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Novel strategies in early management of fracture-related infection; a comprehensive literature review

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Abstract

Fracture-related infection (FRI) remains one of the most consequential complications in orthopedic trauma, imposing effects that extend far beyond localized tissue involvement to include substantial systemic morbidity and notable socioeconomic burden. Its clinical urgency is underscored by a highly variable incidence—ranging from 1%–2% in closed fractures to more than 30% in severe open injuries—and by its detrimental impact on bone healing, functional recovery, and overall quality of life. This literature review synthesizes current knowledge on the epidemiology and clinical significance of FRI, emphasizing incidence patterns, associated functional limitations, long-term risks such as nonunion, amputation, and mortality, and the considerable health-economic implications. Persistent challenges in early diagnosis are highlighted, including nonspecific clinical presentations, inconsistencies in temporal classifications, and the limited ability of available treatments to simultaneously eradicate infection and maintain mechanical stability. Contemporary management strategies—such as debridement, antibiotics, and implant retention (DAIR); staged hardware removal; systemic antimicrobial therapy; and adjunctive local antibiotic-delivery systems—are examined with attention to their evidence gaps and recognized failure points. In addition, emerging modalities that target the underlying pathophysiology of FRI are reviewed, including biofilm-disruptive agents, biodegradable antibiotic carriers, antimicrobial implant coatings, and bacteriophage-based approaches, each offering mechanistic advantages over conventional interventions. Collectively, the current evidence underscores the critical need for standardized diagnostic criteria, timely multidisciplinary management, and rigorous clinical evaluation of innovative therapeutic strategies to improve outcomes, reduce recurrence, and optimize fracture healing in early FRI.

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Introduction

Fracture-related infection (FRI) remains one of the most challenging complications in orthopedic trauma surgery, exerting profound impacts on patient morbidity, functional outcomes, healthcare costs, and healthcare resource utilization (1). Despite advances in surgical techniques, biomaterials, and perioperative care, the incidence of FRI continues to range between 1% and 2% in closed fractures and may reach up to 30% in severe open injuries, particularly in high-energy trauma (2). Such infections complicate the healing process by disrupting the delicate interplay between bone regeneration, vascular supply, and the local immune environment, often culminating in prolonged hospitalization, repeated surgical interventions, and, in refractory cases, limb loss (3,4). The early detection and prompt management of FRI are pivotal for preserving function, preventing chronic osteomyelitis, and reducing the long-term socioeconomic burden (5,6).

The pathogenesis of FRI is multifactorial, typically initiated by bacterial contamination at the time of injury or surgery, with Staphylococcus aureus and Staphylococcus epidermidis being the most frequently implicated pathogens (7). These microorganisms can form biofilms on fracture fixation devices and necrotic bone fragments, creating a microenvironment that hinders immune-mediated clearance and reduces antibiotic penetration (4). This biofilm-associated phenotype contributes to the persistence of infection, therapeutic failures, and the transition from acute to chronic stages (8). Historically, conventional management strategies have centered on a combination of meticulous surgical debridement (7), systemic antibiotic therapy, stabilization of the fracture environment, and staged reconstructive procedures (9). However, these approaches are often challenged by diagnostic delays, antimicrobial resistance, preservation of hardware stability, and host systemic factors such as diabetes,

Key point

Fracture related infection significantly affects healing, function, and survival, with incidence up to 30% in severe open fractures. Early detection remains difficult, and current therapies face eradication–stability trade offs. Emerging biofilm targeted and local delivery strategies offer promise, but require standardized definitions and rigorous clinical validation.

immunosuppression, or poor vascularization of the injury site (10).

Early diagnosis represents a cornerstone in FRI management, yet remains clinically demanding (11). Classical diagnostic criteria, including local signs of inflammation, laboratory biomarkers (e.g., C-reactive protein, erythrocyte sedimentation rate), and radiographic changes, may be nonspecific or delayed in manifestation (12). Recent efforts have shifted toward incorporating advanced imaging modalities, molecular microbiology techniques, and highly sensitive biomarker panels to detect infection at a subclinical stage (13). These evolving diagnostic tools aim to enable rapid and accurate differentiation between infection and aseptic inflammation, thus allowing surgeons to institute targeted intervention before irreversible tissue damage occurs (14).

Over the past decade, several novel strategies have emerged that promise to improve the early management of FRI (11). These include the application of local antibiotic carriers, such as bioabsorbable calcium sulfate beads or polymethylmethacrylate spacers (9), which deliver high concentrations of antimicrobial agents directly to the infected site while minimizing systemic toxicity (15). Adjunctive measures, including negative pressure wound therapy (NPWT), biofilm-disrupting agents, antimicrobial-coated implants, and host immunomodulation, have also gained attention (16). Furthermore, strategies based on precision medicine, such as patient-specific antibiotic regimens guided by genomic and proteomic pathogen profiling, represent a paradigm shift in individualized care (17).

Despite the growing body of evidence supporting these innovative interventions, their optimal integration into standardized treatment algorithms remains undefined (9). Variability in clinical trial designs, heterogeneous patient populations, and inconsistent outcome measures have limited the ability to draw definitive conclusions regarding their superiority over traditional methods (18). This underscores the need for comprehensive literature reviews that synthesize current knowledge, evaluate the quality and applicability of available evidence, and identify critical gaps for future research (19, 20).

Therefore, the present review aims to provide a thorough and up-to-date synthesis of emerging strategies for the early management of FRI. By critically appraising recent advancements and outlining their potential clinical implications, this work seeks to assist orthopedic surgeons, infectious disease specialists, and multidisciplinary teams in optimizing patient outcomes through evidence-based and innovative approaches.

Materials and Methods

A comprehensive literature search was conducted across PubMed, Scopus, and Web of Science databases to identify relevant studies on the early management of FRI. The search strategy incorporated combinations of the following keywords and their synonyms: "fracture-related infection," "orthopedic infection," "biofilm," "early management," "debridement," "local antibiotic delivery," "implant coating," and "bacteriophage." No restrictions were applied regarding the year of publication, and only articles published in English were considered. Titles, abstracts, and full texts were screened to include peer-reviewed original studies, reviews, and relevant clinical guidelines addressing incidence, diagnostic approaches, treatment modalities, and emerging strategies for early FRI management.

Results

The incidence and prevalence of FRI

Fracture-related infection is a relatively uncommon yet serious complication in orthopedic trauma surgery, with considerable variability in incidence depending on the mechanism of injury, fracture location, and the presence of open wounds (21). In closed fractures managed with internal fixation, reported infection rates generally range from 1% to 2%, whereas high-energy open fractures, particularly Gustilo–Anderson type III injuries, demonstrate markedly higher rates, up to 30% in some series (22). These figures are influenced by factors such as the extent of soft-tissue damage, environmental contamination at the time of injury, timing and quality of surgical intervention, and adherence to perioperative antibiotic prophylaxis protocols (23). Robust epidemiological studies have shown that infection risk correlates strongly with the severity of trauma, polytrauma status, and patient comorbidities (24), making FRI both a preventable and context-dependent complication (25).

Globally, variations in FRI prevalence also reflect differences in healthcare infrastructure, surgical expertise, and perioperative guidelines (10). Low- and middle-income countries tend to face disproportionately higher incidence rates due to delayed presentations (26), limited access to advanced imaging and microbiological diagnostics, and restricted availability of multidisciplinary care teams (27). Additionally, evolving definitions of FRI, especially the consensus proposed by the AO/EBJIS (European Bone and Joint Infection Society), have helped standardize diagnostic criteria, leading to more accurate epidemiological reporting (26). However, under-diagnosis remains a concern, particularly in subclinical or chronic cases where biofilm-associated low-grade infections may not meet conventional diagnostic thresholds (28).

Improved surveillance systems and international registries are therefore critical to obtain reliable global prevalence data and guide resource allocation (29).

FRI delays healing, limits function, raises costs

The development of an FRI profoundly disrupts fracture healing, primarily by prolonging the inflammatory phase, impairing angiogenesis, and compromising osteogenic cell activity (30). The establishment of a bacterial biofilm at the fracture site or along fixation hardware creates a hostile microenvironment that hinders callus formation and disrupts the delicate balance between bone resorption and formation (31,32). This pathophysiological cascade often results in delayed union or nonunion, necessitating multiple revision surgeries, prolonged antibiotic therapy, and adjunctive measures such as bone grafting (33). In addition, infection-related soft tissue loss or scarring may limit the success of reconstructive efforts, reducing the likelihood of optimal anatomical alignment and functional recovery (6).

From a patient-centered perspective, FRI is a major determinant of long-term functional impairment (34). Many affected individuals experience chronic pain, reduced range of motion, and persistent swelling, which collectively compromise return-to-work rates and quality of life (35). The economic implications are equally significant: the cost of treating an infected fracture is estimated to be two to five times greater than that of managing an uncomplicated one (36). Expenses arise from extended hospital stays, repeated operative procedures, extended antibiotic regimens, and prolonged rehabilitation (5). Indirect costs, including loss of productivity, disability compensation, and caregiver burden, further amplify the socioeconomic impact, making FRI both a medical and economic challenge with implications for public health policy (37).

Risks; nonunion, limb loss, higher mortality

Long-term outcomes following FRI are frequently unfavorable, especially in cases of delayed diagnosis or inadequate early management (38). Nonunion remains one of the most common sequelae, resulting from chronic infection-induced bone necrosis, segmental bone defects, and compromised vascularity (34). In severe cases, especially when infection coexists with extensive soft-tissue damage or vascular injury, salvage options may be limited, culminating in amputation (35). Reports suggest that amputation rates after severe open FRIs may range from 5% to 15%, with higher rates observed in poly-traumatized or immunocompromised patients (39). Additionally, recurrent or persistent infection can lead to chronic osteomyelitis, which poses ongoing risks of systemic spread and joint involvement (3). Beyond limb-specific outcomes, FRI also carries systemic risks, including sepsis and multi-organ failure in acute stages, as well as increased overall mortality in the long term (40). Population-based studies indicate that patients with chronic osteomyelitis or unresolved FRIs have higher mortality rates compared to matched controls, even when adjusted for comorbidities (38). This elevated risk likely reflects the cumulative physiological stress of recurrent surgeries (19), prolonged systemic inflammation (40), and the indirect impact of immobility-related complications such as venous thromboembolism or cardiopulmonary events (40). Understanding and mitigating these long-term risks require not only prompt infection control but also comprehensive, multidisciplinary follow-up care that addresses functional restoration, infection surveillance, and psychosocial support (41).

Challenges in early diagnosis and management

Diagnosing early FRI is inherently challenging because the clinical presentation often overlaps with the expected physiological inflammatory response following fracture fixation (6). Postoperative signs such as localized warmth, erythema, swelling, and mild discomfort can be manifestations of normal healing, aseptic inflammation, or early sepsis (22). Systemic indicators—including low-grade fever or malaise—are frequently absent or delayed, especially in immunocompromised patients, elderly individuals, or those receiving anti-inflammatory medication (3). Laboratory tests, while widely used, suffer similar limitations (35); C-reactive protein and leukocyte counts may transiently rise after surgery, making it difficult to distinguish infection from trauma-induced inflammation during the critical early phase (42).

The timing of symptom onset further complicates diagnosis. In many cases, early infection progresses insidiously, producing subtle clinical cues that escape detection until the microbial burden is sufficient to disrupt wound healing or induce systemic signs (6). Microbiological cultures may yield false-negative results if samples are collected after empirical antibiotic administration, whereas imaging techniques—such as plain radiography—are insensitive to early bone or implant surface changes (4). Even advanced modalities like MRI or nuclear imaging can be confounded by postoperative alterations in bone marrow and soft tissues (33). This diagnostic ambiguity often delays definitive treatment, inadvertently allowing biofilms to mature and decreasing the likelihood of conservative measures succeeding (43).

Definitions of 'early' vary across studies

The concept of "early" FRI remains inconsistently defined in the literature, complicating comparison between studies and the formulation of evidence-based guidelines (31). Some authors categorize infections occurring within two weeks of fixation as early, based on the hypothesized absence of mature biofilm formation in this window (33). Others extend this definition to four or even twelve weeks, citing variability in microbial growth rates, host immune responses, and implant-tissue integration (19).

This heterogeneity in temporal thresholds often stems from differing clinical traditions, pathogen profiles, and research objectives, rather than from universally accepted microbiological or histopathological criteria (11).

Such inconsistency has significant implications for both clinical practice and research. Variably defined early-stage cohorts make it difficult to pool data in narrative review or to draw robust conclusions regarding optimal intervention timing (37,44). Furthermore, an intervention proven effective in a cohort defined by a two-week cutoff may fail when applied to patients meeting a broader twelve-week definition (45). In the absence of standardized temporal criteria, interpretation of treatment outcomes remains context-dependent, limiting the development of universally applicable algorithms (44). Establishing a globally recognized definition, ideally supported by clinical, microbiological, and molecular evidence, is essential to harmonize research and improve patient management strategies (46).

Methods clear infection and preserve healing

Current management strategies for early FRI aim to eradicate infection while maintaining the stability required for bone healing (19); however, achieving both objectives often proves difficult. Surgical debridement, while necessary to reduce bacterial load, carries the risk of devascularizing tissues and destabilizing the fixation construct (47). Hardware removal may facilitate infection control but can lead to fracture instability, necessitating complex reconstructive procedures and increasing the likelihood of delayed union or nonunion (44). Conversely, retaining implants in the presence of persistent infection risks chronic colonization, recurrent inflammation, and progressive bone loss (48).

Systemic antibiotic therapy, a cornerstone of management, also faces several limitations. Achieving bactericidal concentrations at the fracture site can be challenging due to compromised vascularity, fibrosis, and biofilm-mediated protection of pathogens (39). Prolonged systemic therapy increases the potential for nephrotoxicity, hepatotoxicity, and antimicrobial resistance, while local antibiotic delivery systems, though promising, are not universally effective against all pathogens or biofilm stages (41). Ultimately, the balance between aggressive infection control and preservation of the mechanical environment for fracture healing remains a fine line, with current methods often providing suboptimal results in one domain to protect the other (42). These limitations have stimulated interest in novel strategies capable of addressing both therapeutic goals concurrently (49).

Early FRI care; debridement and antibiotics

In contemporary orthopedic trauma care, early FRI is typically addressed through an integrated surgical and pharmacological approach (49). The surgical component most often consists of debridement, antibiotics, and implant retention (DAIR) when mechanical stability of the fracture fixation is preserved and the infection is identified before biofilm maturation (30). This strategy involves meticulous removal of necrotic tissue, irrigation of the operative field (23), and selective exchange of modular hardware components to reduce microbial load while maintaining fracture alignment (50). In cases where fixation stability is compromised or infection has caused substantial tissue destruction (50), staged hardware removal followed by temporary external fixation may be adopted, with definitive internal fixation deferred until infection eradication is confirmed (24).

Pharmacological management hinges on targeted antimicrobial therapy guided by intraoperative specimens (2). Empirical treatment is typically initiated immediately post-debridement, based on local epidemiology and injury characteristics, and is subsequently refined upon receipt of microbiological culture and sensitivity results (48). A combined regimen of intravenous antibiotics during the acute phase—often for two to six weeks—followed by a tailored course of oral therapy is common practice (6,45). Adjunctive measures, such as the use of local antibiotic delivery systems (e.g., polymethylmethacrylate beads, calcium sulfate pellets), aim to achieve high local drug concentrations and minimize systemic toxicity (10). These combined modalities form the backbone of current early FRI management, balancing infection control with preservation of biomechanical conditions favorable to bone healing (40).

Protocols lack robust evidence and leave key gaps

Despite extensive clinical experience with established FRI treatment algorithms, significant limitations remain in achieving consistent eradication of infection while safeguarding fracture consolidation (3,45). The DAIR procedure's success is highly time-sensitive and dependent on accurate early diagnosis—criteria that are not consistently met in everyday settings due to the nonspecific presentation of early FRI (36). Moreover, while implant retention preserves mechanical stability, it also carries the risk of residual biofilm persistence, leading to recurrent infection after apparent clinical resolution (39). Similarly, aggressive hardware removal, although sometimes necessary, may cause loss of reduction and significantly prolong the time to union, necessitating additional reconstructive interventions (39).

From a pharmacological standpoint, systemic antibiotic regimens often fail to achieve bactericidal concentrations within biofilm-colonized tissue, especially in areas of poor vascularity (10). Moreover, current treatment protocols are predominantly informed by observational studies and expert consensus rather than large-scale randomized controlled trials, resulting in an incomplete evidence base for optimal antibiotic selection, duration, and combination therapy (23,41). The heterogeneity of pathogen profiles, variable host immune responses, and

differing surgical settings further limit the generalizability of existing recommendations (37). These gaps underscore the need for high-quality prospective research and multidisciplinary consensus to refine current practices and integrate emerging therapeutic innovations into standardized, evidence-based care pathways (30,47).

Emerging novel strategies

Recent advances in orthopedic infection science have prompted the development of targeted strategies aimed at overcoming the unique biological challenges posed by FRI (38). Biofilm-targeted therapies are designed to disrupt or eradicate the extracellular polymeric matrix that shields bacteria from both immune surveillance and antibiotic penetration (18). These approaches include enzymatic degradation of biofilm components, use of quorum-sensing inhibitors to prevent bacterial communication, and application of novel antimicrobial peptides with enhanced biofilm-penetrating capabilities (12,30). Additionally, photodynamic and ultrasound-mediated modalities are being explored as adjuncts to increase susceptibility of biofilm-embedded pathogens to conventional antimicrobials (5,34).

Local antibiotic carriers represent another significant innovation, providing high-dose antimicrobial concentrations directly at the infection site while limiting systemic exposure (16). Biodegradable materials such as calcium sulfate or hydroxyapatite are used to deliver broad-spectrum or pathogen-specific antibiotics, ensuring sustained release during the critical early phases of infection control (20, 48). In parallel, the development of antimicrobial coating technologies for orthopedic implants—utilizing substances like silver, iodine, or antibiotic-embedded polymers—aims to prevent microbial adhesion and biofilm establishment on implant surfaces (49,51). Bacteriophage therapy, re-emerging with modern biotechnology, offers pathogen-specific viral agents capable of infecting and lysing bacteria (7), including multidrug-resistant strains, with the potential to complement or even replace conventional antibiotic regimens in selected cases (52).

Targeted interventions for early-stage FRI

The integration of these novel modalities into early FRI management offers several potential benefits that address key shortcomings of current approaches (51). Biofilm-targeted therapies directly confront the principal barrier to infection eradication, enhancing the penetration and efficacy of systemic or locally applied antimicrobials (41,45). By disrupting established microbial communities, these treatments may reduce the likelihood of recurrent infection and the need for radical surgical interventions (51). Similarly, the use of local antibiotic carriers delivers supra-therapeutic antimicrobial concentrations at the site of infection (53), bypassing vascular delivery limitations and minimizing systemic toxicity, which is particularly advantageous in patients with renal or hepatic comorbidities (54).

Antimicrobial coatings on implants serve a preventive function, reducing initial bacterial colonization and biofilm formation in high-risk scenarios (35), thereby preserving the stability of fixation devices and promoting uninterrupted bone healing (55). Bacteriophage therapy adds a level of pathogen specificity unmatched by conventional antibiotics, enabling targeted elimination of resistant organisms while sparing beneficial microbiota (2), and potentially lowering the risk of broad-spectrum antimicrobial resistance (51). Collectively, these emerging strategies promise to shorten treatment duration, reduce reoperation rates, and improve long-term functional outcomes (54). Their successful implementation, however, will depend on rigorous clinical validation, integration into evidence-based protocols, and multidisciplinary adoption within orthopedic trauma practice (56).

Discussion

The early recognition and effective management of FRI remain among the most formidable challenges in orthopedic trauma surgery (16). The findings synthesized in this review reaffirm that FRI, while relatively infrequent in closed fractures, is a prevalent and significant complication in high-energy open injuries (46), particularly those involving severe soft-tissue compromise (53). Reported incidence rates—ranging from 1–2% in closed fractures to as high as 30% in Gustilo–Anderson type III injuries—underscore the need for context-sensitive prevention strategies (55). This variability is compounded by geographic disparities, with low- and middle-income regions experiencing disproportionately higher burdens due to delayed presentation, infrastructural constraints (22,48), and limited access to advanced diagnostics. Such disparities highlight the critical role of global health initiatives in standardizing perioperative infection control measures and ensuring equitable access to expertise and technology (57).

A central clinical concern identified in the results is the profound impact of FRI on fracture healing and long-term patient function (22). The infection-driven disruption of angiogenesis, osteogenesis, and soft-tissue viability predisposes to delayed union or nonunion, often necessitating multiple reconstructive procedures (30). Beyond biomechanical sequelae, the sustained inflammatory milieu has functional and socioeconomic repercussions, manifesting as chronic pain, reduced mobility, prolonged rehabilitation (42), and substantial direct and indirect healthcare costs (30). These findings align with existing epidemiological evidence indicating that the treatment of infected fractures is two to five times more expensive than that of uncomplicated cases (47), with indirect costs from loss of productivity further amplifying the economic burden (53).

The review also draws attention to the high stakes

of delayed diagnosis. The nonspecific and often subtle clinical presentation in early FRI, coupled with the limited specificity of conventional inflammatory markers and the interpretive challenges of early-phase imaging (32), continues to impede timely intervention (44). While the AO/EBJIS consensus has advanced diagnostic standardization, definitional heterogeneity regarding the "early" stage of infection—ranging from two to twelve weeks post-fixation—remains a major obstacle to cross-study comparability and guideline development (26). This definitional variability not only affects epidemiological clarity but also has direct therapeutic implications, as the timing window for effective DAIR (Debridement, Antibiotics, and Implant Retention) is tightly coupled to biofilm maturity (50).

Existing management paradigms, dominated by combinations of surgical debridement, systemic antibiotics, and selective implant retention, exhibit notable limitations(18). The delicate balance between aggressive bacterial eradication and preservation of fracture stability often forces surgical compromises (32). Implant removal enhances infection control in selected cases but risks biomechanical instability; conversely, retention may preserve fixation but allow biofilm persistence (4, 22). Systemic antimicrobial therapy encounters pharmacokinetic barriers at the infection site—particularly within the biofilm matrix and hypoperfused tissue—and is further constrained by host comorbidities and antimicrobial resistance(45). Such shortcomings provide a strong rationale for the clinical integration of innovative therapeutic approaches (58).

Emerging strategies—including biofilm-targeted agents, biodegradable local antibiotic carriers, antimicrobial implant coatings and bacteriophage therapy—offer tangible mechanistic advantages over conventional modalities (32, 33). The ability to directly disrupt biofilm architecture or prevent bacterial adhesion at the implant–tissue interface addresses a core barrier to infection eradication (44). Local antibiotic delivery systems achieve sustained supra-therapeutic concentrations while reducing systemic toxicity, and bacteriophages introduce a highly specific antibacterial modality with potential efficacy against multidrug-resistant organisms (50). These innovations collectively promise to improve infection resolution rates, reduce reoperation frequency, and optimize fracture healing trajectories (28).

However, the transition from promising experimental results to robust clinical adoption requires rigorous evaluation (46). Many of these novel approaches remain under-studied in large, comparative clinical trials, limiting the strength of current recommendations (38). Moreover, practical considerations—including cost-effectiveness, regulatory approval pathways, scalability, and surgeon familiarity—will influence adoption (55). Multidisciplinary collaboration among orthopedic surgeons, infectious disease specialists, microbiologists (25), and biomedical engineers will be essential not only to refine these technologies but also to integrate them into standardized, evidence-based care pathways (59).

The body of evidence supports an urgent need for refined diagnostic algorithms, early targeted therapeutic strategies, and equitable dissemination of novel interventions (46). Addressing both the microbiological and mechanical dimensions of FRI is imperative to improving patient outcomes and reducing the global burden of this complication (14, 46). Future research must prioritize standardized definitions (28), biomarker-enhanced diagnostic protocols, and high-quality clinical trials that assess the synergistic potential of emerging modalities alongside optimized conventional care (16).

Conclusion

Early FRI remains a complex, high-impact complication that compromises bone healing, functional recovery, and healthcare resources. Diagnostic ambiguity and the limitations of current treatments highlight the need for standardized definitions and timely, targeted interventions. Emerging biofilm-focused modalities, local antibiotic platforms, antimicrobial coatings, and bacteriophage therapy hold substantial promise, warranting rigorous clinical validation to optimize infection control while preserving fracture stability.

Authors' contribution

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Conflicts of interest

The authors declare that they have no competing interests.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors utilized Perplexity to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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References

1. Moriarty TF, Metsemakers WJ, Morgenstern M, Hofstee MI, Vallejo Diaz A, Cassat JE, et al. Fracture-related infection. Nat Rev Dis Primers. 2022;8: 67. doi: 10.1038/s41572-022-00396-0.
2. Rupp M, Walter N, Bärtl S, Heyd R, Hitzenbichler F, Alt V. Fracture-Related Infection-Epidemiology, Etiology, Diagnosis, Prevention, and Treatment. Dtsch Arztebl Int. 2024;121:17-24. doi: 10.3238/arztebl.m2023.0233.
3. Woffenden H, Yasen Z, Burden E, Douthwaite A, Elcock SB, Mclean L, et al. Fracture-related infection: Analysis of healthcare utilisation and associated costs. Injury. 2023;54:111109. doi: 10.1016/j.injury.2023.111109.
4. Natoli RM, Malek S. Fracture-related infection blood-based biomarkers: Diagnostic strategies. Injury. 2024;55 Suppl 6:111823. doi: 10.1016/j.injury.2024.111823.
5. De Meo D, Cera G, Ceccarelli G, Castagna V, Aronica R, Pieracci EM, et al. Candida fracture-related infection: a systematic review. J Bone Jt Infect. 2021;6:321-328. doi: 10.5194/jbji-6-321-2021.
6. Walter N, Orbenes N, Rupp M, Alt V. The State of Research in Fracture-Related Infection-A Bibliometric Analysis. Medicina (Kaunas). 2022;58:1170. doi: 10.3390/medicina58091170.
7. Baertl S, Metsemakers WJ, Morgenstern M, Alt V, Richards RG, Moriarty TF, et al. Fracture-related infection. Bone Joint Res. 2021;10:351-353. doi: 10.1302/2046-3758.106.BJR-2021-0167.R1.
8. Liu K, Zhang H, Maimaiti X, Yusufu A. Bifocal versus trifocal bone transport for the management of tibial bone defects caused by fracture-related infection: a meta-analysis. J Orthop Surg Res. 2023;18:140. doi: 10.1186/s13018-023-03636-5.
9. He SY, Yu B, Jiang N. Current Concepts of Fracture-Related Infection. Int J Clin Pract. 2023;2023:4839701. doi: 10.1155/2023/4839701.
10. Valderrama-Molina CO, Pesántez R. Fracture-Related infection - the role of the surgeon and surgery in prevention and treatment. J Orthop Surg (Hong Kong). 2022;30:10225536221118520. doi: 10.1177/10225536221118520.
11. Gitajn I, Werth P, O'Toole RV, Joshi M, Jevsevar D, Wise B, et al. Microbial Interspecies Associations in Fracture-Related Infection. J Orthop Trauma. 2022;36:309-316. doi: 10.1097/BOT.0000000000002314.
12. Dvorak JE, Lasinski AM, Romeo NM, Hirschfeld A, Claridge JA. Fracture related infection and sepsis in orthopedic trauma: A review. Surgery. 2024;176:535-540. doi: 10.1016/j.surg.2024.04.031.
13. McNally M, Govaert G, Dudareva M, Morgenstern M, Metsemakers WJ. Definition and diagnosis of fracture-related infection. EFORT Open Rev. 2020;5:614-619. doi: 10.1302/2058-5241.5.190072.
14. Baertl S, Rupp M, Alt V. The DAIR-procedure in fracture-related infection-When and how. Injury. 2024;55 Suppl 6:111977. doi: 10.1016/j.injury.2024.111977.
15. Hussain SA, Walters S, Ahluwalia AK, Trompeter A. Fracture-related infections. Br J Hosp Med (Lond). 2023;84:1-10. doi: 10.12968/hmed.2022.0545.
16. Haidari S, Buijs MAS, Plate JDJ, Zomer JJ, IJpma FFA, Hietbrink F, et al. Costs of fracture-related infection: the impact on direct hospital costs and healthcare utilisation. Eur J Trauma Emerg Surg. 2024;50:1701-1707. doi: 10.1007/s00068-024-02497-9.
17. Balogh ZJ, Leung F. Fracture related infections. J Orthop Surg (Hong Kong). 2022;30:10225536221137029. doi: 10.1177/10225536221137029.
18. Iliaens J, Onsea J, Hoekstra H, Nijs S, Peetermans WE, Metsemakers WJ. Fracture-related infection in long bone fractures: A comprehensive analysis of the economic impact and influence on quality of life. Injury. 2021;52:3344-3349. doi: 10.1016/j.injury.2021.08.023.
19. Tissingh EK, Marais L, Loro A, Bose D, Paner NT, Ferguson J, et al. Management of fracture-related infection in low resource settings: how applicable are the current consensus guidelines? EFORT Open Rev. 2022;7:422-432. doi: 10.1530/EOR-22-0031.
20. Azi ML, Valderrama-Molina CO, Carabelli G, Cruz MAA, Bidolegui F, Gómez A, et al. Treatment of fracture-related infection in Latin America (FRILA). Proposal for a multicentre regional registry. Injury. 2023;54 Suppl 6:110898. doi: 10.1016/j.injury.2023.110898.
21. Desimone CA, Adams AJ, Kern NP, Kachooei AR, Beredjiklian P. Fracture-Related Infection Diagnostic Tools in the Upper Extremity: A Scoping Review. Acta Orthop Belg. 2024;90:769-776. doi: 10.52628/90.4.13052.
22. Mills H, Donnelly L, Platt S. Locally Delivered Antibiotics in Fracture-Related Infection. Cureus. 2024;16:e73210. doi: 10.7759/cureus.73210.
23. Foster AL, Moriarty TF, Zalavras C, Morgenstern M, Jaiprakash A, Crawford R, et al. The influence of biomechanical stability on bone healing and fracture-related infection: the legacy of Stephan Perren. Injury. 2021;52:43-52. doi: 10.1016/j.injury.2020.06.044.
24. Gundtoft PH, Bue MH, Hansen RL, Gottlieb H, Ravn C, Petersen KK. Fracture-related infections. Ugeskr Laeger. 2022;184:V05220363.
25. Riedl M, Straub J, Walter N, Baertl S, Baumann F, Alt V, et al. Fracture-Related Infection of the Proximal Femur - Diagnostics and Treatment. Geriatr Orthop Surg Rehabil. 2025;16:21514593251324768. doi: 10.1177/21514593251324768.
26. Metsemakers WJ, Moriarty TF, Morgenstern M, Marais L, Onsea J, O'Toole RV, et al. The global burden of fracture-related infection: can we do better? Lancet Infect Dis. 2024;24:e386-e393. doi: 10.1016/S1473-3099(23)00503-0.
27. Freigang V, Walter N, Rupp M, Riedl M, Alt V, Baumann F. Treatment of Fracture-Related Infection after Pelvic Fracture. J Clin Med. 2023;12:6221. doi: 10.3390/jcm12196221.
28. Ahmed EA, Almutairi MK, Alkaseb AT. Accuracy of Tissue and Sonication Fluid Sampling for the Diagnosis of Fracture-Related Infection: Diagnostic Meta-Analysis. Cureus. 2021;13:e14925. doi: 10.7759/cureus.14925.
29. Joseph B Jr, Lindsay Lopez B, Kandemir U. Prevention of Fracture-Related Infection. Instr Course Lect. 2025;74:405-412.
30. Liu C, Gregg AT, Moye SC, Fischer A, Akodu M, Appleton P, et al. Utility of Sonication for Fracture-Related Infection. J Orthop Trauma. 2025. doi: 10.1097/BOT.0000000000003006.
31. Vicenti G, Buono C, Albano F, Ladogana T, Pesare E, Colasuonno G, et al. Early Management for Fracture-Related Infection: A Literature Review. Healthcare (Basel). 2024;12:1306. doi: 10.3390/healthcare12131306.
32. Alt V, McNally M, Wouthuyzen-Bakker M, Metsemakers WJ, Marais L, Zalavras C, et al. The FRI classification - A new classification of fracture-related infections. Injury. 2024;55:111831. doi: 10.1016/j.injury.2024.111831.
33. von Rüden C, Wunder J, Schirdewahn C, Augat P, Hackl S. Initial treatment of severe soft-tissue injuries in closed and open fractures to prevent fracture-related infection. Injury. 2024;55 Suppl 6:111935. doi: 10.1016/j.injury.2024.111935.
34. Maurer E, Walter N, Baumgartner H, Histing T, Alt V, Rupp

M. Quality of life after fracture-related infection of the foot. Foot Ankle Surg. 2022;28:1421-1426. doi: 10.1016/j.fas.2022.08.005.
35. Pilskog K, Høvding P, Fenstad AM, Inderhaug E, Fevang JM, Dale H. Risk factors for fracture-related infection after ankle fracture surgery. Injury. 2023;54:111011. doi: 10.1016/j.injury.2023.111011.
36. Boeckxstaens A, Hoekstra H, Depypere M, Nevens T, Nijs S, Vranckx JJ, et al. Fracture-related infection of the patella: Treatment options and outcome. Injury. 2022;53:1880-1886. doi: 10.1016/j.injury.2022.03.062.
37. Seidelman J, DeBaun M. Fracture-Related Infections. Infect Dis Clin North Am. 2025;39:437-448. doi: 10.1016/j.idc.2025.02.012.
38. Depypere M, Sliepen J, Onsea J, Debaveye Y, Govaert GAM, IJpma FFA, et al. The Microbiological Etiology of Fracture-Related Infection. Front Cell Infect Microbiol. 2022;12:934485. doi: 10.3389/fcimb.2022.934485.
39. Sliepen J, Hoekstra H, Onsea J, Bessems L, Depypere M, Noppe N, et al. Treatment and outcome of fracture-related infection of the clavicle. Injury. 2023;54:110910. doi: 10.1016/j.injury.2023.110910.
40. Stroud S, Kandemir U. Management of Chronic Fracture-Related Infection. Instr Course Lect. 2025;74:421-432.
41. Schaffler BC, Kandemir U, Konda SR. Management of Acute and Subacute Fracture-Related Infection. Instr Course Lect. 2025;74:413-420.
42. Konda SR, Dedhia N, Ganta A, Behery O, Haglin JM, Egol KA. Risk Factors for Gram-Negative Fracture-Related Infection. Orthopedics. 2022;45:91-96. doi: 10.3928/01477447-20220105-04.
43. Craxford S, Vris A, Ahluwalia R, Saini A, Harrison WD, Graham S, et al. Fracture related infection in open tibial fractures. J Orthop. 2024;51:98-102. doi: 10.1016/j.jor.2024.01.010.
44. Shah NS, Simpson NA, Frederickson M, Dowell E, Doyle M, Sabbagh RS, et al. Diagnosis of Occult Infection Using Fracture-Related Infection Criteria at the Time of Nonunion Repair. J Orthop Trauma. 2023;37:276-281. doi: 10.1097/BOT.0000000000002569.
45. Razii N, Hrycaiczuk A, Kennedy IW, Shields DW, Meek RMD, Jamal B. Proceedings of the United Kingdom Periprosthetic Joint Infection Meeting 2022: Fracture-Related Infection Session. Injury. 2024;55:111905. doi: 10.1016/j.injury.2024.111905.
46. De Franco C, Colò G, Melato M, Battini A, Cambursano S, Logrieco GP, et al. Fracture-Related Infection in Bicolumnar Acetabular Fracture: A Case Report. Diagnostics (Basel). 2022;12:2476. doi: 10.3390/diagnostics12102476.
47. Li B, Liu C, Alt V, Rupp M, Zhang N, Cheung WH, et al. Multidisciplinary approach and host optimization for fracture-related infection management. Injury. 2024;55 Suppl 6:111899. doi: 10.1016/j.injury.2024.111899.
48. Morgenstern M, Kuehl R, Zalavras CG, McNally M, Zimmerli W, Burch MA, et al. The influence of duration of infection on outcome of debridement and implant retention in fracture-related infection. Bone Joint J. 2021;103-B:213-21. doi: 10.1302/0301-620X.103B2.BJJ-2020-1010.R1.
49. Jiang N, Xu CP, Stoodley P, McNally MA. Current Concepts and Investigations of Fracture-Related Infection. Biomed Res Int. 2025;2025:9768347. doi: 10.1155/2025/9768347.
50. Hadizie D, Kor YS, Ghani SA, Mohamed-Saat MA. The Incidence of Fracture-Related Infection in Open Tibia Fracture with Different Time Interval of Initial Debridement. Malays Orthop J. 2022;16:24-29. doi: 10.5704/MOJ.2211.005.
51. Haase DR, Haase LR, Moon TJ, Mersereau EJ, Napora JK, Wise BT. Radiographic parameters associated with fracture-related infection in high energy bicondylar tibial plateau fractures managed with two-stage treatment: Identifying the bad actors. Injury. 2023;54:110759. doi: 10.1016/j.injury.2023.04.046.
52. Muller Q, Gerber F, Papadimitriou Olivgeris M, Di Summa P, Boillat Blanco N, Steinmetz S. Multidisciplinary approach to fracture-related infection. Rev Med Suisse. 2022;18:2363-70. doi: 10.53738/revmed.2022.18.808.2363.
53. Mertens B, Van Daele R, Depypere M, Lagrou K, Debaveye Y, Wauters J, et al. Isavuconazole in the Treatment of Aspergillus fumigatus Fracture-Related Infection: Case Report and Literature Review. Antibiotics (Basel). 2022;11:344. doi: 10.3390/antibiotics11030344.
54. Pilskog K, Høvding P, Inderhaug E, Fevang JM, Dale H. Fracture-related infection: Prevalence and application of the new consensus definition in a cohort of 1004 surgically treated ankle fractures. Injury. 2023;54:841-847. doi: 10.1016/j.injury.2022.12.030.
55. Patel KH, Gill LI, Tissingh EK, Galanis A, Hadjihannas I, Iliadis AD, et al. Microbiological Profile of Fracture Related Infection at a UK Major Trauma Centre. Antibiotics (Basel). 2023;12:1358. doi: 10.3390/antibiotics12091358.
56. Scotcher M, Uren N, Qureshi A, Hancock N, Round J. Fracture-related infection in revision proximal femoral intramedullary nails. Injury. 2024;55:111338. doi: 10.1016/j.injury.2024.111338.
57. Li J, Wong RMY, Chung YL, Leung SSY, Chow SK, Ip M, et al. Fracture-related infection in osteoporotic bone causes more severe infection and further delays healing. Bone Joint Res. 2022;11:49-60. doi: 10.1302/2046-3758.112.BJR-2021-0299.R1.
58. Aremu O. Research trends in fracture-related infection: a bibliometric analysis and visualization study from 2017-2025. Arch Orthop Trauma Surg. 2025;145:333. doi: 10.1007/s00402-025-05938-1.
59. Iliadis AD, Shivji F, Debuka E, Trompeter A, Narayan B, Heidari N. Current concepts in the prevention, diagnosis and treatment of fracture-related infection (FRI). Eur J Orthop Surg Traumatol. 2021;31:957-966. doi: 10.1007/s00590-021-02956-8.