Fracture-Related Infection – What Does the Literature Tell Us?

Infección asociada a fractura ¿Qué nos dice la literatura?

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Abstract

Fracture-related infection (FRI) is one of the most frequent and challenging complications of orthopedic trauma; however, its importance has been underestimated. Historically, there has been a lack of standardization in its management. Nevertheless, the available scientific evidence has increased in recent years, given multiple clinical guidelines and expert consensus. This review aims to provide an update for orthopedic trauma surgeons to standardize diagnostic and treatment criteria based on recent scientific evidence.

Keywords
- fracture
- infection
- diagnosis
- treatment

Resumen

La infección asociada a fracturas (IAF) es una de las complicaciones más frecuentes y desafiantes del trauma ortopédico, sin embargo, su importancia ha sido subestimada existiendo históricamente una falta de estandarización en su manejo. En los últimos años la evidencia científica disponible ha ido en aumento, y a consecuencia de ello múltiples guías clínicas y consensos de expertos han sido publicados.
El objetivo de este trabajo es proporcionar una actualización, dirigida principalmente a especialistas en Ortopedia y Traumatología, buscado estandarizar criterios diagnósticos y de tratamiento basado en evidencia científica reciente.

Palabras clave
- infección
- fractura
- diagnóstico
- tratamiento

Introduction

Fracture-related infection (FRI) is one of the most significant complications of orthopedic trauma. It has substantial differences compared to other infectious conditions. The presence of osteosynthesis material to provide the required stability for bone consolidation makes FRI a challenge from its diagnosis to treatment.

Despite advances in prevention measures in recent decades, the incidence of this complication remains high,[1,2] and reported successful treatment rates range from only 70 to 90%.[3,4] FRI results in critical sequelae and represents a considerable global socioeconomic problem.[5,6] However, the real impact of this complication is difficult to estimate due to the lack of a clear definition and diagnostic criteria standardization. In a recent systematic review, Metsemakers

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et al. demonstrated significant variability in the criteria for FRI definition. Metsemakers et al. reported that only 2% of the total randomized controlled studies published to date used a validated definition for FRI diagnosis, 27% used an arbitrary definition created by the authors themselves, and the remaining works did not present any definition.[7]

The lack of rigor in FRI diagnosis has made it difficult to evaluate any result and properly compare different treatments when giving recommendations with a high evidence level. As such, recent years saw an increase in the number of scientific publications on this topic, highlighting several consensuses and expert recommendations.[8–12]

Definition

In 2018, a group of experts from different parts of the world published, based on current evidence, a proposed definition of FRI using a methodology similar to that described by Cats-Baril et al. for periprosthetic infection (PPI).[8,13] Their goal was to provide a tool allowing clinical study standardization and improving the available evidence quality.

This consensus unanimously decided there should be a single definition of FRI without subdivisions regarding time (acute or chronic infection), anatomical location, or infection depth (superficial or deep). This decision has two reasons. First, a potential subdivision would make such a definition unnecessarily complex and difficult to use in daily practice. Second, the classifications described in the literature to date are based mainly on progression time and define deadlines arbitrarily.[14,15]

Infections are acute or chronic, potentially requiring different treatment strategies. However, this should not affect how physicians define FRI.[8]

On the other hand, experts recognize superficial infections may not have any relation with the fracture or the implant. Nonetheless, they understand that the definition of the superficial nature of an infection can only occur retrospectively and cannot guide the treatment.[8] Therefore, for definition (and data collection), surgeons must determine the presence of infection, not its extent, location, or classification.[8,16]

Diagnosis

Two systematic reviews analyzing clinical, laboratory, and imaging features from FRI based on which criteria to determine its diagnosis.[7,17]

For Metsemakers et al., some of these criteria may provide definitive proof of infection, while other less-specific criteria can suggest the diagnosis and occur in patients with no infection. This realization resulted in a set of confirmatory and suggestive criteria[8] (►**Table 1**).

Recently, Onsea et al. evaluated the performance of these diagnostic criteria in a multicenter retrospective cohort study, demonstrating excellent outcomes. These authors detected a sensitivity and specificity of 97.5% and 100%, respectively, for the presence of a confirmatory criterion and a 95% specificity for the suggestive clinical criteria (fever, exudation, local heat, and redness), reaffirming the importance of the physical examination for FRI diagnosis.[18]

It is worth mentioning that, in multiple aspects, solid scientific evidence is scarce; therefore, many criteria are based on expert opinion.[8,17] Scientific evidence on histopathological diagnosis, for instance, is limited.[19] In contrast to the PPI definition, the recently published consensus expert panel did not include the presence of an inflammatory cell infiltrate on histopathological examination (i.e., polymorphonuclear cell count) because there is no clear scientific evidence on a cut-off value for reliable diagnosis determination. Today, there is still no standardized and reproducible protocol for the evaluation of histopathological samples obtained during surgery for FRI.[8,20]

Table 1 Diagnostic Criteria

Confirmatory	Suggestive
1. Operative fistula or dehiscence (osteosynthesis material or bone exposure)	**1.** Clinical: Pain (non-weight bearing, increasing over time, or recent onset), local heat or redness, local swelling, local increase in temperature, fever.
2. Purulent wound discharge or presence of pus during surgery	**2.** Radiological: Osteolysis (at the fracture site or near the implant), implant loosening, sequestration, lack of consolidation progress, periosteum formation (not in fracture focus or a consolidated fracture)
3. Pathogen identification in at least two deep samples (implant-bone interface) cultured separately (also consider samples obtained by sonication)	**3.** Pathogen identification in a single deep culture sample
4. Detection of organisms in deep tissues using special staining techniques (tuberculosis, fungi, etc.)	**4.** Laboratory: Elevation of serum inflammatory markers (white blood cell count, erythrocyte sedimentation rate [ESR], C-reactive protein [PCR] levels)
	5. Persistent, increasing, or new discharge beyond the first postoperative days with no valid alternative explanation
	6. New-onset joint effusion in patients with fracture (remember bone and joint infections can present as adjacent septic arthritis [prosthesis penetrating the joint capsule during application or intra-articular fractures])

On the other hand, a recent systematic review and meta-analysis assessed the diagnostic value of different serum inflammatory markers (C-reactive protein levels, white blood cell count, and erythrocyte sedimentation rate) in suspected chronic or late-onset FRI. This meta-analysis demonstrated a limited diagnostic value for these tests, concluding that they are insufficient to confirm or rule out a chronic or late-onset FRI, therefore considering them suggestive criteria alone.[21]

Imaging studies have three basic indications for greater certainty in FRI diagnosis, including extension, the presence of sequestration or abscesses, and the degree of fracture consolidation and implant stability.[11] Depending on local preference and availability, these techniques range from conventional radiography, computed tomography (CT), or magnetic resonance imaging (MRI) to more complex techniques with lower availability, such as three-phase bone scintigraphy (TPBS), positron emission tomography (PET), and radiolabeled white blood cell scintigraphy (WBCS).

For conventional radiography, a widely available and low-cost test, there are no studies of good methodological quality to evaluate its diagnostic usefulness; however, it provides basic information regarding fracture consolidation and implant stability.

CT has 47% sensitivity and 60% specificity; as such, it is a useful test for determining sequestration or bone cavitation. CT also allows observing implant loosening, osteolysis signs, and nonunion.[8,22,23]

MRI helps in the evaluation of soft tissues. In addition, it is very sensitive in detecting morphological bone changes, allowing the evaluation of the extent of bone and soft tissue involvement, and the presence of sequestration, sinus tracts, and/or subcortical abscesses. However, the differentiation between infection and inflammation-related changes and normal tissue healing may be difficult, and the effect generated by metal implants can affect image quality. MRI sensitivity and specificity reported for FRI range from 82% to 100% and 43% to 60%, respectively.[22–24]

Nuclear medicine studies described in the literature include TPBS, PET, and WBCS. In recent years, hybrid images (single photon emission CT [SPECT]/CT, PET/CT, PET/MRI) became available, improving the results.[22]

TPBS has a high sensitivity (89 to 100%) but a very low specificity (0 to 10%); as a result, it is not recommended for the FRI treatment.[24–26]

WBCS plus SPECT have high sensitivity (79 to 100%) and specificity (89 to 97%).[22,27,28] As a benefit, recent surgeries do not influence them.[28]

Although PET presents a slightly lower sensitivity (65 to 94%) and specificity (76 to 100%), it should not be used for FRI diagnosis within the first month after surgery.[29]

Despite the previously described usefulness of imaging studies, there is not enough scientific evidence to determine whether any of them can be categorical for FRI diagnosis, and this is why they are currently considered suggestive criteria.[8,11]

Determination of the causative pathogen, the cornerstone of treatment, is usually achieved through intraoperative culture. Sample collection must be careful since false-positive or false-negative results can lead to erroneous treatment decisions, compromising the outcomes. Today, FRI diagnosis uses sampling protocols validated for PPI management and a series of recommendations:[8,11,12]

- Avoid antibiotic therapy for at least two weeks before sample collection.
- Take at least five deep tissue or fluid samples, ideally from the interface between the bone and the implant.
- Cultivate all samples separately
- Take and manipulate each sample using different surgical instrumentation to avoid cross-contamination.
- Avoid taking samples from the skin or fistulous tracts.
- Avoid using swabs for sample collection

There is still controversy in the literature regarding the culturing time. Although a 7 to 14-day period is reasonable, the final decision must consider the local reality. As such, adequate coordination between the treating surgeon and the microbiology team at each center is essential to balance the risk of losing a pathogen difficult to culture versus obtaining a culture contaminated with an irrelevant pathogen.[30]

At the same time, the recommendation is to consider using specific cultures for mycobacteria or fungi based on local environmental and epidemiological risk factors..[31]

Treatment

Treatment Team Composition

The management of FRI patients represents a challenge for the entire medical team. Currently, the evidence favoring multidisciplinary FRI management is increasing.[1,32] The team composition relies on the requirements of each patient. However, the recommendation is to have at least members from the traumatology and infectious disease team. In addition, many cases require support from other specialties, such as plastic surgery, anesthesiology, internal medicine, and nutrition. It is advisable to refer the patient to a more complex center if the institution does not have the proper equipment to meet their needs.[1]

Preoperative Optimization

It is essential to identify and correct nutritional and metabolic disorders in FRI patients, including malnutrition and diabetes mellitus, since these conditions can compromise the outcomes and increase the risk of complications, hospitalization time, and costs.[33–35] In this context, several clinical guidelines recommend preoperative optimization and even intraoperative monitoring of blood glucose levels to maintain them between 140 mg/dL and 180 mg/dL throughout the surgery.[36,37]

Hypovitaminosis D is a common condition among trauma patients and a presumed fundamental factor for bone consolidation and infection prevention. However, there is not enough evidence to reliably recommend its routine screening and supplementation.[38,39]

Treatment Strategy

There are two main strategies regarding surgical treatment, and their choice depends on the context. The first alternative

consists of implant retention combined with debridement and antibiotic therapy. The second alternative is implant removal or replacement associated with debridement and antibiotic therapy.

The importance of the present osteosynthesis material lies in the bacterial colonization and biofilm formation ability, allowing the development of local antibiotic resistance and protection against the immune system. These factors let organisms survive antibiotic doses up to 1,000 times higher than in their planktonic state.[40]

Although some concepts described for PPI were a base to establish the diagnostic criteria for FRI, one of the fundamental differences between these conditions is the potential implant removal after fracture consolidation on FRI, with a high probability of infection eradication. This is why complete infection eradication is not always the initial objective, and the surgeon may opt for suppressive management while maintaining an implant as long as it provides adequate stability until bone consolidation.[41]

In recent decades, several published preclinical studies demonstrated the importance of fracture stability in FRI management. The first authors to describe this importance were Ritmann and Perren, who conducted a study on sheep and reported that consolidation is possible during an infection provided the implant is absolutely or relatively stable.[42]

Similarly, different works reaffirmed the importance of this variable not only for bone consolidation but also for infection prevention and eradication.[43–45] The pathophysiology of the lower susceptibility of a stabilized fracture to infection remains unclear. It is difficult to determine whether instability is the cause or consequence of the infection. However, what is currently most accepted is that both act simultaneously, with positive feedback between them.[45]

Considering all the above, Metsemakers et al. proposed the following therapeutic goals for FRI:[41]

1. Fracture consolidation
2. Infection control (eradication versus suppression until fracture consolidation)
3. Soft tissue coverage
4. Prevention of chronic osteomyelitis
5. Functional recovery

Time is a relevant factor in deciding on implant removal or retention since it directly correlates with the biofilm maturity and degree of bone consolidation. It is postulated that in the presence of an immature biofilm, cleansing, debridement, and antibiotic therapy may eradicate the infection without the need to remove the implant.[46]

Morgenstern et al. recently published a systematic review evaluating outcomes of implant retention and its correlation with time. These authors observed good success rates (86% to 100%) based on the absence of recurrent infection and implant retention in infections occurring for less than 3 weeks. In longer infections (with 3 to 10 weeks of duration), the success rates were lower (82 to 89%), decreasing considerably (67%) in cases of more than 10 weeks of progression, with limited literature available for this last scenario. However, the authors concluded that despite the importance of this variable, it should not be the only factor to consider when deciding whether to retain or remove an implant.[46]

Other factors that must be considered when deciding between implant removal or replacement are its stability, whether the reduction obtained is acceptable or not, the patient's baseline medical condition in cases of very severe infections, and the presence of an intramedullary implant whose maintenance can make surgical cleanliness difficult. Based on this last point, there is consensus on the removal of the intramedullary implant as part of FRI treatment after fracture consolidation.[12,41]

Tschudin-Sutter et al. propose a management algorithm considering strict criteria for implant retention. These authors obtained a 90% success rate in a series of 122 patients followed up for 2 years. The inclusion criteria used were symptoms for less than 3 weeks, stable implant, absence of abscess or fistula, identified pathogen, and sensitivity of the pathogen to an antibiotic agent active against the biofilm.[4]

In conclusion, the choice of treatment strategy is a complex process. It is critical to perform a complete study of each patient and consider the multiple variables involved, including time, which is a relevant parameter but not the only factor (►**Fig. 1**).

Surgical Cleansing and Debridement

Irrigation removes bacterial load and debris by dragging, resulting in macroscopically clean tissues. Today, the best quality evidence on irrigation is extrapolated from open fracture treatment. FLOW, a multicenter randomized study, showed the usefulness of irrigation with saline or lactated Ringer's solution at low pressure, not requiring detergents.[47] Although additional antimicrobial solutions could reduce infection rates, this topic remains controversial since in vitro studies demonstrated that some have a cytotoxic effect on osteoblasts.[48–51]

Debridement, a key element in treatment, consists of resecting all necrotic and contaminated tissues, including bone tissues. We must consider that periostized bone remains susceptible to maintenance, while non-periostized bone fragments are avascular and require removal. It is still debatable how to define a critical bone defect requiring additional surgical interventions and what to do with large non-periostized structural fragments. Nevertheless, following their removal, the next treatment strategy needs consideration.[52–54]

Ideally, we must fill this critical bone defect with vital tissue to stimulate neovascularization, allowing the arrival of systemic antibiotics and immune cells. The use of local antibiotics associated with polymethylmethacrylate (PMMA), as described by Masquelet, is a good alternative for these cases because it manages the defect and allows antibiotic release for a longer time.[12,41,55,56]

Finally, in recent years, bioactive glass has gained interest. Bioactive glass is a biocompatible synthetic material with antibacterial, osteoconductive, and angiogenic properties and promising results in managing bone defects in infections.[57,58]

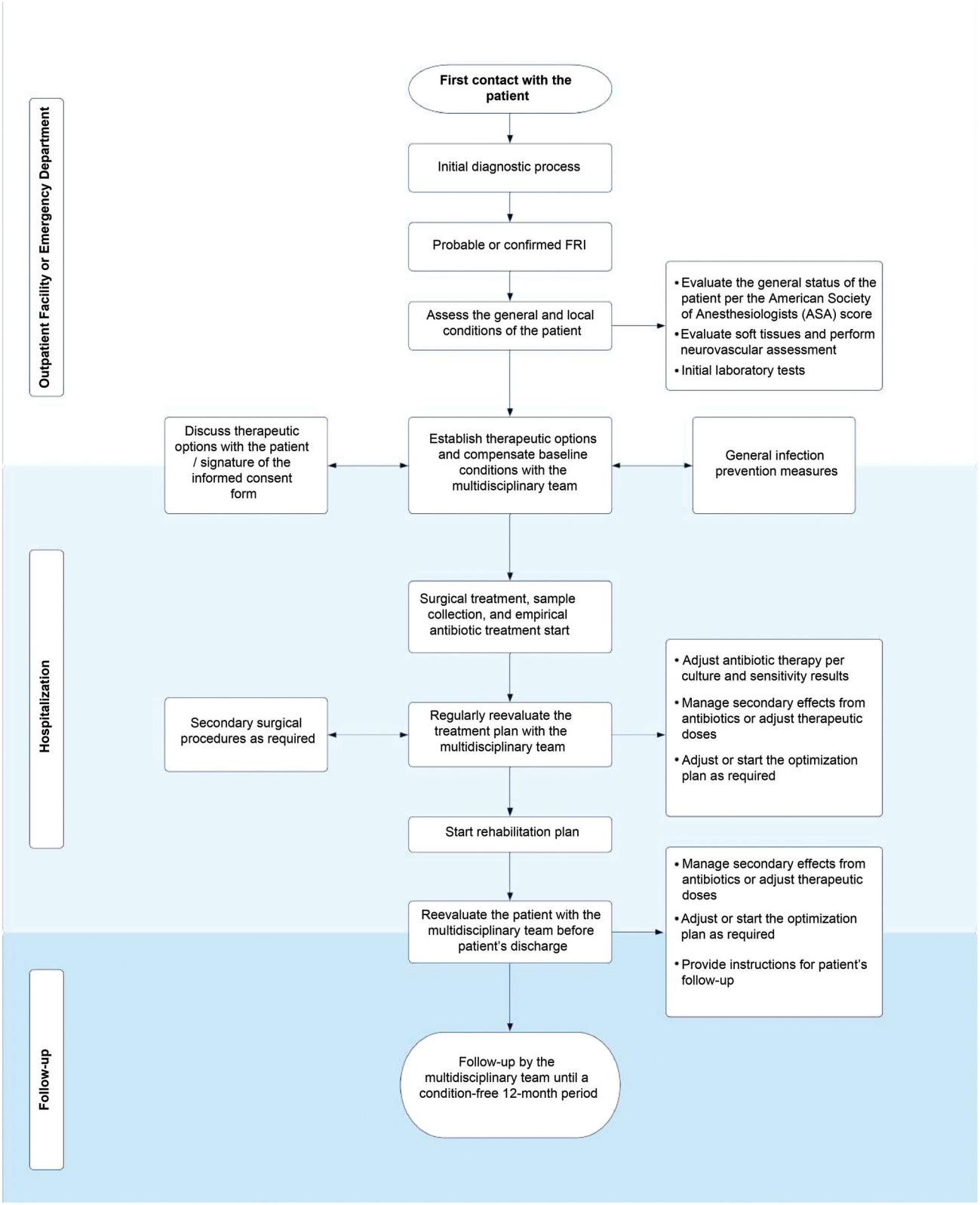

Fig. 1 Flow chart representing the optimal treatment course for a patient with fracture-related infection (FRI). Adapted from Metsemakers et al.[12]

Antibiotic Therapy

Identifying the etiological agent is essential throughout the treatment. This explains why antibiotic therapy before intraoperative culture sample collection should be reserved only for seriously ill patients with systemic involvement or local extremity involvement when empirical treatment is imperative.[9]

In general terms, patients with FRI must undergo inflammatory parameter tests and blood cultures before therapy, as well as follow-up parameters depending on the antibiotic agent (complete blood count, kidney function, liver function, etc.). These tests allow the determination of baseline values and the design of a therapy monitoring curve.[12]

Empirical intravenous antibiotic treatment should start soon after sample collection and debridement to reduce the local bacterial load and the risk of antibiotic resistance.[9,10] Initially, treatment must include broad-spectrum agents per the local reality. In general, it should include a lipopeptide or a glycopeptide and an agent covering gram-negative bacilli. This initial treatment must be modified per the culture and sensitivity results as soon as possible[9] (►**Table 2**).

Although treatment duration remains controversial, the current trend is to reduce the time of intravenous therapy. A recent randomized controlled trial demonstrated that patients treated for up to 7 days with intravenous antibiotic therapy followed by oral therapy had the same outcomes as those with prolonged intravenous therapy.[59]

The curative approach of antibiotic therapy in case of implant retention is only successful when the antibiotic agent is effective against the biofilm. Rifampicin is the antibiotic of choice against most gram-positive bacteria,[60–62] while fluoroquinolones are recommended for gram-negative bacteria.[63,64] Even so, it is worth mentioning that rifampicin must always be combined with a second antibiotic agent due to the rapid development of resistance. For the same reason, its administration should start before the initial reduction in the bacterial load through surgery and antibiotic therapy, removal of all drains, and the presence of a closed, dry wound.[65,66] For staphylococci, quinolones, such as ciprofloxacin or levofloxacin, are the most studied and effective oral antibiotics in association with rifampicin.[67]

For bacteria resistant to antibiotics active against the biofilm, the eradication alternative by retaining the implant is not viable, so the surgeon must seriously consider its removal for proper treatment.[68]

Follow-up duration for FRI patients must extend for a minimum of 12 months after cessation of antibiotic therapy due to the risk of recurrence.[9]

Negative Culture

Culture-negative FRI represents a major challenge for the multidisciplinary treating team. The estimated rate of FRI with negative cultures ranges from 1% to 16%. However, the incidence could be even higher, especially in cases of nonunion.[69–73]

The causes of this phenomenon are variable (low number of cultures, inadequate sample collection site, poor sample handling, fastidious organisms, etc.). In these cases, depending on each institution's availability, additional methods to increase organism detection, including implant sonication or molecular techniques, should be considered. If the causative agent is not identifiable, one must choose the treatment targeting the most likely organism.

On the other hand, if the diagnosis of FRI is not confirmed and cultures are negative, the current recommendation is to suspend empirical antibiotic treatment to observe the clinical progression, and eventually repeat tissue sampling, which avoids antibiotic toxicity and the risk of antibiotic resistance.[9]

Local Antibiotics

The application of local antibiotics is a critical complement to FRI treatment, especially in the presence of a bone defect.[10] A recent systematic review showed a considerable reduction in the risk of infection in open fractures with local antibiotic administration, mostly with polymethylmethacrylate (PMMA) as a distribution form.[55]

Outside of the commercially available preparations of PMMA with antibiotics, antibiotic agent addition is a valid alternative considering the resulting structural stability. To do this, Metsemakers et al. recommended adding up to 10% of the weight of the cement bag, respecting the maximum doses of each antibiotic agent.[10]

Gentamicin and vancomycin are the most commonly used antibiotics in our institution. Nonetheless, there is no solid evidence today to recommend the maximum antibiotic dose for PMMA addition. In a recent article from the consensus FRI group, Metsemakers et al. described, based on the available literature, a dose of 4.8 g for gentamicin and 6 g for vancomycin, recommending 4 g of vancomycin per PMMA bag (40 g).[10]

Other antibiotic agents less frequently used in FRI, including clindamycin, colistin, amphotericin B, cefazolin, and ampicillin, have been described as alternatives.[10] Some drugs are not recommended, such as ß-lactams (due to their limited thermal stability)[74] and fluoroquinolones, rifampicin, tetracyclines, and macrolides (because of their potential local detrimental effects on cell viability and osteogenic activity).[74–76]

In contrast, the recently published VANCO study demonstrated that topical vancomycin directly applied to the surgical area during wound closure reduces gram-positive FRI rates.[77] In turn, vancomycin local application has limited systemic absorption, making it a safe alternative regarding nephrotoxicity.[78]

Although the local administration of antibiotics is usually deemed safe,[78,79] we cannot neglect the potential for local and systemic toxicity.[75,80,81] In addition, there is no solid evidence favoring antibiotic therapy without a local delivery method, except for vancomycin.[82–84] No study evaluated its direct use for FRI treatment.

Table 2 Antibiotic Agents

Organism		Antibiotic agent	Dosage	Frequency	Route
Staphylococcus spp.					
Methicillin-sensitive (MS)	–	Flucloxacillin	2 g	6 h	IV
	and	Rifampicin	300-450 mg	12 h	PO
		Followed by oral treatment (depending on sensitivity)			
	–	Rifampicin	300-450 mg	12 h	PO
		and (per sensitivity)			
	–	Levofloxacin	500 mg	12 h	PO
	or	Trimethoprim/Sulfamethoxazole	960 mg	8 h	PO
	or	Doxycycline	600 mg	12 h	PO
	or	Clindamycin	600 mg	8 h	PO
Methicillin-resistant (MR)	–	Vancomycin	Loading dose: 25-30 mg/kg Maintenance dose: 15 mg/kg	12 h	IV
	and	Rifampicin	300-450 mg	12 h	PO
		Followed by oral treatment (depending on sensitivity)			
	–	Rifampicin	300-450 mg	12 h	PO
		and (per sensitivity)			
	–	Levofloxacin	500 mg	12 h	PO
	or	Trimethoprim/Sulfamethoxazole	960 mg	8 h	PO
	or	Doxycycline	600 mg	12 h	PO
	or	Clindamycin	600 mg	8 h	PO
Rifampicin-resistant		*Intravenous treatment per sensitivity followed by antibiotic suppression until bone consolidation and implant removal*			
Streptococcus spp.		*(per sensitivity)*			
		Penicillin G	5 million units	6 h	IV
	–		or		
			4 million units	5 h	IV
	or	Ceftriaxone	2 g	24 h	IV
		Followed by oral treatment per sensitivity			
	–	Amoxicillin	1 g	6-8 h	PO
	or	Clindamycin	450-600 mg	8 h	PO
Enterococcus spp.					
Penicillin-sensitive	–	Ampicillin	2 g	6 h	IV
	and	Gentamicin	3 mg/kg	24 h	IV
		Followed by oral treatment per sensitivity			
	–	Amoxicillin	1 g	6-8 h	PO
Penicillin-resistant					
	–	Vancomycin	Loading dose: 25-30 mg/kg Maintenance dose: 15 mg/kg	12 h	IV
		Followed by oral treatment per sensitivity			
	–	Linezolid (maximum, 4 weeks)	600 mg	12 h	PO
Gram-negative organisms					
Enterobacteriaceae (e.g., *Escherichia coli*,	–	*Beta-lactam per sensitivity*			

(*Continued*)

Table 2 (*Continued*)

Organism		Antibiotic agent	Dosage	Frequency	Route
Klebsiella spp., and *Enterobacter* spp.)					
		Followed by oral treatment per sensitivity			
	–	Ciprofloxacin	750 mg	12 h	PO
	or	Levofloxacin	500 mg	12 h	PO
Non-fermenting (e.g., *Pseudomonas aeruginosa*, *Acinetobacter* spp.)	–	Meropenem	2 g	8 h	IV
	or	Ceftazidime	2 g	8 h	
	and	Gentamicin (short course)	5 mg/kg	24 h	IV
	or	Tobramycin (short course)	5 mg/kg	24 h	
	or	Amikacin (short course)	15 mg/kg	24 h	IV
		Followed by oral treatment per sensitivity			
	–	Ciprofloxacin	750 mg	12 h	PO
	or	Levofloxacin	500 mg	12 h	PO
Ciprofloxacin-resistant		*Intravenous treatment per sensitivity followed by antibiotic suppression until bone consolidation and implant removal*			
Negative culture	–	Ampicillin/sulbactam (2 weeks)	3 g	8 h	IV
		Followed by oral treatment			
		Rifampicin	300-450 mg	12 h	PO
	and	Levofloxacin	500 mg	12 h	PO

Abbreviations: IV, intravenous; PO, per os.
*The antibiotic treatment must be discussed with the infectious disease team of each center for adaptation to the local reality.
Table adapted from Depypere et al.[9]

Conclusions

FRI continues to be a challenging complication for the entire healthcare team. As such, multidisciplinary confrontation is essential to evaluate and manage these patients in all dimensions. Today, scientific high-level evidence for FRI management guidance is limited. Therefore, diagnosis and treatment standardization per the recently published clinical guidelines seeks to improve outcomes and the level of evidence to guide the management of these patients.

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Conflict of Interests
No.

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