Fracture-related infection

T. Fintan Moriarty1,2,15, Willem-Jan Metsemakers3,4,15, Mario Morgenstern2, Marloes I. Hofsteeg1, Alejandro Vallejo Diaz5,6, James E. Cassat7,8,9, Britt Wildemann15, Melissa Depypere11,12, Edward M. Schwarz2,13 and R. Geoff Richards1,14,15

Abstract | Musculoskeletal trauma leading to broken and damaged bones and soft tissues can be a life-threatening event. Modern orthopaedic trauma surgery, combined with innovation in medical devices, allows many severe injuries to be rapidly repaired and to eventually heal. Unfortunately, one of the persisting complications is fracture-related infection (FRI). In these cases, pathogenic bacteria enter the wound and divert the host responses from a bone-healing course to an inflammatory and antibacterial course that can prevent the bone from healing. FRI can lead to permanent disability, or long courses of therapy lasting from months to years. In the past 5 years, international consensus on a definition of these infections has focused greater attention on FRI, and new guidelines are available for prevention, diagnosis and treatment. Further improvements in understanding the role of perioperative antibiotic prophylaxis and the optimal treatment approach would be transformative for the field. Basic science and engineering innovations will be required to reduce infection rates, with interventions such as more efficient delivery of antibiotics, new antimicrobials, and optimizing host defences among the most likely to improve the care of patients with FRI.

Although infection has been recognized for centuries as a complication of fracture care, much of the literature and guidance on the classification and treatment concepts for FRI has historically been based on osteomyelitis or PJI. However, the greater total global burden of trauma relative to arthroplasty eventually spurred the development of a generally accepted terminology, guidance documents on management and diagnosis, and dedicated scientific literature that focused on FRI1. This Primer presents the current state of the art in the clinical management of FRI, including incidence and treatment, as well as a description of the basic science underscoring the pathology and microbiological aspects of FRI. Finally, the latest innovations in therapeutic targeting of FRI are described, including new approaches implemented in the clinic in the past 5 years, or those currently in preclinical research with significant potential to reduce the burden of FRI in all patients.

Epidemiology

Incidence

The 2019 Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) estimated a total global burden of bone fractures of 178 million new fractures per year, or 2,296 incident cases per 100,000 population1. Although both operative and non-operative fracture fixation protocols are highly successful, with low frequencies of complications such as malalignment or non-union1, one of the most challenging and persistent complications in musculoskeletal surgery is FRI. Considering
Antimicrobial treatment.

Microorganisms to withstand the musculoskeletal system of open fractures, adopted Gustilo and Anderson overlying skin is breached. Bone fractures where the soft tissue or bone damage. Complex fractures based on the severity of the soft tissue injury, the complexity of the fracture and neurovascular injury. Such systems have shown a correlation between injury severity and infection risk. A large-scale analysis of 3,060 open fractures of the tibia showed infection rates of 1.8% (range 0–3.6%) for GA type I, 3.3% (range 0–11%) for GA type II, 5% (range 0–28.6%) for GA type III, 12.3% (range 0–36%) for GA type IIIb and 16.1% (range 16–18%) for GA type IIC fractures. A major factor responsible for the greater incidence of FRI compared with PJI is the loss of integrity of the overlying skin in an open fracture. These open fractures are inevitably contaminated because of prolonged exposure to infectious agents before medical treatment, and any additional vascular damage can compromise the local blood supply, leading to impaired perfusion of host immune cells and systematically administered antibiotics.

Another risk factor for developing an FRI is the anatomical location of the fracture. Clinical data show that fractures of the lower extremity have a higher infection risk than upper extremity injuries, with the highest rates being described for calcaneal and ankle fractures. The higher infection rates may be explained by the lesser soft tissue coverage, the increased incidence of compromised arterial perfusion and the greater impact of the trauma. Infections occur more often in polytrauma patients, although this is not directly correlated with injury severity scores (ISS).

Comorbidities can also increase the risk of an FRI compared with the risk in healthy individuals, including diabetes mellitus (25% versus 13.8%) and smoking (17.7% versus 13.8%). Patient optimization, such as controlling weight, smoking cessation, optimization of blood glucose levels in patients with diabetes, and arterial as well as venous perfusion can successfully reduce complications in elective surgery, although this is generally not possible in a trauma setting.

Antibiotic-resistant pathogens

The increasing prevalence of antibiotic-resistant pathogens is a major global health concern according to the US Centers for Disease Control and Prevention and one of the top five global public health issues identified by the World Health Organization (WHO). As a result of drug resistance, antibiotics become ineffective and infections become increasingly difficult or impossible to treat, resulting in increased mortality. Antimicrobial resistance (AMR) occurs as a natural evolutionary response to antimicrobial exposure and overuse and improper use of antimicrobials, poor infection control practices, international travel and extensive antibiotic use in livestock farming are important drivers of the emergence and spread of AMR.

AMR has also affected the epidemiology of FRI. In general, the prevalence of methicillin-resistant (MRSA) has declined in Europe over the past 10 years. In two European studies, the prevalence of MRSA in FRI was ~1% in one of the top five global public health issues identified by the World Health Organization (WHO). As a result of drug resistance, antibiotics become ineffective and infections become increasingly difficult or impossible to treat, resulting in increased mortality. Antimicrobial resistance (AMR) occurs as a natural evolutionary response to antimicrobial exposure and overuse and improper use of antimicrobials, poor infection control practices, international travel and extensive antibiotic use in livestock farming are important drivers of the emergence and spread of AMR.

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Although S. aureus is a central focus in the effort to define the epidemiology of antibiotic-resistant FRI, additional established and emerging antibiotic-resistant bacterial pathogens are important causes of FRI. These include Staphylococcus epidermidis, which is frequently methicillin-resistant, as well as a number of Gram-positive pathogens (for example, Enterococcus spp.) and Gram-negative pathogens.
(for example, Enterobacterales) found in the gastrointestinal tract. Few data are available on the prevalence of vancomycin-resistant enterococci (VRE) and multidrug resistance in Enterobacterales or Pseudomonas spp. in patients with FRI. One European study found a 5.6% prevalence of extended-spectrum β-lactamase (ESBL) during the period 2013–2017 [REF.30]. In that same period, VRE accounted for 6.7% of cases30. A 2017 Chinese study found that 18% of Enterobacter cloacae-positive FRIs were resistant to ertapenem25. In general, resistance to carbapenems in Klebsiella pneumoniae is increasing, and resistance to colistin, a last resort treatment, is also frequently detected. The rate of resistance to ciprofloxacin, an antibiotic commonly used for FRI, has reached 92% in some regions31. Taken together, these data present an ominous trend of increasing AMR in the setting of FRI. Moreover, as AMR becomes more widespread, clinicians must make difficult decisions regarding appropriate empirical antibiotic coverage for patients with suspected FRI. This increasingly results in the clinical provision of broad-spectrum antibiotics as empirical therapy, which can further perpetuate AMR.

**Mechanisms/pathophysiology**

**Sources of infection**

Most FRIs are acquired exogenously by the penetrating trauma itself preoperatively, during insertion of the fixation device or, in the case of an open fracture, during delayed wound healing or soft tissue coverage32–35. In general, FRIs can be classified into one of three different routes of infection2,33: perioperative, through inoculation of microorganisms into the surgical wound during surgery or immediately after; contiguous due to the penetrating trauma or from an adjacent focus of infection (skin and soft tissue lesions); or haematogenous transmission of pathogens through the blood or lymphatic system.

**Fig. 1 | Clinical course of a complex bone fracture, subsequent fracture-related infection and eventual recovery.**

Initial trauma (parts a and b). Conventional radiograph (part a) shows comminuted segmental fracture in a patient suffering an open Gustilo and Anderson (GA) type IIIA humeral shaft fracture in 2013. Postoperative image (part b) after operative debridement and management with negative pressure wound therapy. Initial treatment (parts c–g). The fracture was fixed with a metal plate, and antibiotic-loaded bone cement was placed in the dead space after removal of a segment of bone (part c). Conventional radiograph (part d) shows treatment with autologous bone graft performed 8 weeks after cement placement. Conventional radiograph (part e) shows lack of bone regeneration after 12 months, with no diagnosis of fracture-related infection (FRI) at that time. Thereafter, two plate revisions followed (2014 and 2016), owing to failure of the bone to regenerate. CT image (part f) shows failure of the second plate, 3 years after the injury. Conventional radiograph (part g), with breakage of screws (not visible), of the third plate osteosynthesis and continued failure of the bone to heal, 1 year after the previous plate revision. Treatment of FRI (parts h and i). Finally, in 2017, all metalware was removed, and an external fixator was applied (part h). After further debridement, where substantial necrotic bone was removed, the dead space was managed with placement of antibiotic-loaded bone cement (part i). Bacteriological culture identified Staphylococcus epidermidis, and systemic antibiotic therapy was started. Treatment of the bone defect (parts j–m). Conventional radiograph (part j) shows a free vascularized fibula graft with double plating to create a stable construct, which supports bony integration of the graft. Two years after surgery, the fibula graft had integrated (part k). CT image (part l) shows a cross section through the bone, confirming recovery. Photograph (part m) shows good clinical outcome without signs of recurrence.
fluid from a distant focus of infection (such as skin, lung and urinary tract infection)\(^{32-34}\).

Perioperative infections and infections caused exogenously by the penetrating trauma (preoperatively) are widely considered as the most common causes of FRI. In general, most of these infections are caused by \textit{S. aureus}, as generally are all other orthopaedic device-related infections \(^ {36-39}\). Less virulent skin organisms such as coagulase-negative staphylococci can be as frequent as \textit{S. aureus}, particularly in late-onset infections \(^ {32,40}\). \textit{Cutibacterium acnes}, a dominant organism in sebaceous follicles of the skin, mainly on the skin of the shoulder girdle, has also been described as a causative pathogen in FRI\(^ {41}\).

Contiguous infections are most often related to open injuries. They are often polymicrobial in origin and caused by environmental pathogens such as \textit{Clostridium} species, \textit{Aeromonas} species, \textit{Pseudomonas aeruginosa} and \textit{Acinetobacter} species\(^ {32,42}\). Fungi, although quite rare, can also be an important cause of contiguous infection\(^ {43,44}\).

Although there is a lifelong risk of haematogenous seeding on any orthopaedic device, haematogenous transmission is less frequent in cases of FRI\(^ {34,47,48}\). This risk is clearly lower for internal fixation devices than for artificial joints\(^ {27,48}\), possibly because prosthetic joints are surrounded by a well-perfused joint capsule that facilitates haematogenous translocation. Most cases of haematogenous FRI have been observed after bacteraemia due to \textit{S. aureus}\(^ {48}\).

**Biofilm**

A community of bacteria within a self-produced matrix of extracellular polymeric substances, which may also involve extracellular DNA or host-derived macromolecules, growing on a substrate such as an implanted fracture fixation device.

**Staphylococcal abscess community (SAC)**. An accumulation of many \textit{S. aureus} bacterial cells within a self-produced fibrin pseudocapsule.

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**Fig. 2 | Risk factors for the development of fracture-related infection.** The risk of fracture-related infection (FRI) is closely related to injury severity. Closed fractures have a low infection rate, with single-dose antibiotic prophylaxis offering good overall protection against FRI. Open fractures have elevated infection risk, due to exposure of the injured tissue to environmental contamination. As injury severity increases, infection risk also increases, with the greatest risks associated with injuries with vascular and severe soft tissue damage. Perioperative antibiotic prophylaxis is an effective means of preventing FRI, with duration dependent on injury severity. Adapted with permission from Ref.\(^ {180}\).
Accessory gene regulator (Agr). The agr locus encodes a quorum-sensing and two-component regulatory system that controls expression of multiple virulence factors in *S. aureus* and *S. epidermidis*.

Surgical debridement
A surgical procedure to remove necrotic or infected tissue, which includes irrigation, excision and removal of foreign material.

Osteoblasts
Cells responsible for bone formation.

Mineralization
The addition of minerals (such as calcium or phosphorus) to callus, leading to calcified tissue.

Callus
Tissue formed at the fracture site during the healing process, with cartilaginous composition at earlier stages, transitioning to calcified tissue at a later stage.

as a fracture fixation device or a vital bone fragment, *S. aureus* coagulase activates host prothrombin, resulting in cleavage of fibrinogen into fibrin, which encases the bacteria within the first 24 h of infection. The biofilm that then develops on the surface comprises extracellular polymeric substances such as bacterial exopolysaccharides and extracellular DNA of host and bacterial origin and is complete within days. Subsequent accessory gene regulator (Agr)-dependent *S. aureus* extravasation leads to dissemination of infection within 1 week of infection. These bacteria within biofilms are characterized by reduced metabolic activity and increased antibiotic tolerance, which is a crucial challenge in the treatment of FRI.

*S. aureus* assembly into SACs has been described in mouse models of osteomyelitis and FRI. Although surrounded by many immune cell types such as neutrophils, monocytes and M2 anti-inflammatory macrophages, the SAC supports long-term bacterial survival, ultimately leading to the formation of abscesses and bacterial origin and is complete within days. Subsequent *agr*-dependent *S. aureus* extracellular matrix-mediated dissemination of host tissues, it is now recognized that reinfection following surgery might be due to bacteria, including *S. aureus* and *Streptococcus agalactiae* (also known as group B streptococcus), which colonize the OLCN of live cortical bone beyond the surgical margins.

Intracellular survival is another important microbiological aspect in FRI. Although described in osteoblasts, there are more data regarding intracellular survival in macrophages. Bacterial intracellular survival might contribute to antibiotic escape, dissemination and persistence, although it is challenging to identify host cells containing intracellular bacteria in vivo and to monitor them over time. Finally, small colony variants (SCVs) of staphylococci have also been found in multiple experimental studies and in a smaller number of clinical studies. SCVs are generally present when there is long-term bacterial survival in hosts after antibiotic exposure or other stress; they display properties of increased antibiotic tolerance and have reduced expression of virulence factors, which is presumably an adaptation to chronic persistent infection.

**Bone erosion due to FRI**
Under normal conditions, a bone fracture will undergo a process of self-healing and restoration of mechanical stability of the injured tissues to the pre-injured state. The first step is the formation of a haematoma due to rupture of blood vessels, facilitating migration of immune cells and stromal progenitor cells to the injury site and initiation of the healing cascade. Healing proceeds through the mineralization of a fibrous soft callus and a well-balanced process of inflammation over 6–8 weeks that leads to successful fracture healing.

However, the presence of bacteria in the wound completely interrupts and diverts this process from a healing response to an inflammatory, antibacterial response that is incompatible with fracture healing. If there is bacterial contamination in the perioperative phase, the inflammatory cell infiltration and marrow oedema resulting from the presence of bacteria normally occur within the first few days. Ultimately, there is induction of osteoclastogenesis that leads to bone resorption and marrow fibrosis. Within several weeks to months, the FRI will manifest as non-union, with fracture instability and the formation of sequestra (FIG. 4). These macroscopic changes first manifest in soft tissues with redness, swelling, heat and pain, and within several weeks, radiographic changes such as osteolysis and reactive periosteal bone formation are visible.

In the presence of invading pathogens, pattern recognition receptors on skeletal and immune cells detect pathogen-associated molecular patterns, resulting in the production of osteoclastogenic cytokines such as IL-1, IL-6, and TNF. TNF signalling through its receptor TNFFR1 on monocyte lineage cells can synergize with receptor activator of nuclear factor-xB (RANK) signaling to promote osteoclastogenesis. TNF also induces IL-1 production by stromal cells, which in turn promotes osteoclastogenesis in osteoclast progenitors primed by receptor activator of nuclear factor-xB ligand (RANKL).

IL-1 in particular was originally identified as ‘osteoclast activating factor’ and stimulates bone loss through direct effects on osteoclast progenitors and by inducing RANKL expression in osteoblasts. IL-1 directly induces the multinucleation and bone-resorptive capacity of osteoclasts, even in the absence of osteoblasts or other stromal cells. Mice lacking the IL-1 receptor...
**Normal fracture healing**

**Fracture-related infection**

**Osteoclastogenesis**

The formation of bone-resorbing cells, osteoclasts, from myeloid precursor cells.

**Sequestra**

Pieces of dead bone separated from surrounding bone due to infection and necrosis.

**Cytokines**

Large group of secreted proteins that are important for cell communication and signaling, during inflammation, they can have pro-inflammatory or anti-inflammatory effects.

**Receptor activator of nuclear factor-κB ligand (RANKL)**. A key mediator of bone resorption that stimulates the formation and activity of osteoclasts by binding to the RANK receptor.

**Osteoclasts**

Cells responsible for bone resorption.

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**Fig. 4 | Disruption of normal bone healing in fracture-related infection.**

The events in the normal fracture healing cascade involve the formation of a fracture haematoma, the induction of a controlled immune response, followed by a repair and remodelling phase mediated by mineralization of the fracture callus. By contrast, in a fracture-related infection (FRI), there is iatrogenic entry of contaminating bacteria at the time of fracture or soon afterwards. These bacteria adhere to extracellular matrix components within the injury site and develop tolerance to antibiotics. Soon after, these bacteria infect the fracture callus. By contrast, in a fracture haematoma, the induction of a controlled immune response, followed by a repair and remodelling phase mediated by mineralization of the fracture callus. By contrast, in a fracture-related infection (FRI), there is iatrogenic entry of contaminating bacteria at the time of fracture or soon afterwards. These bacteria adhere to extracellular matrix components within the injury site and develop tolerance to antibiotics. Soon after, these bacteria infect the fracture callus.

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**Staphylococcal protein A** contributes to bone erosion by triggering osteoblast apoptosis, increasing RANKL expression by osteoblast lineage cells, and directly stimulating osteoclastogenesis. A range of bacterial toxins can kill both immune and skeletal cells. For example, the phenol-soluble modulins (PSMs) are amphipathic peptides that trigger lysis of many cell types, including, notably, osteoblasts, osteoclast precursors and mature osteoclasts. Inactivation of α-type PSMs or the upstream regulator AgrA substantially reduces cytotoxicity and limits bone damage. Moreover, pharmacological targeting of the Agr system is efficacious as an osteoprotective strategy. The contributions of other S. aureus toxins to bone damage are more difficult to ascertain owing to high species-level specificity to host targets. Humanized mouse models of FRI could be particularly helpful in studying these toxins and their effects.

**Local and systemic immune responses**

Neutrophils are actively recruited to the site of an acute FRI in response to pro-inflammatory molecules such as IL-8, IL-6, TNF, IL-17, IL-1β, G-CSF, GM-CSF, MIP1α, MIP1β and MIP2. These neutrophils attempt to clear the infection by generation of reactive oxygen species, neutrophil extracellular trap production, degranulation of antimicrobial peptides and phagocytosis. Some pathogens have developed ways to circumvent these mechanisms, which results in the persistence of the pathogen and the presence of bacteria is detected, there is an excessive infiltration of neutrophils that mount an antibacterial response, and the normal process of bone repair is interrupted. This excessive inflammatory response eventually leads to activation of osteoclasts and erosion of bone, inhibition and death of bone-forming osteoblasts and fibrosis of the bone marrow. Ultimately, these events lead to failure of bony bridging and healing, instability across the fracture and possibly sequestra formation — that is, an FRI.

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**Sequestrum**

Pieces of dead bone separated from surrounding bone due to infection and necrosis.
immunosuppressive macrophages, regulatory T cells and myeloid-derived suppressor cells have also been identified in the bone marrow of mice with a late-stage FRI, which dampen immune responses that are needed to combat the infection and, thus, facilitate chronicity rather than directly targeting the infection.

As FRI constitutes ‘deep infection’, the robustness of the host response includes both innate and adaptive immune responses with systemic consequences. The most concerning aspect of this robust response is a hyper-immune response to secreted bacterial toxins and superantigens, which can lead to toxic shock syndrome and death from cytokine storm. In addition, because bone infections can be caused by commensal pathogens that live on human skin (for example, S. aureus), the adaptive response must overcome immunological memory that includes immunosuppressive regulatory T cells that prevent cytokine storm, and other pathologies from concomitant immunity in tissues distal to the FRI. To better understand adaptive cell-mediated and humoral immune responses during FRI, investigators have been working towards elucidating the ‘immune proteome’ in patients with bone infections. In the case of S. aureus osteomyelitis, serum antibodies...

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**Fig. 5 | Mechanisms of bone changes during bacterial infection in fracture-related infection.** Planktonic bacteria express microbial surface components recognizing adhesive matrix molecules (MSCRAMMs) that promote their adhesion to bone and abiotic surfaces, thereby promoting biofilm formation. Planktonic bacteria also express surface protein A, which promotes their internalization into host immune cells and evasion of humoral immunity. Pathogen-associated molecular patterns (PAMPs) produced by Staphylococcus aureus can be recognized by Toll-like receptors (TLRs) on innate immune and bone cells to promote increased expression of pro-osteoclastogenic cytokines and the canonical osteoclast differentiation factor, receptor activator of nuclear factor-κB ligand (RANKL). Finally, S. aureus can produce secreted toxins, such as the phenol-soluble modulins, which directly induce osteoblast-lineage and osteoclast-lineage cell death. Biofilm formation on fracture fixation devices leads to recruitment of immune cells such as monocytes, macrophages, neutrophils and T lymphocytes. Biofilm-grown bacteria can modulate the differentiation and activation of these immune cells, ultimately resulting in the production of pro-osteoclastogenic cytokines such as IL-1, IL-6, IL-17 and TNF. These cytokines promote osteoclast differentiation and bone resorption, leading to osteolysis at the infectious focus. S. aureus also forms characteristic microcolonies known as staphylococcal abscess communities (SACs) in the centre of abscesses in bone marrow and adjacent soft tissues. Immediately surrounding SACs are viable and necrotic neutrophils, which are encompassed by a layer of macrophages. SAC formation contributes to bacterial persistence during fracture-related infection, ultimately sustaining inflammatory responses that contribute to osteolysis. S. aureus can also invade the osteocyte lacunocanalicular network (OLCN), resulting in osteocyte cell death and deformation of canaliculi. These events increase osteoclastogenesis and promote infection-associated osteolysis. PMN, polymorphonuclear cell; T_{h} cell, T helper 1 cell; T_{h} cell, T helper 17 cell.
Sinus tracts
Small channels from sites of infection to the surface of the skin.

to the bacteria are predictive of treatment success in patients with bone infections. Humoral immunity against several Staphylococcus aureus proteins (including Alta, Hla, SCIN and CHIPS) was associated with infection control, whereas patients with high antibody titres to the iron-regulated surface determinant (Isd) proteins tended to have severe adverse outcomes. Statistically, the study showed a 51–69% reduction in the risk of an adverse outcome for every tenfold increase in initial concentration of IgGs to the protective antigens. Pathogenic anti-IsdB antibodies, which facilitate Trojan horse macrophage formation to disseminate S. aureus from the site of FRI to internal organs, were sustained at high levels in patients with poor outcomes. Specifically, there was a trending 2.6-fold increased risk (OR 2.555) of an adverse event for every tenfold change in the ratio of anti-Isd to anti-Atl IgG in serum at enrolment. Humoral immunity over the course of treatment correlated with adverse outcomes, and levels of antibodies to protective antigens decreased with positive outcomes. Thus, further understanding the systemic immune response to bone pathogens is critical for patient care and development of vaccines for FRI.

Diagnosis, screening and prevention
The first consensus definition for FRI was published in 2018 and was subsequently updated in 2020 (REFS 105,106). Two levels of certainty around diagnostic features were defined: five confirmatory criteria and a list of suggestive criteria (BOX 1). Any single confirmatory criterion is sufficient to diagnose FRI, while a suggestive criterion should prompt further investigation. A validation study showed that the presence of at least one confirmatory criterion identifies most patients with FRI and that some suggestive signs (for example, wound drainage) are highly suggestive of FRI. In this study, 480 of the 637 included patients were diagnosed with an FRI. The presence of at least one confirmatory sign was associated with a sensitivity of 97.5%, a specificity of 100% and a high discriminatory value (area under the receiver operating characteristic curve of 0.99, P < 0.001).

Imaging modalities
The most useful and commonly applied imaging modalities for diagnosing FRI are conventional radiography (that is, X-ray), CT, MRI and nuclear imaging techniques (such as three-phase bone scan, white blood cell or anti-granulocyte antibody scintigraphy and fluorodeoxyglucose (FDG) PET). These imaging modalities may also support surgical planning, by visualizing the anatomical details of the disease (for example, sequestra, sinus tracts and/or subcortical abscesses). Failure of progression of bone healing (that is, non-union), implant loosening, bone lysis, sequestrum and periosteal bone formation are easily monitored by conventional radiography, and more accurate estimates of these might be achieved by CT imaging. Although systematic reviews previously revealed a high diagnostic accuracy for nuclear imaging, this costly diagnostic modality is still not seen as a conclusive test to diagnose an FRI, and therefore is regarded as a suggestive criterion.

Laboratory tests
A number of blood tests that are routinely observed in patients with infections, such as leucocyte count, C-reactive protein and erythrocyte sedimentation rate, can also be elevated after trauma or surgery, and as such are not specific for FRI. Therefore, these tests provide only limited diagnostic value in the diagnostic work-up of FRIs and are seen as suggestive criteria. However, a secondary rise after an initial decrease, or an otherwise unexplained consistent elevation, are more likely associated with infection.

Microbiology
Correct sampling is the cornerstone for a well-established diagnosis that can lead to the correct targeted antimicrobial treatment. During surgical debridement, deep tissue samples are taken from the area of the perceived infection for microbiological and histopathological analysis. Positive cultures with an identical pathogen from at least two separate deep tissue specimens are considered confirmatory for FRI. In case of highly virulent pathogens (for example, S. aureus, Escherichia coli, and β-haemolytic streptococci), one positive sample should raise a high suspicion of infection. Sonication of removed implants is recommended in the 2020 consensus guidelines, as this step removes biofilm-growing bacteria from the implant, which may increase detection sensitivity. This step might be particularly valuable...
in patients concurrently receiving antibiotic therapy or those infected with low-virulence microorganisms, where diagnosis of infection can be particularly challenging. Although sonication offers the potential for earlier availability of results, and an earlier start of targeted therapy, the added value in FRI needs to be fully established, as a systematic review112 and a clinical study113 showed that sonication is not always superior to tissue cultures in the diagnosis of FRI.

Histopathological diagnosis
The direct identification of a microorganism from deep-tissue specimens using specific staining techniques (such as Gram or Ziehl–Neelsen staining for bacteria or Grocott’s methenamine silver staining for fungi) is pathognomonic for FRI. Quantitative histopathology showing more than five polymorphonuclear cells (PMNs) per high-power (×400) field105,115 has been validated for diagnosis of late-onset FRIs, as the early phase of bone healing may show histological overlap with acute infection in terms of neutrophil abundance. Moreover, histological findings of both acute and chronic inflammation can be present simultaneously, and therefore histopathology is not always predictive of infection chronicity105. The presence of more than five PMNs per high-power field in chronic or late-onset FRIs has a positive predictive value for infection of 100%, while the complete absence of any PMNs is almost always indicative of the absence of infection105.

Prevention strategies
Perioperative antibiotic prophylaxis. The early administration of prophylactic antibiotics has a protective effect in FRI101. First-generation and second-generation cephalosporins are currently recommended116. In patients with closed fractures, antibiotic prophylaxis is limited to a single dose before surgery, and in the case of GA type I–II injuries, the duration should not exceed 24 h109. Owing to a lack of comparative studies, the duration of pre-emptive therapy is still not clear in patients with GA type III injuries. However, it is advised that administration of prophylactic antibiotics be discontinued after 72 h or 24 h after wound closure, whichever comes first118. These guidelines are consistent with a systematic review117 that found that prolonged administration of prophylactic antibiotics does not seem to be beneficial in the prevention of FRI in open fractures, based on the available data, which aligns with general antibiotic stewardship practices and recent guidelines from the American Association of Orthopaedic Surgeons118.

Local antibiotics in prevention of FRI. Finally, especially in the case of open fractures, systemic antibiotics alone are often not sufficient owing to the damage to the surrounding tissues and blood vessels by which systemic antibiotics would normally reach the tissue–implant interface119,120. Although based on limited data, a systematic review showed a significant reduction in infection risk when prophylactic local antibiotics were used in addition to systemic antibiotics in open fractures111. Recent studies investigating the use of antibiotic powder, the delivery of antibiotics through absorbable carriers and coated implants have all shown promising results110,111.

Surgical strategies for infection prevention
Surgical debridement, irrigation and meticulous soft tissue management are important perioperative measures for infection prevention, as they enable removal of damaged, devitalized tissue and foreign material that may be present in the traumatic wound120. This debridement may be repeated 24–48 h later to achieve a clean wound with viable tissue margins121. Lavage (washing of the wound) is commonly performed, although the appropriate method to perform this technique (that is, type of solution and amount of pressure) is not always defined. The toxicity of antiseptic solutions to host cells, particularly at high concentrations122–124, suggests that saline might be more appropriate. The largest human clinical trial, the Fluid Lavage of Open Wounds (FLOW) trial, confirmed the superiority of normal saline over a soap solution125 and also suggested that low to very low pressure is the method of choice for irrigation in open fractures, as high-pressure lavage might lead to bacterial seeding into the intramedullary canal126,127.

The timing of definitive soft tissue coverage remains an important issue in prevention of infection in open fractures. Overall guidelines state that for GA type III open fractures, definitive soft tissue coverage is ideal within 3 to 7 days of the injury115,116. A multicentre randomized trial performed in the UK Major Trauma Network, among patients with severe open fracture of the lower limb, showed that the use of negative pressure wound therapy did not improve the self-rated disability at 12 months compared with standard wound dressings, although how this translates to other nations with different wound management guidelines remains to be determined123.

Management
General concepts
Although not possible in many centres, and still requiring confirmatory evaluation on a cost–benefit basis, multidisciplinary teams have been shown to improve patient outcomes124. For example, antibiotic stewardship programmes require such multidisciplinary teams to oversee antibiotic interventions and ensure selection of the optimal antibiotic130. These actions support improved treatment outcomes as well as improving patient safety and reducing health-care costs131. Within the FRI community, there is a consensus that multidisciplinary teamwork is a key aspect in the management of this sometimes devastating disease entity132.

Surgical treatment
The goal of every surgical revision is a judicious debridement with removal of all dead tissues and acquisition of deep tissue biopsy samples for microbiology and histopathology133,134. Debridement, building from seminal work of Tetsworth and Gierny135, is followed by osseous stabilization (if required), dead space management, delivery of antimicrobial therapy and adequate soft tissue coverage.
One of the main aspects that distinguishes FRI from PJI is the presence of a fracture and the related bony instability that results from the fracture. Stability is important for fracture healing, but is also required to facilitate treatment of infection. The classical experimental studies by Perren showed the positive influence of stability on infection in fracture care. This is an important concept that has been adopted by the orthopaedic trauma community. Mechanistic insights from mouse models also support this finding, whereby stability leads to a more inflammatory local environment that magnifies the subsequent effects of infection.

In contrast to PJI, fracture fixation devices primarily aim for fracture consolidation and can be removed after the fracture has healed, thereby removing the biofilm and resulting in a high probability of eradicating the infection. This means that complete eradication of infection may not always be the initial goal of treatment. The surgical management of FRI is based on two main concepts: debridement, antimicrobial therapy and implant retention (DAIR), or debridement, antimicrobial therapy and implant removal (if the fracture is healed) or implant exchange (in one or multiple stages) if the fracture is not healed. A systematic review showed that acute or early-onset FRI, with a short duration of infection, can be successfully treated with DAIR up to 10 weeks after fracture fixation. By contrast, in chronic or late-onset FRI, treatment with DAIR is associated with a higher rate of recurrence. Important preconditions for successful DAIR are a vital soft tissue envelope, a stable osteosynthesis construct, access to debridement and absence of substantial local or systemic comorbidities.

Antibiotic therapy

Empirical antibiotic therapy can be started as early as after surgical debridement and fixation in case of high suspicion of infection. Key factors to consider in selecting empirical therapy include patient history (past antibiotic courses, comorbidities, allergies and past infections) and the local epidemiology. Most often, empirical therapy should include a lipopeptide or glycopeptide antibiotic and a second agent covering Gram-negative bacteria and generally should switch to targeted therapy as soon as culture and sensitivity results are available.

Targeted antimicrobial therapy

Once the infecting pathogen has been identified and antibiotic susceptibility assessed, targeted therapy commences. The duration of targeted antibiotic therapy is not based on comparative trials but rather on expert opinion. Historically, 12 weeks antibiotic therapy was commonplace for treatment of patients with an implant present. In the DATIPO trial, a total therapy duration of 6 weeks was not non-inferior to 12 weeks in patients with PJI, but rather led to a greater number of patients with a poor outcome. In the more recent OVIVA trial, in which 1,054 adults with bone or joint infections were randomly assigned to receive either intravenous or oral antibiotics, oral antibiotics were non-inferior to intravenous antibiotics. Current recommendations in patients with FRI is to limit intravenous therapy to 1–2 weeks.

Antibiotic therapy regimens for FRI are based largely on the guidelines for PJI. Guidelines are readily available and are not extensively discussed here. However, several key points are crucial for successful therapeutic outcomes. Rifampicin has emerged as a key antibiotic in the treatment of device-related staphylococcal infection owing to its ability to target metabolically inactive bacteria that reside in the bacterial biofilm at the centre of a FRI. An early clinical trial with a rifampicin combination (flucloxacillin, or vancomycin) in treating PJI was stopped due to its obvious superiority to the placebo–antibiotic combination before conclusion of the study; however, more recent studies were less conclusive. However, a multicentre, randomized controlled trial showed no statistically significant advantage of adding rifampicin to standard antimicrobial treatment (flucloxacillin, or vancomycin for MRSA) in staphylococcal PJI. A crucial drawback of using rifampicin is the ease with which resistance develops, so it is always given in conjunction with another antibiotic.

Therapy is usually started after incisional wounds are dry to reduce the risk of superinfection with resistant microorganisms. A study evaluated the outcome in patients treated with and without rifampicin and analysed the influence of timing of treatment, finding that rifampicin within 5 days of surgical debridement was a predictor of treatment failure. However, this observation may be partially explained by the fact that patients who received rifampicin within 5 days of surgical debridement generally had more severe infection. Further clarification will be needed in future studies. Initial intravenous therapy of methicillin-resistant staphylococci should include glycopeptide antibiotics (vancomycin or teicoplanin). In recent years, there has been renewed interest in the use of fosfomycin for the treatment of bone and joint infections. Based on the available data, intravenous fosfomycin, especially when used in combination with other antibiotics, resulted in clinically successful treatment in 82.2% of patients. Fosfomycin may be beneficial for empirical and targeted first-line treatment in staphylococcal (and enterococcal) bone and joint infection.

Fluoroquinolones seem to show a beneficial effect against Gram-negative biofilms similar to that shown by rifampicin against Gram-positive biofilms. Therefore, in terms of antibiotic therapy options, rifampicin and/or fluoroquinolone resistance are a greater concern in treating FRI than, for example, methicillin resistance. Ultimately, clinical outcomes are poorer in patients with rifampicin-resistant Staphylococcus spp. or fluoroquinolone-resistant Gram-negative bacilli.

Among the emerging practices in FRI, a systematic review showed favourable outcomes when the lipopeptide antibiotic daptoxicin was used in patients with bone and joint infections caused by Gram-positive bacteria. Similarly, the broad-spectrum antibiotic fosfomycin is regaining popularity, owing to its activity against staphylococcal, enterococcal and ESBL-producing E. coli biofilms, particularly in combination with other antimicrobials, as well as its bactericidal activity against bacteria persisting intracellularly (such as S. aureus).
Local antibiotics in FRI treatment. The treatment pathway for FRI often includes adjunctive local antibiotic administration. Polymethyl methacrylate (PMMA), more commonly known as bone cement, has been used as a carrier for local antimicrobials for many decades. PMMA is often fashioned intraoperatively into customized shapes based on the dead space available within the surgical field. This approach includes the intraoperative addition of antibiotic-loaded bone cement to the surface of intramedullary nails or plates. In a clinical case series of retrieved gentamicin-loaded PMMA beads after revision surgery for PJs, the beads from 90% of the patients were culture-positive, and furthermore, a substantial proportion of the cultured strains were resistant to gentamicin. Bone cement may also be loaded with other antibiotics, including vancomycin, tobramycin and clindamycin; however, over the course of the past decades a number of concerns have been raised related to the use of antibiotic-loaded PMMA, leading to a search for different carriers; examples include biodegradable ceramics that offer advantages over PMMA, such as not requiring additional removal surgery and having an improved release profile (when carrying antimicrobials).

An approach that does not involve the application of antibiotics is to fill the fracture area and dead space with bioactive glass. The degradation of the bioactive glass has two effects in the body: first, it results in a pH shift towards an alkaline pH, which negatively affects bacterial growth, and second, it stimulates new bone formation. Efficacy was shown in a retrospective review of patients with chronic osteomyelitis. However, to date, no randomized controlled clinical trial has been performed and the efficacy of bioactive glass in preventing FRI has not been investigated.

Quality of life
FRI is associated with prolonged hospitalizations and antimicrobial therapy, as well as multiple surgical revisions, which may result in delayed recovery and transient or permanent loss of function. Consequently, FRI is a considerable burden not only for the patient but also for the treating physicians and health-care systems. A systematic review showed that, depending on certain preconditions, success rates (that is, infection eradication) ranges from 100% to less than 70%. A global prospective bone infection registry reported a cure rate for long-bone FRI at 12 months of only 66%. Even 1 year after surgical revision, physical and mental health were compromised and lower in patients with FRI than in the US norm-based population. These results are consistent with the limited published data of the effect of FRI on quality of life (QOL). Even 4 years after successful treatment of long-bone FRI, QOL is substantially lower in comparison to normative data. Patients with complex bone involvement, multidrug-resistant isolates or significant comorbidities reported lower QOL than those without complications. Patients with FRI also have poorer functional outcomes and greater pain interference as measured using the Patient Reported Outcomes Measurement Information System (PROMIS) scale than patients without infection.

Quantification of the socioeconomic costs of FRI showed that FRI is an important economic burden. Two studies found that hospital-related (direct) costs for patients with FRI were sevenfold to eightfold times higher than for patients with uninfected fractures, with median costs of over US$100,000 (interquartile range US$61,841 to US$150,972) per patient. These additional costs are mainly driven by a prolonged length of hospital stay.

Outlook
Innovation in treatment and management of FRI
It is perhaps not surprising that the management of FRI has not changed substantially in the past three decades, considering how recently the formal definitions and guidelines for FRI were developed. These definitions and guidelines have enabled the economic impact of FRI to be estimated, subsequently justifying the expense of clinical trials to prove efficacy. Nevertheless, the pace of development of anti-infective technologies is slowly increasing and is expected to accelerate further in the coming years (Table 1).

| Approach                  | Strategy                           | Mode of action                                      | Status          |
|---------------------------|------------------------------------|-----------------------------------------------------|-----------------|
| Metal ions                | Material modification              | Kill bacteria                                       | In clinical use*|
| Nanostructured surfaces   | Surface modification               | Reduce bacterial adhesion, promote osteointegration | In clinical useb|
| Antifouling coatings      | Hydrophobic surface modifications  | Prevent bacterial adhesion                          | Under development|
| Antibacterial coatings    | Drug loading                       | Kill bacteria                                       | In clinical use  |
| Drug-loaded materials     | Cements, hydroxyapatite, calcium   | Kill bacteria                                       | In clinical use  |
|                          | sulfates and phosphates           |                                                     |                 |
| Antibiotic-loaded hydrogels| Delivery uncoupled from device    | Kill bacteria                                       | In clinical use or under development|
|                          | surfaces, without spatial restriction|                                                     |                 |
| Encapsulated antimicrobial drugs | Sustained release                | Kill bacteria                                       | Under development|
| Triggered-release materials| On-demand release triggered by    | Kill bacteria                                       | Under development|
|                          | endogenous or exogenous stimuli   |                                                     |                 |
| Novel antimicrobial       | AMPs, phage, immunotherapy        | Kill bacteria, destroy biofilm                      | Under development|

AMPs, antimicrobial peptides. *For tumour prosthesis. bFor prosthesis.
Several paste or hydrogel-like formulations have been described and applied to patients with fractures in the past 5 years. In the case of the antibiotic-loaded fast-resorbable hydrogel coating Defensive Antibacterial Coating (DAC), which provides a mechanical barrier to implant colonization, preliminary studies showed efficacy in preventing FRI, although to date, case numbers are insufficient to make definitive claims\(^{164}\). Preclinical data show the efficacy of a thermoresponsive hyaluronic acid-based hydrogel loaded with antibiotics gentamicin and/or vancomycin in preventing\(^{165-167}\) and treating\(^{168,169}\) FRI. In contrast to the DAC, which acts as a mechanical barrier to bacteria attaching to the implant, the antibiotic-loaded hydrogel is considered a dedicated antibiotic delivery vehicle and so might find greater application in patients without an implant or in those in whom the infection spreads beyond the implant surface. Considering their greater efficacy in treating MRSA infection in single-stage or two-stage exchange compared with systemic antibiotics, with and without antibiotic-loaded bone cement, these hydrogels might offer substantial improvements in the care of patients with FRI. They offer several advantages over coating protocols, not least of which is the ease of production compared with coating the myriad of orthopaedic implants. The potential for elevated local antibiotic levels is a major advantage over bone cement, which retains most of the incorporated antibiotic. However, there are challenges to overcome for these materials. For example, as a dedicated antibiotic delivery concept, these products might be regulated differently from coated devices, which might require clinical studies that are far larger than those centred on conventional devices.

In the longer term, there are many innovations that might yet translate to patient care. For example, bacteriophage therapy is re-emerging as a viable therapeutic for antibiotic-resistant pathogens. Bacteriophages are viruses with specific activity against a restricted range of bacterial isolates\(^{170}\). Early human trials are scarce, but indications suggest that there is a place for phage therapy, particularly in difficult to treat musculoskeletal infections\(^{171}\). Many questions remain about phage therapy, including dosage, route of administration, phage selection protocols and phage production\(^{170,171}\). Nevertheless, significant effort is being expended to address these issues and validate phage therapy as a potential new tool in FRI treatment. Furthermore, considering the important role of OLCN invasion by bacteria, dedicated therapy such as bone-targeting antibiotics\(^{172}\) — drugs that specifically target OLCN invasion\(^{172}\) — might be needed to eradicate these bacteria to increase the success of surgery for FRI.

**Innovation in immune-based interventions**

Another area of research is the use of vaccines to reduce the burden of infection, as has been successfully applied to many infectious diseases. To date, all vaccination strategies against *S. aureus* have been unsuccessful, which might be attributed to redundancy of virulence factors, over-reliance on animal models that may not reflect human immunity, and the complexities of preventing infections involving biofilms on foreign materials that are protected from host defences\(^{173}\). Preclinical studies have assessed combining vaccination with antibiotic therapy and the results suggest that these immunizations could support rather than replace conventional treatment\(^{174}\). A further promising immunotherapeutic approach is the use of antibodies to components of the biofilm. The destruction of the bacteria-encapsulating biofilm will make the bacteria more susceptible to antibiotics. A phase I clinical trial used a biofilm-destroying antibody for the treatment of PJI (NCT04763759)\(^{175}\). Preclinical studies in a mouse model of implant infection demonstrated high efficacy of the antibody in combination with an antibiotic\(^{176}\). Because the development of an infection cannot be predicted, an antimicrobial substance that is only induced by the infection (that is, ‘on demand’ release) might be beneficial\(^{177}\).

**Hurdles and future interventions required to impact FRI**

As the concepts for the treatment of FRI have only been established in the past 2 years, the outlook for improved patient care is promising. Certainly, a large number of issues still need to be addressed for patient care to be markedly improved, but a roadmap is now appearing\(^{178}\). The global impact of trauma is enormous, but the global impact of FRI has not been accurately estimated. With a better understanding of the morbidity and economic impact of FRI, the support for interventional and diagnostic accuracy studies should increase, both in terms of research budgets as well as insurance coverage of preventive, therapeutic and diagnostic strategies. With regard to prevention, randomized controlled trials of perioperative antibiotic prophylaxis for fracture fixation are needed to determine the optimal regimen, and could potentially radically reduce infection rate and substantially reduce total antibiotic dosages in patients with trauma. Such studies would also be enormously beneficial for optimizing local antibiotic strategies. Similarly, a suitably designed, sufficiently powered randomized controlled trial or large-scale clinical study to determine efficacy of defined treatment algorithms would be extremely beneficial and could be transformative for the management of FRI, although the costs for such a trial could be challenging. Accurate estimation of the impact of FRI on long-term QOL and psychological health is another aspect that has yet to be adequately addressed in FRI. In many cases FRI extends fracture healing by many months, extending to years if recurrence and bone loss are involved. The true impact of this prolonged healing on patient wellbeing is not sufficiently understood.

From a basic science perspective, there have been several key developments in the past 5 years, most notably an improved understanding of the reasons for failure of antibiotic therapy. A future challenge will be to leverage this understanding by developing antibacterial strategies to overcome the barriers to treatment efficacy. On a surgical level, the potential for improved identification of necrotic tissues and instruments to excise affected tissues more efficiently should increase treatment efficacy, although once again, determining clinical efficacy may not be easy. For example, the VELscope provides...
an easy way for the fluorescence-assisted, intraoperative detection of necrotic and viable bone that can help surgeons optimize intraoperative bone resection in chronic FRIs by differentiating viable from necrotic bone tissue178. This approach might help improve resection techniques and eventually treatment outcome in patients in the future. In support of the preclinical assessment of these interventions, there is a need for appropriate in vivo models that might offer superior efficacy assessment. For example, in the case of FRI, interventions may need to factor in the role of fracture healing, stability and soft tissue involvement, which have not been commonly incorporated in these models to date. Validated, reproducible models that can include all such aspects would be an ideal addition to the preclinical assessment of innovation in FRI. Finally, the interventions that are currently at the early clinical trial stages should emerge into the clinic in the coming years. Coated implants, antibiotic-delivering injectable biomaterials and phage-related interventions seem poised to enter major clinical trials, with their clinical impact being evaluated in the coming years179,197.

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