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Editorial

Fracture Related Infection (FRI): Navigating the Evolving Landscape of Definition, Diagnosis, and Management

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Abstract

Fracture-related infection (FRI) represents one of the most challenging and debilitating complications in orthopaedic trauma surgery. With an estimated global incidence of approximately 1.8 million cases annually, FRI imposes a substantial burden on patients, healthcare systems, and economies. This editorial synthesizes contemporary evidence on the epidemiology, diagnostic workup, and multidisciplinary management of FRI.

Keywords: *Fracture-Related Infection; FRI; DAIR; Implant-Associated Infection; Biofilm; Orthopaedic Trauma; Antimicrobial Therapy*

Introduction

Infection following fracture fixation has been recognized as a serious complication for centuries, yet it was only in 2018 that the international orthopaedic community formally adopted a standardized definition for Fracture-Related Infection (FRI). Prior to this, the field was plagued by heterogeneous definitions, inconsistent reporting, and non-comparable study outcomes. A systematic review by Metsemakers., *et al*. revealed that 70% of clinical trials investigating infectious complications after fracture fixation did not mention a definition for FRI, and only 2% referred to validated criteria [1]. The introduction of the FRI consensus definition by an international expert group, supported by the AO Foundation and the European Bone and Joint Infection Society (EBJIS) represents a landmark achievement [1]. The definition distinguishes between confirmatory criteria (pathognomonic for infection) and suggestive criteria (warranting further investigation), providing clinicians with a structured and tiered diagnostic framework [2].

FRI is increasingly prevalent, driven by the growing volume of surgical fracture fixation procedures globally, an aging population with more comorbidities, and the rise of antibiotic-resistant organisms. In Germany alone, 7,253 inpatient FRI cases were documented in 2018, corresponding to an incidence of 10.7 per 100,000 persons per year [3]. Globally, the burden is estimated at approximately 1.8 million cases annually [4]. The economic cost is enormous and studies suggest FRI costs are four times greater than those of periprosthetic joint infection (PJI), owing to multiple re-operations, prolonged antibiotic courses, and extended hospital stays [4].

Aim of the Study

This editorial aims to consolidate the current state of knowledge on FRI; from definition and epidemiology through to clinical workup and surgical management in a practically useful format for the orthopaedic trauma surgeons.

Definition and diagnostic criteria

The consensus definition

The consensus definition of FRI, first published in 2018 and updated in 2020, classifies diagnostic features into two tiers of certainty - confirmatory criteria and suggestive criteria [1,2] (Figure 1). Confirmatory criteria are pathognomonic for FRI. The presence of any single confirmatory criterion mandates immediate initiation of treatment. These include: the presence of a fistula or sinus tract communicating to bone or implant; wound breakdown with visible implant or bone; frank purulent drainage; isolation of the same pathogen from two or more separate deep tissue cultures; histopathological finding of more than 5 polymorphonuclear neutrophils per high-power field at 400× magnification (added in the 2020 update); and a single positive intraoperative culture with a virulent organism [1,2].

Suggestive criteria, while not individually diagnostic, raise clinical suspicion and warrant further investigation. These encompass clinical signs such as local redness, swelling, or fever; persistent wound drainage beyond seven days; elevation of inflammatory biomarkers (CRP, ESR, WBC - though with limited specificity); radiological evidence of periosteal reaction, bone lysis, or implant loosening; nuclear imaging abnormalities (^{18}F-FDG PET-CT, added in 2020); and unexpected fracture non-union or implant failure [2,5].

A key insight from recent validation studies is that confirmatory criteria show excellent diagnostic discriminatory value, with specificities exceeding 95% for classical signs such as wound breakdown and purulent drainage [5,6]. However, in up to 23% of confirmed FRI cases, confirmatory criteria may be absent [7], necessitating reliance on the combined assessment of suggestive features and further workup.

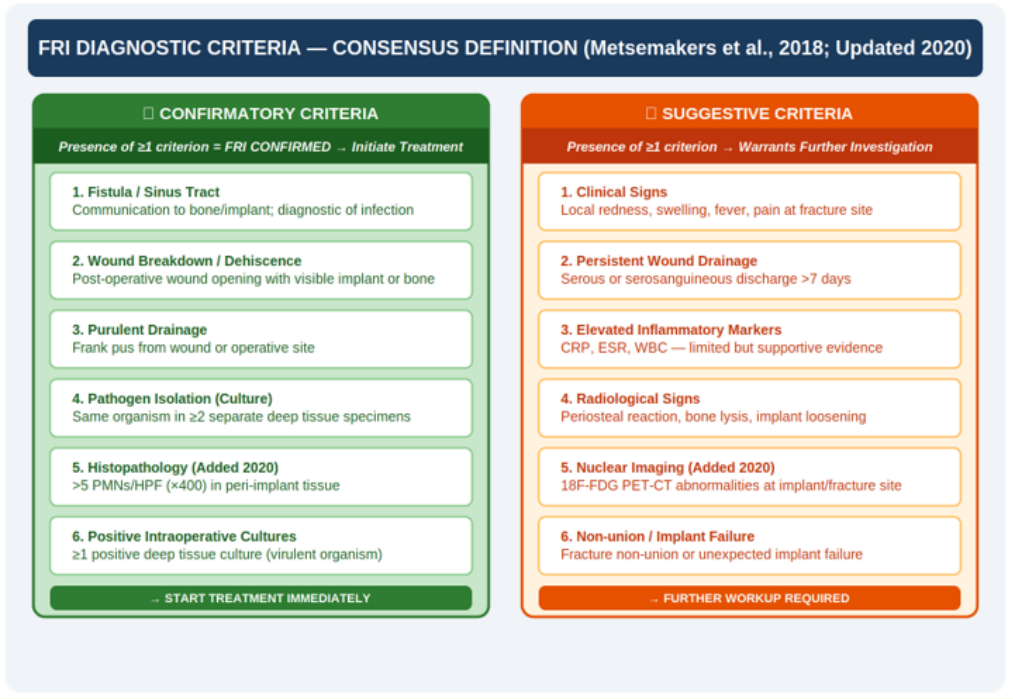

Figure 1: *The FRI diagnostic criteria framework. Confirmatory criteria (left, green) establish diagnosis and mandate treatment. Suggestive criteria (right, orange) necessitate further investigation.*

The FRI classification system

Recognizing the need for a practical classification system to guide treatment decisions and enhance research comparability, Alt., *et al*. (2024) proposed the FRI Classification System, incorporating three dimensions: Fracture status (F), patient-Related factors (R), and soft-tissue Impairment (I) [8]. This framework provides a structured approach that parallels the Cierny-Mader system for osteomyelitis, aiming to stratify patients for treatment planning and prognostication. The system acknowledges that fracture healing status, host physiological condition, and soft tissue envelope integrity are the three most critical variables influencing treatment strategy and outcome in FRI [9].

Epidemiology, microbiology, and risk factors (Figure 2)

Epidemiology

The incidence of FRI varies widely depending on fracture type, energy of injury, anatomical location, and geographic setting. For closed, low-energy fractures, infection rates are generally below 3%. However, for open tibial fractures of the Gustilo-Anderson Type IIIB category, rates can reach 30% or higher [3,4]. In sub-Saharan African settings, where delays to definitive care, resource constraints, and wound contamination are prevalent, rates following open fractures can approach 52% [10]. The tibia and femur are the most commonly affected long bones due to their poor soft tissue envelope and high exposure to injury forces [3].

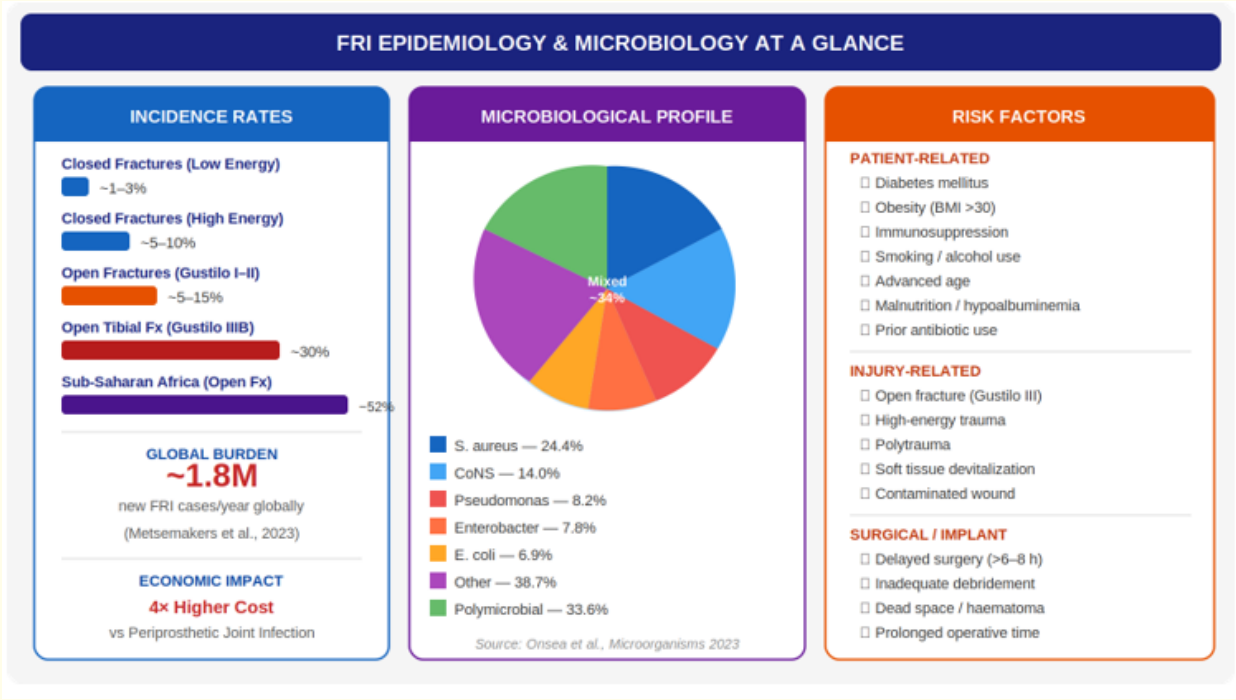

Figure 2: *Epidemiology and microbiology of FRI at a glance [3,4,10]. Left: Incidence rates stratified by fracture type. Centre: microbiological profile showing organism distribution [10]. Right: Key patient-, injury-, and surgical-related risk factors.*

Microbiological profile

Staphylococcus aureus remains the most frequently identified pathogen in FRI, accounting for approximately 24.4% of isolates [11]. Coagulase-negative staphylococci (CoNS), particularly *S. epidermidis*, represent the next most common group (14%), followed by Gram-

negative organisms including *Pseudomonas aeruginosa* (8.2%), *Enterobacter* species (7.8%), and *Escherichia coli* (6.9%). Critically, polymicrobial infections are identified in up to 33.6% of cases, particularly in open fractures and chronic or delayed presentations [11,12].

The prevalence of resistant organisms is a growing concern. Extended-spectrum beta-lactamase (ESBL)-producing Gram-negatives and carbapenemase-producing organisms account for up to 13.6% of resistant isolates in some series, while methicillin-resistant *Staphylococcus aureus* (MRSA) constitutes approximately 3.3% [11]. These patterns have significant implications for empirical antibiotic selection and underscore the importance of culture-directed targeted therapy.

Biofilm formation is a cardinal pathophysiological mechanism in FRI. Bacteria adhering to implant surfaces form a structured extracellular matrix that protects them from host immune responses and systemic antibiotics. The maturity of the biofilm progressing from an immature, planktonic phase in the first days to a mature, complex matrix over weeks, is one of the key determinants of whether implant retention is feasible [4,13].

Risk factors

Risk factors for FRI can be broadly categorized into patient-related, injury-related, and surgical factors. Patient-related risk factors include diabetes mellitus, obesity, immunosuppression (including chronic steroid use and malignancy), smoking, alcohol use, advanced age, and hypoalbuminemia. Injury-related risk factors include open fractures (particularly Gustilo-Anderson Type III), high-energy trauma mechanisms, polytrauma, and wound contamination. Surgical risk factors include prolonged operative time, inadequate debridement, dead space creation, haematoma formation, and delayed operative intervention beyond 6 - 8 hours from injury [3,4].

Diagnostic workup

Clinical evaluation

Clinical assessment forms the foundation of FRI diagnosis. The treating surgeon must carefully evaluate the wound for signs of infection erythema, warmth, swelling, wound breakdown, purulent discharge, or the presence of a sinus tract. A detailed history should document the time elapsed since fracture fixation, any prior antibiotic exposure, and the course of wound healing. Fever may be present in acute FRI, though its absence does not exclude infection, particularly in chronic or low-grade presentations [5,6].

Laboratory investigations

Serum inflammatory markers such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and white blood cell count (WBC) serve as adjuncts but possess limited sensitivity and specificity for FRI in isolation. A systematic analysis confirmed that while elevations in these markers constitute suggestive criteria, normal values do not reliably exclude FRI [2,5]. More recently, novel biomarkers such as serum procalcitonin and the platelet count to mean platelet volume ratio have been evaluated as adjuncts, though none have yet replaced conventional markers in routine practice [6].

Microbiological sampling

The gold standard for microbiological diagnosis remains intraoperative deep tissue culture. Current consensus recommends collection of 3 to 5 deep tissue samples from different sites, with avoidance of pre-operative antibiotics unless sepsis mandates immediate treatment [14]. Swab cultures from superficial wound surfaces are unreliable and should not substitute for deep tissue sampling. Sonication of explanted implants by dislodging and quantifying biofilm bacteria, has been shown to increase diagnostic yield, particularly in delayed and chronic FRI [3]. Molecular techniques including 16S rRNA gene sequencing and multiplex PCR panels offer adjunctive value in culture-negative cases or in patients who have received prior antibiotics [6].

Imaging

Plain radiographs remain the first-line imaging modality, capable of detecting periosteal reaction, cortical lucency, implant loosening, or non-union may suggest underlying infection. CT scan provides superior bony detail and allows assessment of underlying sequestrum, cortical destruction, and bone lysis at bone-implant interface. MRI is particularly valuable for soft tissue assessment and early medullary signal changes, though metallic, cause susceptibility artifact that limits interpretation [5,15].

Nuclear imaging with ^{18}F-FDG PET-CT has emerged as a valuable tool in the evaluation of chronic or low-grade FRI, where conventional imaging and biomarkers may be uninformative. A systematic review by Lemans., *et al*. demonstrated a pooled sensitivity of 84% and specificity of 77% for PET-CT in diagnosing FRI [16]. As a result, PET-CT abnormalities were incorporated into the updated 2020 FRI diagnostic criteria as a suggestive feature [2].

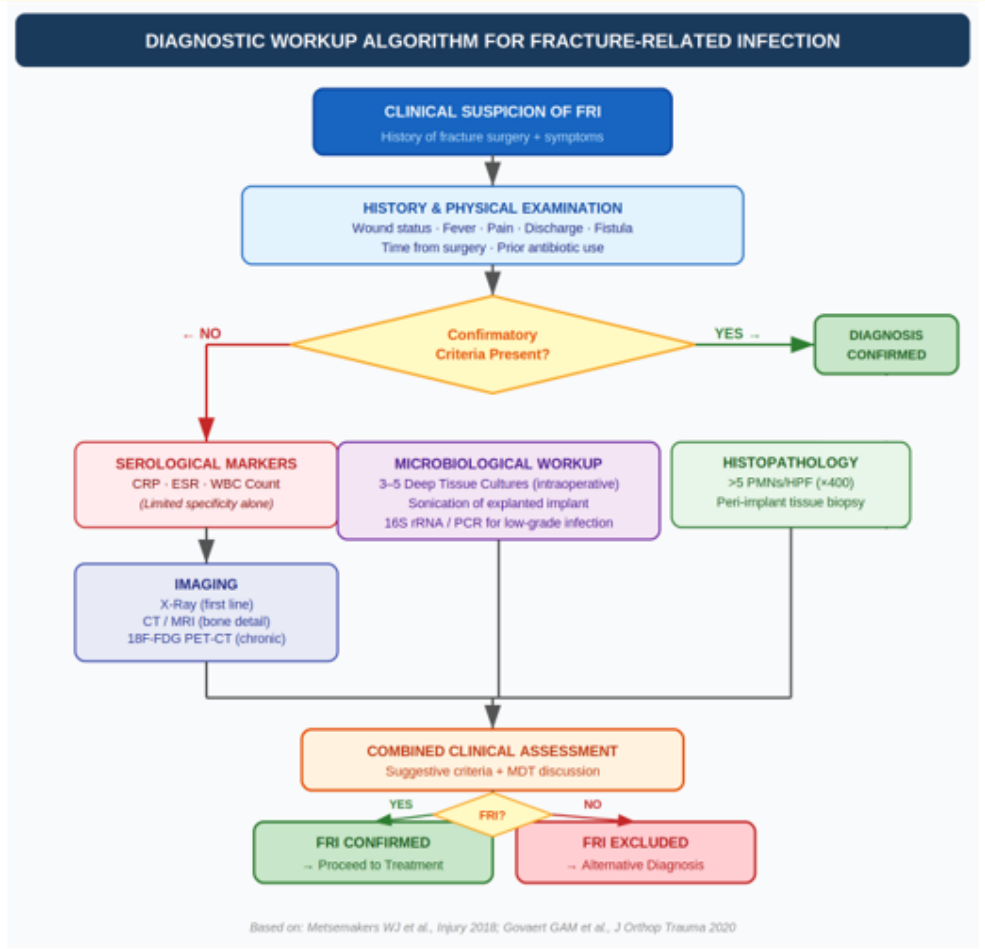

Figure 3: *Diagnostic workup algorithm for FRI [1,2]. A stepwise approach integrating clinical, laboratory, microbiological, and imaging findings to confirm or exclude FRI. The presence of any confirmatory criterion mandates immediate treatment initiation.*

Principles of management

Multidisciplinary team approach

Effective FRI management demands a coordinated multidisciplinary team (MDT) comprising orthopaedic trauma surgeons, infectious disease specialists, clinical microbiologists, plastic and reconstructive surgeons, radiologists, and physiotherapists [14]. No single specialist can optimize all aspects of care in this complex condition. MDT governance ensures culture-guided antibiotic selection, appropriate surgical strategy, soft tissue reconstruction planning, and patient-centred rehabilitation goals. The concept of a dedicated "bone infection unit" as practised in several European centres is increasingly advocated in the literature [6,14].

Host optimization

Pre-operative optimization of modifiable host factors is an important component of FRI management. Glycaemic control should be optimized in diabetic patients; nutritional deficiencies should be corrected; immunosuppressive medications should be reviewed in consultation with relevant specialists; and smoking cessation strongly encouraged. The Cierny-Mader host classification (A: normal host, B: locally or systemically compromised, C: severe compromise) provides a framework for assessing risk and tailoring the aggressiveness of surgical intervention accordingly [3,14].

Surgical strategy

The choice of surgical strategy in FRI is guided by four primary variables: fracture healing status, implant stability, infection duration (and hence biofilm maturity), and host physiological status [8,13,17]. Three broad surgical pathways exist: a) Implant Removal with Debridement**:** When the fracture has fully healed, the infected implant can be removed and thorough debridement of the implant bed performed. This is the simplest and most definitive approach, offering excellent infection eradication rates [3,17]. b) DAIR (Debridement, Antibiotics and Implant Retention): Indicated for acute or early FRI (typically within 10 weeks of symptom onset) where the implant is stable, fracture reduction is satisfactory, soft tissue coverage is viable, and biofilm is presumed to be immature. DAIR success rates are 86 - 100% for acute presentations, declining to 67% when symptoms have been present beyond 10 weeks [13,20]. c) DAIEX (Debridement, Antibiotics and Implant Exchange): Single-stage or two-stage exchange is preferred for delayed or chronic FRI with mature biofilm, unstable or malaligned fixation, difficult-to-treat (DTT) pathogens, failed DAIR, or poor host physiology. Contemporary evidence suggests one-stage exchange is not inferior to two-stage exchange in most cases [17].

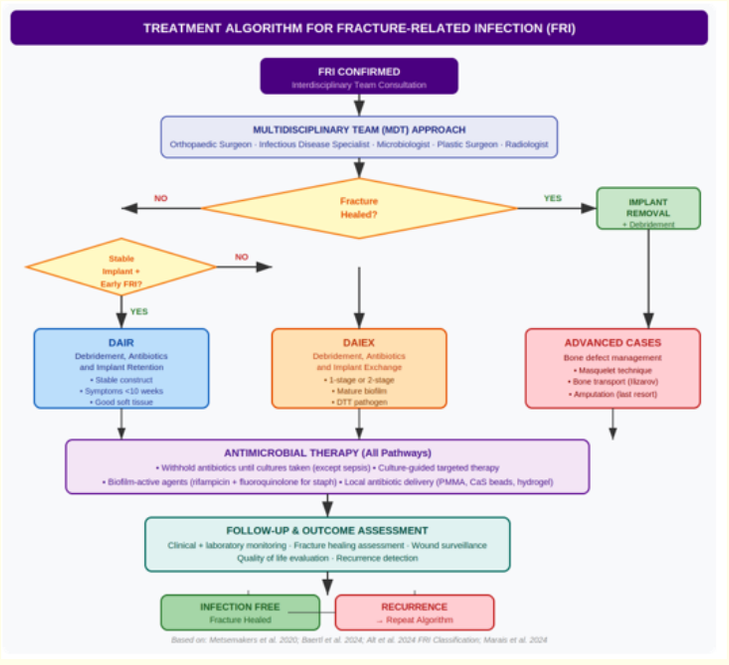

Figure 4: *Treatment algorithm for FRI [13,14,16,17]. Decision pathways for implant removal, DAIR, and DAIEX based on fracture healing status, implant stability, and infection chronicity. All pathways converge on culture-guided antimicrobial therapy and MDT oversight.*

Dead space management

Management of dead space which is the volumetric void left after debridement of necrotic tissue and implant removal is a critical adjunct to surgical treatment. Options include antibiotic-loaded calcium sulphate or calcium phosphate beads, PMMA (polymethylmethacrylate) cement spacers, local antibiotic hydrogels, and flap reconstruction in cases of significant soft tissue loss [14]. The Masquelet technique (induced membrane technique) is employed for intercalary bone defects [18,19], while bone transport using a circular fixator (Ilizarov technique) addresses larger segmental defects [4].

Antimicrobial therapy

Antibiotic therapy forms the second cornerstone of FRI treatment and must be guided by culture and sensitivity results. Antibiotics should be withheld until deep tissue samples have been collected, unless the patient presents with sepsis requiring emergency treatment [14]. The duration of systemic antibiotics typically ranges up to 6 weeks for bone and joint infections.

For staphylococcal FRI, the addition of rifampicin, a biofilm-active agent in combination with a fluoroquinolone (typically ciprofloxacin or levofloxacin) is recommended where sensitivity permits, as it significantly improves eradication rates against both MSSA and MRSA [3,14]. Local antibiotic delivery systems including antibiotic-loaded PMMA beads, calcium sulphate carriers, and antibiotic-loaded hydrogels achieve high local drug concentrations at the infection site while minimizing systemic toxicity. These are now strongly endorsed in FRI management guidelines [14].

Special considerations

FRI in low- and middle-income countries (LMICs)

The global burden of FRI disproportionately affects LMICs, where high rates of open fractures, delayed access to care, resource constraints, and limited microbiological infrastructure converge [9]. A recent prospective study comparing FRI management in a low-income country against international consensus guidelines demonstrated substantial gaps in adherence to recommended practices particularly in microbiological sampling adequacy and local antibiotic delivery [10]. Adapting evidence-based FRI guidelines to resource-limited settings remains an urgent global health priority.

Emerging diagnostic tools

Beyond conventional culture, several emerging diagnostic modalities are under investigation. Sonication of explanted implants has achieved high-level evidence for superior yield over conventional tissue culture in delayed infections [3]. Next-generation sequencing technologies enable comprehensive metagenomic profiling of polymicrobial infections, with particular utility in culture-negative FRI [6]. Host immune response biomarkers including synovial fluid alpha-defensins and specific cytokine profiles are being explored as adjunct diagnostic tools, though their role in FRI (as opposed to PJI) remains investigational.

Bacteriophage therapy

Perhaps the most exciting frontier in FRI management is the re-emergence of bacteriophage therapy as a treatment for difficult-to-treat, multidrug-resistant bone and joint infections. Phages are viruses that infect and lyse specific bacteria; they can penetrate biofilms and operate against organisms resistant to all conventional antibiotics. Early clinical case series, particularly for *Pseudomonas aeruginosa* and *Staphylococcus aureus* bone infections have demonstrated encouraging results, and regulatory frameworks for compassionate use are now in place in several countries [21]. Dedicated clinical trials are underway.

Quality of life and long-term outcomes

FRI has a profound and often underappreciated impact on patient quality of life (QoL). Long-term follow-up studies have demonstrated significantly reduced physical function, psychological wellbeing, and return-to-work rates in FRI patients compared to matched controls

[20,22]. Walter., *et al*. documented persisting QoL deficits in patients years after apparently successful FRI treatment, highlighting the importance of holistic rehabilitation, psychological support, and patient-reported outcome measurement in clinical practice [22].

Summary recommendations for clinical practice

The following table synthesizes key evidence-based recommendations for the clinical management of FRI, distilled from the FRI Consensus Group guidelines [1,2,14] and the most recent published literature [3,8,13,17,20].

Domain	Recommendation
Definition	Apply the consensus FRI definition with confirmatory and suggestive criteria. One confirmatory criterion mandates immediate treatment [1,2].
Sampling	Collect 3-5 deep tissue cultures intraoperatively. Avoid peri-operative antibiotics unless sepsis. Consider sonication of explanted implants in delayed/chronic cases [3,14].
Imaging	Plain X-ray first line; CT for bone detail; MRI for soft tissue/marrow assessment; ^{18}F-FDG PET-CT for chronic or low-grade FRI [2,15].
MDT	Mandatory MDT involvement: orthopaedic surgery, infectious disease, microbiology, plastic surgery, and rehabilitation [14].
Surgery - DAIR	Preferred for acute FRI (<10 weeks), stable implant, viable soft tissue envelope. Success rates 86-100% early, declining with duration [13,20].
Surgery - DAIEX	For delayed/chronic FRI, mature biofilm, DTT pathogens, unstable fixation, or failed DAIR. One-stage not inferior to two-stage in most cases [17].
Antibiotics	Culture-guided therapy; withhold until samples taken. Rifampicin + fluoroquinolone for sensitive staphylococci. Duration 6-12 weeks based on surgical strategy [3,14].
Local Delivery	Antibiotic-loaded PMMA, calcium sulphate, or hydrogel carriers for local delivery. Strongly recommended [14].
Host Optimisation	Optimise glycaemic control, nutrition, immunosuppression, and smoking status pre- and peri-operatively [3,14].
Follow-Up	Clinical and laboratory surveillance for recurrence. Patient-reported outcome measures at one year. QoL assessment and rehabilitation planning [21].

Table

Fracture-Related Infection (FRI) stands at a transformative juncture. The past decade has witnessed the formalization of a consensus definition [1,2], the development of standardized diagnostic criteria, and growing evidence for multidisciplinary surgical and antimicrobial management strategies [14]. Yet significant challenges remain: diagnostic uncertainty in the absence of confirmatory criteria [7]; the global disparity in FRI burden and management capacity [10]; the threat of antimicrobial resistance [11]; and the persistent long-term impact of FRI on patient quality of life [22].

The newly proposed FRI Classification System [8] promises to enhance treatment stratification and research comparability. Emerging technologies from PET-CT imaging [15] and molecular diagnostics to biofilm-disrupting agents and bacteriophage therapy [21] are expanding the diagnostic and therapeutic repertoire. Robust randomized controlled trial data, currently lacking in many areas of FRI management, are urgently needed [4].

For the orthopaedic surgeon in clinical practice, the key message is clear: FRI demands early recognition, structured diagnostic evaluation using the consensus criteria [1,2], prompt microbiological sampling [14], coordinated multidisciplinary decision-making, and

individualized surgical and antimicrobial management [13,16,17]. Patient-centred outcomes including functional recovery, quality of life, and return to activity must remain at the forefront of care [22].

Conflict of Interest

The authors declare no conflicts of interest relevant to this editorial.

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Ethical Approval

Not applicable.

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