion*

[*] Clinical signs (local & systemic): redness, pain, swelling, fever (>38.3 °C), persistent/increasing or new onset wound drainage, increased local temperature.

[**] Failure of progression of bone healing (nonunion), implant loosening, bone lysis, sequestration, periosteal bone formation, cloacae, sinus tracts, and/or subcortical abscesses and increased tracer uptake.

Adapted from McNally M, Govaert G, Dudareva M, Morgenstern M, Metsemakers W-J. Definition and diagnosis of fracture-related infection. EFORT Open Reviews 2020;5:614–9 [13].

[1] Fracture-Related Infection.

[2] Only a confirmatory criterion in FRI with an onset ≥ 8 weeks [13].

Data collection

Data was collected using the combined FRI database of both study centres and additionally by reviewing electronic patient files of the included patients. All relevant data with regard to the management of FRI were collected, including patient demographics, treatment characteristics and outpatient follow-up along with documentation of all re-admissions and re-operations for each patient. All data was entered and stored in the data capturing program Castor EDC (Castor Electronic Data Capture, v2021.5.3) and was pseudonymised [16].

Patient characteristics were identified, including sex, age, Body Mass Index (BMI), American Society of Anaesthesiologists (ASA) classification, comorbidities such as diabetes mellitus and obesity, and possible risk factors such as alcohol abuse, smoking and drug use [11,17,18]. The Injury Severity Score (ISS) was used to assess the severity of the trauma that caused the fracture [19]. Fractures were classified according to the Arbeitsgemeinschaft für Osteosynthesefragen/Orthopaedic Trauma Association (AO/OTA) fracture classification [20]. Furthermore, open fractures were classified according to the Gustilo-Anderson classification [21]. Thresholds of 5.0 mg/L and $10 \bullet 10^9$/L were utilised to assess C-reactive protein (CRP) and leucocyte Count (LC), respectively [22].

Study outcomes

The primary endpoint of this study was the recurrence rate after early onset FRI in patients treated with a DAIR procedure. A recurrent FRI was defined as the re-appearance of at least one confirmatory FRI criterion after completion of the surgical and antibiotic treatment of the initial early onset FRI. Infection control was defined as absence of amputation, absence of confirmatory FRI criteria and absence of ongoing treatment with antimicrobials at the last follow-up appointment. The secondary endpoint was to establish the number of surgical procedures. Need for additional surgical procedures was defined as the need for any extra operative washout and/or debridement procedure(s) to treat ongoing infection during the treatment period following the first presentation of early FRI, frequently due to persisting wound leakage. This could either be executed as an additional DAIR or a non-DAIR procedure. The tertiary endpoint was the identification of possible predictors of a recurrent FRI.

Statistical analysis

Data was either presented as dichotomised variables in counts and percentages (n (%)) or as continuous variables with mean and standard deviation (SD) when normally distributed, or as median and interquartile range (IQR) when not normally distributed. A Chi-Squared test or Fisher's exact test was performed for dichotomised values according to the estimated cell size. An independent *t*-test or Mann-Whitney U test was performed for continuous variables, depending on the normality of the variable.

A univariate analysis was performed to identify possible predictors that could lead to a recurrent FRI. Variables that were previously thought to contribute to an increased recurrence rate [23] were selected and tested individually against the primary outcome in a logistic regression model. All variables demonstrating a p-value of <0.10 after univariate analysis were selected and included in the initial model. If overfitting of the model was imminent when using the selected variables at a p-value of <0.10, a lower p-value was used, so that a minimum of 5–10 events per predictor were utilised. A backward, stepwise logistic method was subsequently used, excluding variables from the multivariate model until only variables with a p-value of <0.05 remained [24]. The corresponding odds ratio (OR) with 95% confidence interval (95% CI) were calculated for each parameter to demonstrate its contribution to FRI recurrence. A p-value of <0.05 was considered as statistically significant. All data analyses were executed in Statistical Package for the Social Sciences (SPSS®) statistics (version 26.0, Armonk, NY, USA: IBM Corp.).

Results

Baseline characteristics

The FRI database used for this study consisted of 352 patients and 141 patients were ultimately included in this study. Of these

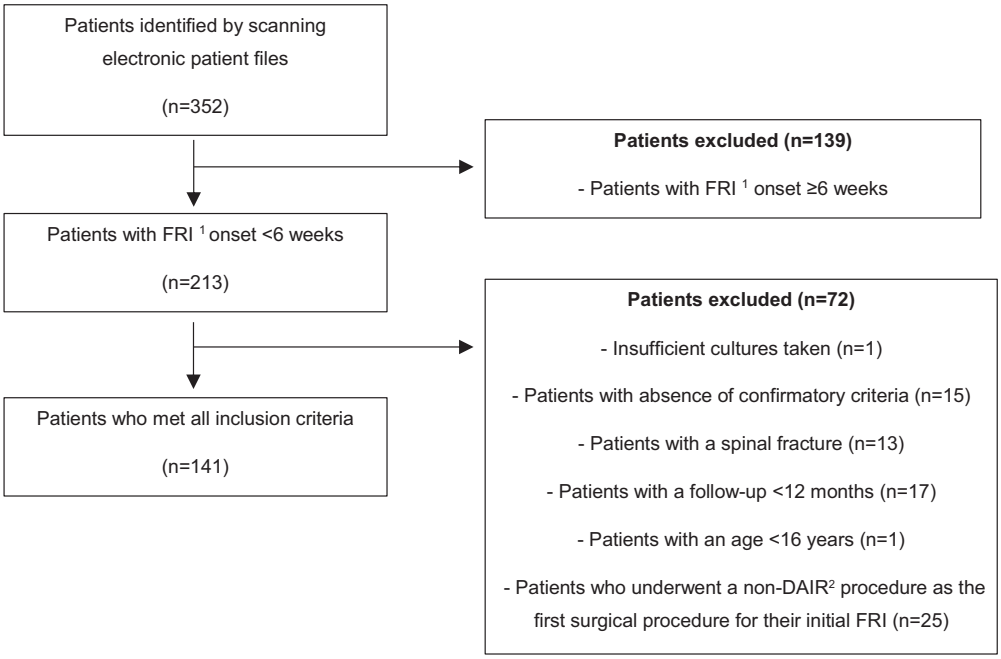

Fig. 1. In- and exclusion diagram of early onset FRI [1] patients.
[1] Fracture-Related Infection.
[2] Debridement, Antibiotics and Implant Retention.

141 patients, whom all underwent a DAIR procedure as per study protocol, 101 patients (72%) were treated in the UMCU and 40 (28%) in the UMCG. The flow diagram of the in- and exclusion process is shown in Fig. 1.

The baseline characteristics are displayed in Tables 2 and 3. The cohort consisted of a majority of males (64%, $n = 90$). The median age was 54.0 years (IQR 34.5–64.0). The most common fracture sites were the tibia/fibula (48%, $n = 67$), femur (20%, $n = 28$) and pelvis (15%, $n = 21$). Of all fractures, 71% ($n = 100$) were closed fractures. The median timeframe between the latest osseous operation and onset of FRI symptoms was 14.0 days (IQR 10.0–19.0) (Table 2). In total, 129 patients (91%) started immediately with empiric broad spectrum IV antimicrobial therapy, which was subsequently narrowed according to the microbiological results. Of the 12 patients (9%) that were not started on IV antimicrobial therapy immediately, nine patients (6%) received IV antimicrobial therapy as soon as the obtained cultures became positive, two patients (1%) received oral antimicrobial therapy only and one patient (1%) did not receive antimicrobial therapy due to amputation of the affected limb. The total duration of the initial course of antimicrobial therapy was 12.0 weeks (IQR 11.0–13.0), as per institutional protocol. Addition of Rifampicin during the treatment of the initial FRI was common and administered to 65% ($n = 91$) of patients.

Clinical confirmatory and suggestive criteria

Clinical and operative confirmatory signs were present in 48% ($n = 68$) and 50% ($n = 71$) of patients, respectively. Purulent discharge (29%, $n = 41$) and wound dehiscence (23%, $n = 32$) were the most common confirmatory clinical signs. Suggestive clinical signs were common, redness (64%, $n = 90$) and persistent wound leakage (49%, $n = 69$) were the most frequently described symptoms. Elevated CRP and LC was seen in 95% ($n = 124/131$) and 53% ($n = 75/129$) of the patients, respectively. Radiological signs such as implant loosening or breakage, sequestrae and halo-signs around implants were present in 22% ($n = 16/74$) of the cases. During the operation, an abscess was the most frequently seen (47%, $n = 66$) confirmatory criterion. A more in-depth view of the confirmatory and suggestive criteria is available in Appendix 1.

Table 2
Baseline patient- and fracture characteristics.

	All patients ($n = 141$)	No recurrent FRI ($n = 116$)	Recurrent FRI ($n = 25$)	p-value
Patient characteristics				
Sex (male)	90 (64%)	74 (64%)	16 (64%)	0.98
Age (years)	54.0 (34.5–64.0)	53.5 (34.3–65.0)	57.0 (38.5–60.5)	0.60
Body Mass Index (kg/m) (n = 140)	26.4 (23.4–30.3)	26.4 (23.4–30.6)	26.4 (23.5–30.2)	0.98
Injury Severity Score (n = 122)	13.0 (9.0-22.0)	13.0 (9.0-22.0)	10.0 (6.5-15.0)	0.06
Injury Severity Score categorised (n = 122)				0.23
<16	75 (61%)	56 (58%)	19 (76%)	
16–24	25 (20%)	21 (22%)	4 (16%)	
>24	22 (18%)	20 (21%)	2 (8%)	
Follow-up (months)	23.1 (15.3–36.4)	21.8 (14.7–33.5)	27.6 (20.5–43.1)	**0.008**
Comorbidities				
Diabetes mellitus	17 (12%)	15 (13%)	2 (8%)	0.78
Obesity (n = 140)	37 (26%)	30 (26%)	7 (28%)	0.84
Risk factors				
Smoking (n = 136)	39 (29%)	34 (31%)	5 (20%)	0.29
Drugs (n = 132)	7 (5%)	7 (7%)	0 (0%)	0.35
Alcohol abuse (n = 139)	9 (6%)	9 (8%)	0 (0%)	0.36
ASA classification [1]				0.28
ASA 1	34 (24%)	28 (24%)	6 (24%)	
ASA 2	75 (53%)	58 (50%)	17 (68%)	
ASA 3	29 (21%)	27 (23%)	2 (8%)	
ASA 4	3 (2%)	3 (3%)	0 (0%)	
Fracture characteristics				
Fracture location				0.46
Humerus/clavicle/scapula/chest	9 (6%)	8 (7%)	1 (4%)	
Forearm	6 (4%)	6 (5%)	0 (0%)	
Femur	28 (20%)	24 (21%)	4 (16%)	
Tibia/fibula	67 (48%)	51 (44%)	16 (64%)	
Pelvis	21 (15%)	17 (15%)	4 (16%)	
Foot	10 (7%)	10 (9%)	0 (0%)	
Open fracture	41 (29%)	31 (27%)	10 (40%)	0.19
Gustilo-Anderson classification (n = 41)				0.55
Grade I	4 (10%)	3 (10%)	1 (10%)	
Grade II	10 (24%)	9 (29%)	1 (10%)	
Grade III	27 (66%)	19 (61%)	8 (80%)	
Implant used at index operation				0.85
Dynamic Hip Screw or similar	3 (2%)	3 (3%)	0 (0%)	
G-nail, PFNA [2] *or similar*	13 (9%)	10 (9%)	3 (12%)	
Intramedullary nail	19 (13%)	13 (11%)	6 (24%)	
Plate	91 (65%)	76 (66%)	15 (60%)	
Screws or K-wires	8 (6%)	8 (7%)	0 (0%)	
External fixation as definite treatment	2 (1%)	1 (1%)	1 (4%)	
Implant removal only	5 (4%)	5 (4%)	0 (0%)	
External fixation before index surgery	36 (26%)	30 (26%)	6 (24%)	0.43
Time between latest osseous operation and FRI suspicion (days)	14.0 (10.0–19.0)	14.0 (10.0–18.0)	16.0 (11.0–23.5)	0.14

Dichotomised variables: n (%)
Continuous variables: median (IQR)

[1] American Society of Anaesthesiologists.
[2] Proximal Femoral Nail Antirotation.

Table 3
FRI [1] and microbiological characteristics.

	All patients (n = 141)	No recurrent FRI (n = 116)	Recurrent FRI (n = 25)	p-value
FRI signs				
Confirmatory clinical signs	68 (48%)	55 (47%)	13 (52%)	0.35
Only suggestive clinical signs	71 (50%)	60 (52%)	11 (44%)	0.35
Operative findings & procedure				
Soft tissue reconstruction (n = 30)				0.60
Free/local flap	24 (80%)	19 (83%)	5 (71%)	
Split Skin Graft only	6 (20%)	4 (17%)	2 (29%)	
Microbiology & antimicrobial therapy				
At least two phenotypically identical cultures	35 (96%)	112 (97%)	23 (92%)	0.29
Polymicrobial (n = 135) [2]	70 (52%)	55 (49%)	15 (65%)	0.16
Immediate start empiric IV antimicrobial therapy	9 (91%)	106 (91%)	23 (92%)	1.00
Duration IV antimicrobial therapy (days) (n = 129)	14.0 (10.0–21.0)	14.0 (10.0–20.3)	13.0 (10.0–21.0)	0.71
Total duration initial antimicrobial therapy (weeks) (n = 131)	12.0 (11.0–13.0)	12.0 (12.0–13.0)	12.0 (11.0–14.0)	0.99
Duration of admission				
Length-of-stay in hospital (days)	21.0 (13.5–31.5)	21.5 (14.0–31.0)	20.0 (13.0–38.0)	0.69
	Dichotomised variables: n (%)			
	Continuous variables: median (IQR)			

[1] Fracture-Related Infection.
[2] Polymicrobial infection was defined as the presence of at least two pathogens cultured from at least two cultures obtained during the operation [2].

Microbiology results

A total of 135 patients (96%) demonstrated at least two phenotypically identical cultures obtained during the operative intervention, the remaining six patients were diagnosed based on other confirmative criteria. Just over half of the patients with confirmatory positive cultures (52%, n = 70/135) had a polymicrobial FRI. Staphylococcus aureus, Staphylococcus epidermidis and Enterobacter cloacae complex were most frequently cultured in monomicrobial early onset FRI. Staphylococcus aureus and Staphylococcus epidermidis were also the most common causative pathogens in polymicrobial FRI. Furthermore, in comparison to the monomicrobial FRI group, Corynebacterium species, Enterococcus faecalis and Escherichia coli were more often detected in the polymicrobial group. An overview of the microbiology results is available in Appendix 2.

Clinical outcomes

The FRI recurrence rate at one year follow-up was 13% (n = 19). The overall recurrence rate in our cohort was 18% (n = 25) within a median follow-up of 23.1 months (IQR 15.3–36.4). In total, 122 patients (87%) had a follow-up of at least 12 months. A total of 19 patients (13%) did not complete the 12-month follow-up term because of discharge from follow-up after healing of the fracture and curation of the FRI (63% (n = 12/19)), death (none related to the FRI) (32% (n = 6/19)) or amputation of the affected limb (5% (n = 1/19)). These patients were not lost to follow up and were therefore included in this study. As per both hospital's policies, all patients who were discharged from follow-up received strict instructions to contact the treating centre in case of recurrence of symptoms. Overall infection control was achieved in 94% (n = 127/135) of cases, excluding deceased patients. Only 93 patients underwent imaging during follow-up, in this group complete fracture consolidation was seen in 65 patients (70%) at 12.0 months and 74 patients (80%) at 23.1 months. 19 patients (20%) did not achieve complete fracture consolidation. Consolidation rates were higher in the polymicrobial group (84%) compared to the monomicrobial group (72%). The median length-of-stay (LOS) in hospital after the diagnosis of FRI was 21.0 days (IQR 13.5–31.5) (Table 3). A total of 73 patients (52%) underwent at least two surgical procedures in order to treat the ongoing infection during the first presentation of early FRI (Table 4). The overall recurrence rate after completion of the surgical and antimicrobial treatment was 12% (n = 8/68) for patients who were treated with only one initial FRI procedure, 19% (n = 10/54) for patients with two to three surgical procedures and 41% (n = 7/17) for patients with four to five surgical procedures.

Table 4
Correlation of need for additional surgical procedures during the primary FRI [1] treatment plan and overall recurrence rate.

	All patients (n = 141)	Recurrence rate
Number of surgical procedures [2]		
1 procedure	68 (48%)	8 (12%)
2 to 3 procedures	54 (38%)	10 (19%)
4 to 5 procedures	17 (12%)	7 (41%)
6+ procedures	2 (1%)	0 (0%)
Total number of patients	141	25
	Dichotomised variables: n (%)	

[1] Fracture-Related Infection.
[2] Additional procedures are re-operations that can either be a washout and/or debridement procedure during the primary FRI treatment or a complete revision with exchange of implant after initial DAIR.

Risk factor analysis

A total of 32 variables were included in the univariate analysis (Table 5). One variable was statistically significant (p-value of <0.05), which was the need for additional washout and debridement procedures to treat the ongoing infection during the first presentation of early FRI (p = 0.033). Four additional variables demonstrated a p-value of <0.10, which were a decreased ISS (p = 0.054), a tibia/fibula fracture (p = 0.073), a Gustilo-Anderson grade 3 open fracture (p = 0.078) and use of an intramedullary nail during the index operation (p = 0.097). The five aforementioned variables were included in the multivariate logistic regression analysis. Overfitting was taken into account, due to the number of variables with a p-value <0.10, adjustment of this p-value was not required. Other variables were not eligible for inclusion in this analysis due to their insignificant value.

The multivariate logistic regression was executed with the five aforementioned variables, which are need for additional surgical procedures, a decreased ISS, tibia/fibula fracture, a Gustilo-Anderson grade 3 fracture and use of an intramedullary nail. After a backward selection of the variables with a p-value >0.05 ((Gustilo-Anderson grade 3 fracture (OR 1.4 (95% CI 0.4–4.8), p = 0.55) and (tibia/fibula fracture (OR 1.9 (95% CI 0.7–5.1), p = 0.21))), only three variables with a p-value <0.05 remained, which were the use of an intramedullary nail during the index

Table 5
Univariate analysis of predictors for recurrent FRI [1].

	OR (95% CI) [2]	p-value
Patient- and fracture characteristics		
Sex (male)	1.0 (0.4–2.5)	0.98
Age (years)	1.0 (1.0–1.0)	0.74
Body Mass Index (kg/m²)	1.0 (0.9–1.1)	0.73
ASA classification [3]	0.7 (0.4–1.3)	0.21
Fracture location		
Humerus/clavicle/scapula/chest	0.6 (0.1–4.7)	0.60
Forearm	0.0 (0.0–0.0)	1.00
Femur	0.7 (0.2–2.3)	0.60
Tibia/fibula	2.3 (0.9–5.6)	0.073
Pelvis	1.1 (0.3–3.6)	0.86
Foot	0.0 (0.0–0.0)	1.00
Open fracture	0.5 (0.2–1.3)	0.19
Gustilo-Anderson classification		
Grade I	1.6 (0.2–15.7)	0.70
Grade II	0.5 (0.1–4.1)	0.52
Grade III	2.4 (0.9–6.4)	0.078
Injury Severity Score (per point decrease)	1.1 (1.0–1.1)*	0.054
Implant used at index operation		
Dynamic Hip Screw or similar	0.0 (0.0–0.0)	1.00
G-nail, PFNA [4] *or similar*	1.4 (0.4–5.7)	0.60
Intramedullary nail	2.5 (0.8–7.4)	0.097
Plate	0.8 (0.3–1.9)	0.60
Screws or K-wires	0.0 (0.0–0.0)	1.00
External fixation as definite treatment	4.8 (0.3–79.3)	0.27
Implant removal only	0.0 (0.0–0.0)	1.00
External fixation before index surgery	1.1 (0.4–3.0)	0.85
Risk factors and comorbidities		
Diabetes mellitus	0.6 (0.1–2.7)	0.50
Obesity	1.1 (0.4–2.9)	0.84
Smoking	0.6 (0.2–1.6)	0.29
Drugs	0.0 (0.0–0.0)	1.00
Alcohol abuse	0.0 (0.0–0.0)	1.00
FRI and operation characteristics		
Soft tissue reconstruction	1.9 (0.3–13.5)	0.52
Need for additional surgical procedures	1.8 (1.0–3.2)	**0.033**
Microbiology & antimicrobial therapy		
Polymicrobial	1.9 (0.8–4.9)	0.16
Immediate start empiric IV antimicrobial therapy	0.9 (0.2–4.5)	0.92

[1] Fracture-Related Infection.
[2] Odds Ratio and 95% Confidence Interval.
[3] American Society of Anaesthesiologists.
[4] Proximal Femoral Nail Antirotation.
* Inverted Odds Ratio.

Table 6
Multivariate analysis of predictors for recurrent FRI [1].

	OR (95% CI) [2]	p-value
Selected patients (n = 122)		
Need for additional surgical procedures	1.9 (1.1–3.5)	**0.029**
Use of an intramedullary nail	4.0 (1.1–13.8)	**0.030**
Injury Severity Score (per point decrease)	1.1 (1.0–1.1)*	**0.040**

[1] Fracture-Related Infection.
[2] Odds Ratio and 95% Confidence Interval.
* Inverted Odds Ratio.

operation (OR 4.0 (95% CI 1.1–13.8), p = 0.030), the need for additional washout and debridement procedures during the first presentation of early FRI (OR 1.9 (95% CI 1.1–3.5), p = 0.029) and a decreased ISS (inverted OR 1.1 (95% CI 1.0–1.1), p = 0.040) (Table 6).

Discussion

In our study, the FRI recurrence rate in patients with early onset FRI treated with a DAIR procedure was 13% and 18% after a median of 12.0 and 23.1 months, respectively. Overall infection control was achieved in 94% of cases. A total of 73 patients (52%) underwent at least two surgical procedures in order to treat the ongoing infection during the first presentation of early FRI. The recurrence rate significantly correlated with the use of an intramedullary nail during the index operation, the need for additional surgical procedures and a decreased ISS. It is important to realise that this study does not provide information on the development of FRI. This study focuses on infection control, ongoing infection and recurrence rate after treatment of early onset FRI in patients who underwent a DAIR procedure. It is, to our knowledge, one of the first studies that focuses on the expected course of this disease in this subgroup of patients. Factors that may have contributed to the overall recurrence rate of 18%, as well as the need for additional surgical procedures in 52% of cases will be discussed along with the results of the multivariate analysis.

The recurrence rate in the present cohort demonstrated to be in line with the majority of recent literature, reported between 8%–43% [12,25,26]. However, it is difficult to exactly compare the results of those studies with our study, especially due to the differences between study populations. In addition, neither of these studies focuses on the early onset FRI population. This allows us to consider the outcomes of our study, in particular with regard to the recurrence rate and the number of surgical procedures, as new data for early onset (<6 weeks) FRI. In our study, a cut-off of 6 weeks was preferred over the classification of Willenegger et al. where FRI are divided in early (≤2 weeks), delayed (3 to 10 weeks) and late onset (>10 weeks) infections [5]. This preference was related to the fact that UMCU and UMCG guidelines use an arbitrary cut-off of 6 weeks for the treatment of early FRI [3].

In our multivariate analysis, the use of an intramedullary nail during the index operation, the need for additional surgical procedures and a decreased ISS remained significant independent predictors for recurrent FRI. Firstly, the use of an intramedullary nail was a significant predictor of recurrence (OR 4.0) in this cohort of early FRI patients treated with a DAIR procedure. This can also be explained by the fact that it is more challenging to adequately debride the medullary canal when the implant remains in situ [11]. This observation is confirmed by the findings of Berkes et al. in their study regarding predictors for recurrent FRI in early FRI patients, in which an intramedullary nail was also identified as a predictor of recurrent FRI [27].

Secondly, the recurrence rate increased in relation to the number of surgical procedures that were needed to control the infection after the initial FRI operation (12% for one procedure vs. 19% for two to three procedures vs. 41% for four to five procedures). This finding is not surprising as it is understandable that more severe infections have a higher risk of incomplete debridement in a DAIR procedure, which could consequently lead to the need for additional surgical procedures and development of recurrent FRI.

Lastly, when considering the ISS, it shows that the recurrence rate for patients with an ISS of <16 was 25%, for an ISS of 16–24 16% and for an ISS of >24 9%, respectively. This implies that a lower ISS is associated with a higher FRI recurrence rate. Previous studies demonstrated an opposite correlation between lower ISS and the occurrence of both FRI and recurrent FRI [28,29], so this finding is remarkable. An explanation for the higher recurrence rate in patients with a lower ISS in our cohort might be that there were more tibia/fibula fractures in the group with an ISS of <16 (52% ISS <16 vs. 32% ISS ≥16). Although these injuries are commonly present in low-energy injuries [30], they often have a challenging soft tissue status which makes them prone for the development of FRI [26]. It is possible that this influenced the results of the multivariate risk factor analysis in which the ISS was the dominant overlapping parameter. An alternative hypothesis is that the association between an increase in ISS and a lower recurrence rate might be related to the altered immune response of polytrauma patients, although underlying mechanisms need to be further elucidated [31–33]. In addition, it can be hypothesised that severely injured patients receive antimicrobial therapy more

frequently during the course of their overall treatment for other infections [34] which might have acted as suppressive antibiotic therapy in case of FRI.

The diagnosis FRI was confirmed by the presence of one of the confirmatory consensus criteria, including two phenotypically identical pathogens in deep tissue/implant samples taken during the operative intervention [13]. This criterion was met by 96% of all patients in our study, the remaining 4% of patients were diagnosed based on other confirmatory FRI criteria alone. The top three pathogens in our study, Staphylococcus aureus, Staphylococcus epidermidis and Enterobacter cloacae complex, are in accordance with the literature [35,36].

After the operative intervention, 91% of the patients were immediately started on empiric broad spectrum IV antimicrobial therapy. Empiric therapy was replaced by targeted antimicrobial therapy when culture results and antibiogram were available and, as per protocol, continued for a total duration of 12.0 weeks. The total duration of the antimicrobial treatment in our study was in line with the recommendations of the Fracture-Related Infection Group [6,15] and the Dutch FRI Guideline and common practice in both study centres [3]. The percentage of patients with immediate start of IV antibiotics should ideally be higher in case of FRI suspicion [6], yet in our cohort this was possibly influenced by the assumed absence of clinical signs of infection during the FRI operation in several patients. Furthermore, intravenous antimicrobial therapy was given for an average of 14.0 days, which was in accordance with the FRI treatment protocols at that time [11]. Results of the Oral versus Intravenous Antibiotics for Bone and Joint Infection (OVIVA) trial have affected the average duration of IV antimicrobial therapy due to an earlier switch to oral antimicrobial therapy after publication of that study [37]. The duration of administration of IV antibiotics was adapted in the UMCU on April 15th 2019, which reduced the use of IV antibiotics with a median of 2.0 days in this specific subgroup.

Complete fracture consolidation was seen in 65 of the 93 patients who underwent radiographic follow-up (70%) at 12 months and was achieved in 74 patients (80%) overall. These numbers are similar to the results of Müller et al., where fracture consolidation was achieved in 74% of patients nine months after soft tissue reconstruction due to FRI [38]. Their study identified polymicrobial infection as a possible risk factor for the absence of fracture consolidation [38]. In the present cohort, this finding was not confirmed as higher consolidation rates were seen in the polymicrobial group (84%) in comparison with the monomicrobial group (72%). It is possible that incomplete fracture consolidation is potentially caused by the presence of a low-grade (chronic) infection in patients without clinical signs of infection. This was demonstrated by recent research of Hackl et al., in which time to complete fracture consolidation was significantly increased in patients with low-grade infection [39].

This study is subject to several limitations. First, due to the retrospective nature of this study, there may be selection bias and missing data. Patients were selected after the outcome was known, therefore the results may not apply to the entire early onset FRI population treated with a DAIR procedure. However, selection bias is thought to be limited due to the use of consecutive patients. In addition, 87% of patients had a follow-up duration of at least 12 months and follow-up data was regularly updated during the course of this study. Secondly, the sample size of this cohort may be considered limited. Nevertheless, this is one of the largest series evaluating risk factors and treatment outcome of early onset FRI. Lastly, with this being a multicentre study, it is possible that the centres differed in both fracture- and infection treatment. However, due to the use of the same national guidelines and standardised protocols [3], this difference is also thought to be minor.

In conclusion, results of this study can be used for management and preoperative counselling of early onset FRI patients. Patients can be informed that a recurrence rate of 13% at one year follow-up and an overall recurrence rate of 18% were seen in our cohort. At least two surgical procedures to gain control of the initial infection were needed in 52% of patients. Independent predictors for developing recurrent FRI were the use of an intramedullary nail during the index operation, need for additional surgical procedures and a decreased ISS.

Declarations of Competing Interest

The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. The authors declare that they did not receive funding for this study.

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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.2022.10.017.

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