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The effect of guideline-based antimicrobial therapy on the outcome of fracture-related infections (EAT FRI Study)

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SUMMARY

Aim: This study investigated the compliance with a guideline-based antibiotic regimen on the outcome of patients surgically treated for a fracture-related infection (FRI).

Method: In this international multicenter observational study, patients were included when diagnosed with an FRI between 2015 and 2019. FRI was defined according to the FRI consensus definition. All patients were followed for at least one year. The chosen antibiotic regimens were compared to the published guidelines from the FRI Consensus Group and correlated to outcome. Treatment success was defined as the eradication of infection with limb preservation.

Results: A total of 433 patients (mean age 49.7 ± 16.1 years) with FRIs of mostly the tibia (50.6%) and femur (21.7%) were included. Full compliance of the antibiotic regime to the published guidelines was observed in 107 (24.7%) cases. Non-compliance was mostly due to deviations from the recommended dosing, followed by the administration of an alternative antibiotic than the one recommended or an incorrect use or non-use of rifampin. Non-compliance was not associated with a worse outcome: treatment failure was 12.1% in compliant versus 13.2% in non-compliant cases ($p = 0.87$).

Conclusions: We report good outcomes in the treatment of FRI and demonstrated that minor deviations from the FRI guideline are not associated with poorer outcomes.

Introduction

Fracture-related infection (FRI) can be a devastating complication of musculoskeletal trauma, often requiring multiple surgeries and long-term antibiotic treatment. They pose a unique problem in orthopedic infections due to soft tissue defects and the risk of impaired bone healing. Recently, much progress has been made in defining FRI and in developing an evidence-based approach to managing these complex infections.[1–7] Comprehensive guidelines have been published by the FRI consensus group in which, amongst others, recommendations on antibiotic treatment have been made according to the isolated pathogen.[5] In addition, the use of antibiotics demonstrated in animal and/or *in-vitro* models to be more active against bacterial biofilms is recommended in cases where metal implants are retained (i.e. rifampin based regimens for staphylococci and fluoroquinolones for Gram negatives[8,9]). However, most recommendations made by the FRI Consensus Group[5] are expert opinion and are mainly extrapolated from the treatment of periprosthetic joint infections. Since FRI encompasses unique features of complexity of infection, validating these recommendations is of utmost importance. For example, although rifampin has been shown to be effective against staphylococcal infections in orthopedic devices,[8] its use can potentially be associated with the development of resistance in FRI. To date, experts in the field advise that rifampin is withheld until drains are

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removed and the wound is dry to limit the emergence of resistance.[9] Likewise, the selection of rifampin resistance may occur in FRI patients with severe soft tissue defects due to the selection of rifampin resistant strains on the surface. In addition, in contrast to prosthetic joints, a metal device that has been implanted in case of a fracture can be removed after fracture healing. All of these factors should be taken into account when choosing the optimal antibiotic regimen. Therefore, the aim of this study was to evaluate whether compliance with the recommendations on antibiotic treatment made by the FRI Consensus Group was associated with a higher treatment success in patients with confirmed FRI.

Materials and methods

Patient population

Patients treated for FRI between 1st January 2015 and 31st December 2019 at one of the three participating centers (Nuffield Orthopaedic Centre, University Medical Center Groningen, University Medical Center Utrecht) were retrospectively evaluated. Ethical approval was obtained or waived by the participating centers (waiver 20-004/C). Patients were eligible for inclusion if they received appropriate operative treatment for FRI, as defined by the treating trauma surgeon, had at least three surgically obtained deep tissue samples taken at the time of infection surgery[11] and had a minimum follow up of at least one year with documentation of clinical outcome. For all patients, antibiotic therapy had been stopped at least two weeks before sampling, as long as it was safe to do so. FRI was defined according to the FRI Consensus definition.[2,3] Clinical confirmatory criteria included the presence of a fistula or sinus tract, pus and/or wound breakdown to the bone or implant. Surgical confirmatory criteria included pus around the fracture, isolation of phenotypically indistinguishable organisms from two or more deep tissue samples or positive histology (>5 neutrophils per high power field at 400x magnification or microscopically visible microorganisms). Patients with and without a fixation device were included. The presence of fixation was defined as any type of internal fixation (nails, plates and including screws and wires), or external fixation.

Definition of causative pathogen

As per the FRI Consensus definition, any phenotypically distinct microorganism isolated from two or more surgically obtained deep tissue specimens were considered both diagnostic of FRI and classified as causative pathogen.[2,3] When the definition of FRI was met based on other non-microbiological criteria, then an uncommon contaminant isolated from a single deep tissue specimen was considered as the causative pathogen. The following microorganisms were considered as uncommon contaminants by the expert opinion of infectious disease specialists and medical microbiologists: *Staphylococcus aureus, Staphylococcus lugdunensis,* Beta-haemolytic Streptococci, *Streptococcus anginosus* group, *Enterococci* spp., Enterobacterales, *Pseudomonas aeruginosa*, Anaerobic gram-negative rods and *Candida* spp. Similarly, infections were described as polymicrobial if two or more pathogens or single positive cultures from an uncommon pathogen meeting either of the above criteria were isolated from surgically obtained deep tissue samples. Cultures from superficial samples or swabs were not considered.

Definition of outcome

Treatment failure was defined as recurrence of infection and/or limb amputation after surgery. Clinical failure was defined as the presence of any of the following: i) recurrence of infection (fulfilling FRI definition), ii) unplanned surgery outside the period of the definitive surgery for infection or skin coverage, iii) an unhealed wound or discharge from the surgical site beyond three months after the period of definitive surgery, iv) commencement of further antibiotic therapy for infection related to the surgical site (other than for external fixator pin site infection) after the initial planned antibiotic regime has stopped. Three surgical specialists (xxx), all experienced FRI surgeons, assessed each patient individually to determine the outcome. Any case that was doubted was resolved in consensus.

Compliance to antibiotic treatment recommendations

Four infectious disease specialists or microbiologists (xxx), with no access to data regarding outcome, assessed each targeted antibiotic regime per pathogen against the recently published FRI Consensus document.[5] Non-compliance to the guidelines was preassigned as a major or minor deviation by agreement between the authors of this study, including a member of the original Consensus Group with no involvement in data collection or analysis (MD). Deviations were considered as major deviations, unless they were classified as minor as described in Appendix 1. Data regarding the use of a biofilm active antibiotic (rifampin for staphylococci and a fluoroquinolone for Gram negative rods) together with the presence or absence of a metal fixation device was also collected. In case of a polymicrobial infection, the overall regimen was considered non-compliant if any of the isolated causative pathogens was not treated according to the guideline. In addition, the overall regime was marked as appropriate or inappropriate, based on available susceptibility reports and the expertise of the microbiologist and infectious disease specialist. Compliance was only evaluated in relation to the type and dose of antimicrobial treatment. The antibiotic duration was routine practice in the participating centers. The majority of patients in which the implant was retained received 3 months of antibiotic treatment and patients without an implant 6 weeks.

Statistical analysis

Continuous variables were presented as mean and standard deviation (SD) or as median and interquartile range (IQR) when not normally distributed. A Chi-square test was used to analyse the difference between groups for categorical variables, and a student t-test (or Mann-Whitney U test when data was not normally distributed) for continuous variables. Logistic regression analysis was performed to identify independent predictors for treatment failure. Variables with a difference between groups, defined as a p-value < 0.1 in the univariate analysis were included in the multivariate analysis. Statistical significance was defined as a two-tailed p-value <0.05. Statistical analyses were performed using IBM SPSS Statistics (version 24.0; Chicago, IL, USA).

Results

Patient population

A total of 433 FRI cases were included. Most patients were male (73.4%), and the mean age of the cohort was 49.7 years (± 16.1 SD). The tibia was the most affected bone in 50.6% of cases, followed by the femur in 21.7%. *Staphylococcus aureus* was the most commonly isolated microorganism (45.5%). The infection was polymicrobial in 35.6% and culture negative in 18.5% of cases. A metal fixation device was present in 326 cases, in which the infected implant was debrided and retained in 42%. A total of 58% of patients were treated with local antibiotics incorporated into a carrier. Treatment failure was observed in 59 (14%) and clinical failure in 146 cases (33.7%). The mean follow up period was 26 months (±

Table 1
Patient characteristics according to treatment failure and clinical failure.

Variable	Treatment success (N=374)	Treatment failure (N=59)	P-value	Clinical success (N=287)	Clinical failure (N=146)	P-value
Age (mean ± SD)	49.9 ± 16.4	48.2 ± 13.9	0.46	50.4 ± 16.3	48.3 ± 15.7	0.21
Male sex	72.2%	81.4%	0.14	73.9%	72.6%	0.78
BMI (mean ± SD)	27.5 ± 5.8	27.4 ± 5.7	0.59	27.3 ± 5.8	27.8 ± 5.8	0.46
Current smoking	22.5%	47.5%	**< 0.001**	23.0%	32.0%	0.06
Diabetes mellitus	10.4%	13.6%	0.47	9.4%	13.7%	0.18
Immunosuppressant use	3.8%	5.1%	0.63	3.5%	4.8%	0.51
Diagnostic criteria						
Sinus tract	53.1%	41.4%	0.10	51.0%	52.4%	0.79
Wound breakdown to bone or implant	13.9%	15.3%	0.78	13.9%	14.4%	0.90
Purulence	36.9%	42.4%	0.42	36.6%	39.7%	0.52
> = 2 specimens culture positive	75.4%	86.4%	0.06	76.3%	78.1%	0.68
Positive histopathology	69.8%	82.4%	0.27	70.7%	70.6%	0.99
Bone						
Tibia	48.8%	62.7%	0.05	49.5%	53.1%	0.48
Femur	21.7%	22.0%	0.96	21.3%	22.8%	0.72
Pelvis	7%	0%	**0.04**	7.7%	2.8%	**0.04**
Fibula	3.2%	1.7%	0.53	2.1%	4.8%	0.12
Humerus	5.4%	0%	0.07	5.6%	2.8%	0.19
Radius/ulna	6.4%	3.4%	0.36	5.9%	6.2%	0.91
Most common isolated microorganisms						
Staphylococcus aureus	44.1%	54.2%	0.15	44.3%	47.9%	0.47
Coagulase negative staphylococci	18.7%	20.3%	0.77	20.6%	15.8%	0.23
Streptococci	9.6%	10.2%	0.90	10.1%	8.9%	0.69
Enterococci	10.4%	11.9%	0.74	10.1%	11.6	0.62
Corynebacterium species	5.3%	6.8%	0.66	4.9%	6.8%	0.40
Enterobacter species	6.4%	5.1%	0.69	7.3%	4.1%	0.19
Pseudomonas aeruginosa	7.5%	1.7%	0.10	6.6%	6.8%	0.93
Escherichia coli	5.9%	8.5%	0.44	5.9%	6.8%	0.71
Polymicrobial	33.2%	50.8%	**0.008**	34.8%	37.0%	0.66
Culture negative	19.8%	10.2%	0.07	18.5%	18.5%	0.99
Surgical approach						
Internal fixation with metal work	34.9%	54.2%	**0.004**	33.6%	45.2%	**0.02**
Fixateur externe	0.8%	6.8%	**0.001**	0.3%	4.1%	**0.003**
Muscle flap	29.4%	23.7%	0.37	28.9%	28.1%	0.86
VAC dressing	12.0%	32.2%	**< 0.001**	11.8%	20.5%	**0.02**

12 SD). Table 1 shows the patient characteristics of the total cohort according to treatment failure and clinical failure. Logistic regression analysis identified smoking, having a polymicrobial infection, the use of fixation with metal work and the use of Negative Wound Pressure Therapy (NWPT) as predictors for failure.

Compliance towards the antibiotic treatment recommendations

The chosen antibiotic regimen was compared with the recommendations made by the FRI Consensus group. Full compliance was observed in 24.7% (107/433). When excluding minor deviations from the protocol (Appendix 1), compliance was observed in 36.3% (157/433) of cases. In 57% of these non-compliant cases (157/276), the antibiotic regimen was still considered appropriate for the treatment of FRI as judged by the expert panel. Full compliance to the regimen was observed in 25.2% of the monomicrobial cases (69/274) and in 25.2% of the polymicrobial cases (38/151) ($p = 1.000$).

Table 2 shows the most common reasons for non-compliance per isolated pathogen. Non-compliance was mostly due to a deviation from the recommended dosing in around half of the cases, followed by the administration of an alternative antibiotic than the one the FRI Consensus Group guideline recommended or an incorrect use or non-use of rifampin. Also, systemic antibiotic treatment was withheld in some cases that fulfilled the diagnostic criteria for FRI. Non-compliance to the recommendations was most often observed in culture negative cases, in which not administering rifampin was the main cause of non-compliance. The other main pathogens in which non-compliance was observed were *S. aureus*, Gram positive anaerobes and penicillin resistant enterococci.

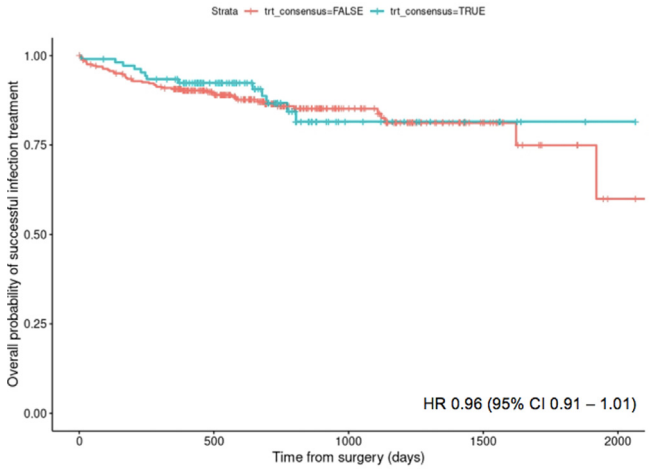

Fig. 1. Treatment success according to antibiotic treatment compliance.
Kaplan Meier curve depicting the treatment success according to full compliance (=TRUE, blue line) compared to non-compliance (=FALSE, red line).

Outcome in relation to compliance antibiotic treatment recommendations

Fig. 1 and Fig. 2 show the treatment success and clinical success in relation to compliance towards the FRI antibiotic treatment recommendations. In all analyses, no relation between compliance and outcome was observed (Fig. 1, Fig. 2A and 2C). We additionally

Table 2
Non-compliance and outcome on pathogen level.

Pathogen involved	n	% full compliance	% compliance excluding minor deviations	Reasons major deviations	Treatment failure	Clinical failure
Methicillin susceptible Staphylococcus spp.	211	37%	52%	34% Dosing clindamycin too low (450mg TID) 16% Dosing ciprofloxacin too high (750mg BID) 11% Beta-lactam os oral regimen 10% Rifampin not administered while metal work *in situ* 5% No antibiotic treatment 4% Ceftriaxon as IV beta-lactam 4% Rifampin combined with linezolid 16% Other reasons	17%	37%
Methicillin resistant *Staphylococcus aureus*	11	18%	82%	50% Dosing clindamycin too low (450 mg TID) 50% Rifampin combined with fusidic acid	8%	17%
Coagulase negative staphylococci	69	43%	67%	30% Dosing clindamycin too low (450mg TID) 17% No antibiotic treatment 5% Rifampin combined with linezolid 5% Dosing ciprofloxacin too high (750mg BID) 30% Other reasons	12%	27%
Streptococcus spp.	46	59%	61%	39% Dosing amoxicillin too low (500mg TID) 17% Moxifloxacin as oral regimen 5% Linezolid as oral regimen 5% No antibiotic treatment 33% Other reasons	16%	34%
Enterococcus spp. (penicillin susceptible)	33	61%	64%	42% Dosing amoxicillin too low (500mg TID) 23% A different antibiotic choice (vancomycin, levofloxacin or cotrimoxazole) 33% Other reasons	19%	42%
Enterococcus spp. (penicillin resistant)	13	46%	54%	33% Rifampin used for enterococci 33% A different antibiotic choice (tetracyclin) 17% No antibiotic treatment 17% Dosing vancomycin too low	8%	31%
Enterobacteriaceae	105	53%	68%	40% Another oral regimen than ciprofloxacin or levofloxacin 19% Use of rifampin 13% Use of moxifloxacin 6% No antibiotic treatment 22% Other reasons	12%	26%
Non fermenters	34	88%	88%	25% Dosing of ciprofloxacin too low 25% Ciprofloxacin prematurely ended do to long QT interval 25% No antibiotic treatment 25% Other reasons	3%	32%
Gram positive anaerobes	51	24%	39%	74% Another oral regimen chosen 10% No antibiotic treatment 6% Dosing amoxcillin too low 10% Other reasons	21%	31%
Gram negative anaerobes	10	60%	60%	75% Another oral regimen chosen 25% Dosing clindamycin too low	10%	20%
Culture negative	80	0%	10%	67% No rifampin 26% Another oral regimen chosen (including rifampin) 7% No antibiotic treatment	8%	34%

analyzed whether an "appropriate antibiotic regimen" as judged by the expert panel was associated with a higher treatment or clinical success, but also in these analyses, no statistically significant associations were found: treatment failure was 14.2% in appropriate regimens versus 12.1% for inappropriate regimens ($p = 0.56$) and clinical failure was 36.2% in appropriate regimens versus 27.4% for inappropriate regimens ($p = 0.08$) (Fig. 2C and 2D). For cases who did not receive any targeted systemic antibiotic treatment despite being diagnosed with FRI, treatment failure was higher compared to those who did receive targeted antibiotic treatment (30.4% [7/23] versus 12.7% [52/410]) respectively, $p = 0.016$). Most of these cases (67%) did not receive local antibiotics.

Fig. 3 shows the treatment success according to the administration of antibiofilm agents (rifampin for staphylococci and fluoroquinolones for Gram negative rods) in cases with a retained metal fixation device. No significant benefit on outcome was found. For staphylococci (n = 291), treatment failure was 19.6% in cases treated with rifampin versus 17.6% in cases in whom this was withheld ($p = 0.85$). Clinical failure was 40.2% versus 52.9%, respectively ($p = 0.33$). When excluding cases treated with NWPT ($n = 44$), no difference in outcome was found in staphylococcal cases treated with rifampin versus no rifampin (data not shown). For Gram-negative rods (n = 139), treatment failure was 10.7% in cases treated with ciprofloxacin versus 0% in cases where this was withheld ($p = 0.49$). Clinical failure was 17.9% versus 50.0%, respectively ($p = 0.15$).

Discussion

Although the current antibiotic FRI recommendations are valuable and provide practical guidance in FRI treatment, particular for centres less experienced in managing FRI, we demonstrated in a large cohort of 433 FRI cases, that some deviations from the recommendations were not associated with a worse clinical outcome. It must be noted that all three participating centers are experienced in the treatment of FRI, and all included patients received appropriate surgical treatment as judged by the participating trauma surgeons. All centers also had the benefit of dedicated

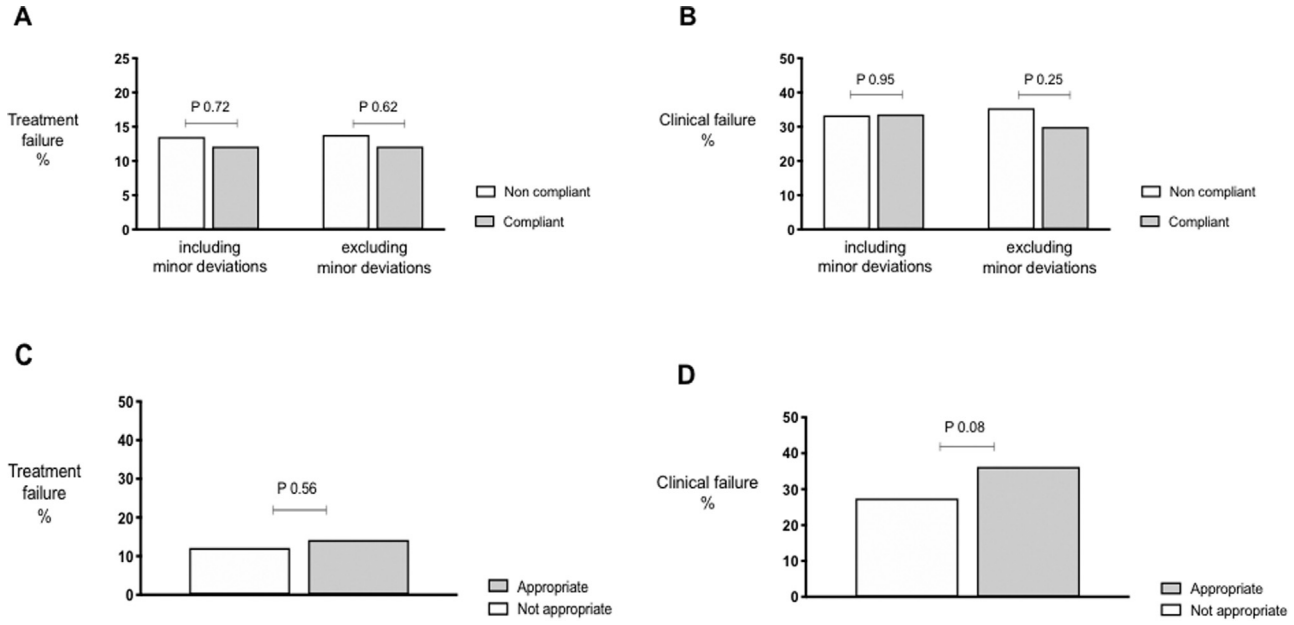

Fig. 2. Failure according to compliance and appropriateness of antibiotic therapy.
Treatment failure (A, C) and clinical failure (B, D) according to the compliance to the FRI antibiotic treatment guideline recommendations (A, B) and appropriateness of antibiotic therapy (C, D) according to the expert panel.

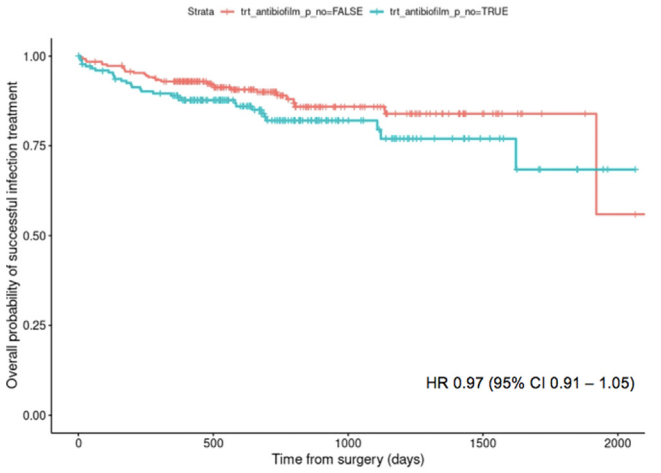

Fig. 3. Treatment success according to the use of antibiofilm agents.
Kaplan Meier curve depicting the treatment success according to the use of antibiofilm agents (=TRUE, blue line) compared to not using antibiofilm agents (=FALSE, red line).

infection specialists (infectious disease specialists and/or microbiologist) with an interest in orthopedic infections.

Our data do suggest that, when appropriate surgery is performed, i.e. adequate debridement, removal of sequestra, dead space management, fracture stabilization and soft tissue closure, the role of continuing systemic antibiotics may be less important.[12–14] Indeed, several studies indicate that, in particular thorough surgical debridement,[15] dead space management and adequate soft tissue coverage are the most important pillars that determine infection outcome.[16] These findings are reflected in recent and ongoing trials indicating that an early switch to oral antibiotics and a shorter duration of systemic antibiotic treatment is probably justified when adequate surgery has been performed.[17,18] It has been shown in small series that adequate surgery and the use of local antibiotics may suffice and that the addition of systemic antibiotics may be redundant in selected cases.[19–22] Although the withholding of systemic antibiotics in a subset of patients in our cohort was associated with a worse outcome, only a minority of them received local antibiotics. The majority of patients in our cohort did receive local antibiotics. These findings, together with details on surgical techniques in relation to outcome, should be investigated in detail in future analyses.

In addition to the importance of appropriate surgical treatment, another explanation for the lack of relationship between compliance to the antibiotic treatment recommendations and outcome is that, although marked as major deviations, some major deviations can be considered as more relevant than others. For example, administration of an insufficient oral dose of antibiotics or no antibiotics at all, can be considered as a much more important deviation than the administration of a higher than recommended dose (with the risk of toxicity and side effects) or the use of an alternative antibiotic with sufficient bioavailability and bone penetration. In addition, dosing may be adjusted in patients with a lower bodyweight (e.g. for example in case of clindamycin). The balance between dosing' efficacy and adverse drug effects, and knowledge of the pharmacodynamics and kinetics of the chosen regimen requires expertise and underlines the importance of an experienced team in the treatment of FRI.

We performed a separate analysis in which we evaluated whether the use of "classical" antibiofilm antibiotics (i.e. rifampin for staphylococci and fluoroquinolones for Gram negatives) was associated with a better outcome in patients with retained metal devices. Although clinical failure was 12.5% higher in staphylococcal cases not treated with rifampin, this difference was not statistically significant. The clinical benefit of antibiofilm agents (according to *in vitro* data) is still a matter of debate, even in the treatment of periprosthetic joint infections despite many observational studies demonstrating its benefit.[8–10,23,24] This study shows lack of definite benefit in FRIs. Possible explanations could be that surgical reduction of the biofilm burden can be better achieved in long bones compared to joints or that a large proportion of patients in our study received local antibiotics, circumventing the need for additional antibiofilm agents by already achieving high doses lo-

cally. This high local elution of antibiotics might be able to exceed the minimum inhibitory concentration (MIC) or even the minimum biofilm eradication concentration (MBEC).[25–27]

Our study should be viewed in the light of certain limitations. First, the FRI Consensus treatment recommendations were recently published and compliance towards these recommendations was analyzed in retrospect. Second, as indicated above, although some deviations from the protocol were classified as major deviations, the clinical relevance of these deviations can be debated. Third, we did not take antibiotic treatment duration into account. When patients are treated with a shorter duration of systemic antibiotic treatment (i.e. less than 6 weeks), then the type of systemic antibiotics may become more important. However, the evidence around duration of therapy in FRI is very limited. Fourth, in case of a polymicrobial infection, the regimen was considered as non-compliant if one antibiotic was not according to the recommendation made per pathogen. Despite this limitation, we did not find any differences in outcome between mono- and polymicrobial infections. Fifth, the minimum follow-up in our study was 1 year. However, mean follow-up was over two years (26 months) and most recurrences can be expected within the first two years.[28] Finally, for some pathogens, no recommendations are made by the FRI guidelines and therefore, could not be evaluated. The most common isolated microorganisms for which no recommendation is available are Corynebacterium species.

In conclusion, our data suggest that strict compliance to the FRI recommendations is not mandatory if antibiotic treatment is advised by a team experienced in the treatment of FRI and if appropriate surgery has been performed.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2023.01.028.

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