Special Collection on Fracture Surgery Associated Infection

Journal of Orthopaedic Surgery

Journal of Orthopaedic Surgery
30(3) 1–11

DOI: 10.1177/10225536221118512
journals.sagepub.com/home/osj
SAGE

Microbiology of fracture related infections

David Graan[1] **and Zsolt J Balogh**[2]

Abstract

Fracture related infection remains a challenging complication that creates a heavy burden for orthopaedic trauma patients, their families, treating physicians and healthcare systems. Even current curative approaches (radical debridement, revision surgery and long-term antibiotics) often result in significant socioeconomic costs and the risk of life-long functional impairment to the patient. The prevalence of osteomyelitis due to trauma and surgical complications does not seem to be diminishing in our society and the emergence of antimicrobial resistance is a major health related concern with global relevance. Despite multi-drug resistant bacteria being on the rise universally, perioperative antibiotic prophylaxis in orthopaedic trauma care has only slightly changed in the last 25 years. *Staphylococcus* infections remain an increasing global concern, partially due to the resistance mechanisms developed by staphylococci to evade the host immune system and antibiotic treatment, and as such antibiotics are becoming increasingly ineffective. This paper will address fracture related infections in trauma patients, looking at the bacteriology of these infections, its clinical implications and evolving nature.

Keywords

trauma, polytrauma, trauma centre, Fracture related infection, fracture care, osteomyelitis

Date received: 7 April 2022; Received revised 21 June 2022; accepted: 4 July 2022

Introduction

Orthopaedic trauma surgery often involves the open reduction and internal fixation of fractured bones to restore skeletal stability and musculoskeletal function. Infection is one of the most common and serious complications in orthopaedic trauma patients. Fracture related infection (FRI) is a recent concept only defined in 2018 which uses confirmatory and suggestive criteria established by international consensus. FRI causes significant morbidity, including permanent loss of function or even amputation of the affected limb.[1] The likelihood of having a FRI ranges from 1% in closed low energy injuries and up to 30% in complex open fractures.[2]

Trauma patients frequently undergo multiple surgical procedures, receive transfusions, require ventilation in the intensive care unit and reach a catabolic and hyperinflamed state, which all increase their risk for infection even without open fractures.[3] Patients with surgical site infection (SSI) in general are at a higher risk of thromboembolic events, further nosocomial infections, fracture non-unions and dependency on post-hospital care.[4] FRI have a burden on the patient, surgeon and the healthcare system at a physical, emotional and economic level.[5,6] Most treatment principles are currently based on research that has been conducted on prosthetic joint infections. However, FRIs have unique features such as systemic response to injury, bone healing, soft tissue injury and general condition of the patient that need to be considered.[7]

Antimicrobial resistance (AMR) occurs when bacteria, viruses, fungi and parasites change over time and no longer respond to previously effective pharmacological treatment,

[1]John Hunter Department of Traumatology, John Hunter Hospital, Newcastle, NSW, Australia
[2]Department of Traumatology and Discipline of Surgery, John Hunter Hospital and University of Newcastle, Newcastle, NSW, Australia

Corresponding author:
Zsolt J Balogh, Department of Traumatology and Discipline of Surgery, John Hunter Hospital and University of Newcastle, Lookout Road, Newcastle, NSW 2310, Australia.
Email: zsolt.balogh@health.nsw.gov.au

which makes infections harder to treat and increasing the risk of disease spread, severe illness and death. Increasing antimicrobial resistance is one of the top 10 global public health issues identified by the WHO.[8] Standardised surveillance has long been recognised as a minimum and necessary requirement for effectual prevention strategies[9] and diminishing SSI rates have been noted following the implementation of these surveillance programs.[10]

Local guidelines are widely available for surgical antibiotic propylaxis.[11] However, evaluation of pathogen specific data concerning infections complicating the range of surgical procedures has not been performed to determine whether guidelines are concordant with local epidemiology. Clarifying the clinical characteristics and dominant pathogenic strains of current FRI is of great importance for guiding clinical treatment. This paper will address the microbiology of fracture related infections in trauma patients.

Definitions

Surgical site infection

A surgical site infection is an infection following a surgical procedure occurring at or near the incision site. Surgical site infections as defined by the CDC[12] occur within three categories, superficial incisional, deep incisional and organ or space infection.

Superficial incisional infections occur within 30 days of a procedure, involve only the incision skin and subcutaneous tissue and requires either clinical signs (purulent drainage from the incision, local pain, tenderness, swelling, erythema or heat) or identification of microorganisms in aseptically collected specimens for the purpose of diagnosis or treatment.

Deep incisional infections occur within 30 days or 90 days with open reduction of a fracture or prosthesis insertion. Deep incisional infections involve the deep soft tissues of the incision such as the fascial or muscle layers. They require either:

- Purulent drainage from the deep incision
- Spontaneous dehiscence or surgical opening for the purpose of diagnosis, microorganism identification from the deep soft tissue and fever or local pain or tenderness.
- Abscess or gross anatomical, histopathologic, or imaging assessment indicative of deep incision infection.

Organ or space infections are those occurring within 30–90 days of the procedure and occur in the tissue spaces deep to the fascial and muscle layers that are manipulated during surgery. They require either:

- Purulent drainage from a drain that is inserted into the organ or space
- Organism identification from the fluid or tissue in the organ or space
- Abscess or gross anatomical, histopathologic, or imaging assessment evidence of infection AND meets at least one criterion for a specific organ/space infection site. Some orthopaedic examples include osteomyelitis, joint space infection, periprosthetic infection, disc space or spinal infection.

Fracture related infections

There has been a paucity in the literature surrounding fracture related infection secondary to the lack of a standardised definition. An international survey distributed to all AO Foundation Trauma registered users showed over 90% of responders suggested the need for a clear definition.[13] A consensus definition for fracture related infection was developed and adopted in 2018, by the Fracture related infection consensus group, an expert panel.

This definition includes confirmatory and suggestive criteria as described by WJ Metsemakers et al.[13]

Confirmatory criteria – at least one of:

- Fistula, Sinus or Wound Breakdown
- Purulent drainage from the wound or presence of pus during surgery
- Phenotypically indistinguishable pathogens identified by culture from at least two separate deep tissue or implant specimens
- Histopathological confirmation of presence of microorganisms in deep tissue collected during surgical intervention.

Suggestive criteria:

1. Clinical signs – any one of:
   a. Pain (non-weightbearing, increasing and new onset)
   b. Local erythema
   c. Local swelling
   d. Increased local temperature
   e. Fever (oral measurement ≥38.3°C)
2. Radiological signs – any one of:
   a. Bone lysis (at the fracture site, or close proximity to the implant)
   b. Implant loosening
   c. Sequestration (occurring over time)
   d. Failure of progression of bone healing (non-union)
   e. Presence of periosteal bone formation (in locations outside the fracture site or in the setting of a healed fracture)

3. A pathogenic organism identified by culture from a single deep tissue/implant (including sonication-fluid) specimen taken during an operative intervention. In case of tissue, multiple specimens (≥3) should be taken, each with clean instruments (not superficial or sinus tract swabs). In cases of joint effusion arising in a joint adjacent to a fractured bone, a fluid sample obtained by sterile puncture is permitted.
4. Elevated serum inflammatory markers: In musculoskeletal trauma, these should be interpreted with caution. They are included as suggestive signs in case of a secondary rise (after an initial decrease) or a consistent elevation over a period in time, and after exclusion of other infectious foci or inflammatory processes:
   a. Erythrocyte Sedimentation Rate (ESR)
   b. C-reactive protein (CRP)
   c. White blood cell count (WBC)
5. Persistent, increasing or new-onset wound drainage, beyond the first few days postoperatively, without solid alternative explanation.
6. New-onset of joint effusion in fracture patients. Surgeons should be aware that FRI can present as an adjacent septic arthritis in the following cases:
   a. Implant material which penetrates the joint capsule (e.g. femoral nailing)
   b. Intra-articular fractures

This definition is further demonstrated in a diagnostic pathway by Govaert et al.[14]

Osteomyelitis

Infections can be superficial, deep or progress to acute or chronic osteomyelitis. Osteomyelitis' literal translation is inflammation of the bone marrow. The pathology is characterised by severe inflammation, impairment of vasculature, and localised bone loss and destruction.[15] It is notoriously difficult to treat. Three clinical mechanisms lead to bone infection: osteomyelitis resulting from the spread of a contiguous source (trauma or surgical contamination), occurring secondary to vascular insufficiency or neuropathy (diabetic foot ulcers) and acute haematogenous spread (more common in paediatrics).[16] Although fungal species can cause osteomyelitis, the vast majority are caused by bacterial species.

Antimicrobial resistance

Antimicrobial Resistance (AMR) occurs when bacteria, viruses, fungi, and parasites become able to adapt and grow in the presence of pharmacological treatments that once impacted them.[17] Antibiotic resistance compromises a human immune system's capacity to fight infectious diseases and also contributes to different complications in vulnerable patients including those undergoing trauma surgery.

Epidemiology and Magnitude of the problem

Fracture related infection is a relatively new term with a wide spectrum of conditions included in its recent definition and so the epidemiology and magnitude of FRI is still not well understood. Historical evidence suggest that 1–2% of closed fractures[18] and up to 30% of open fracture[19] that have surgical fixation will develop an infection. The risk of secondary infection according to the Gustilo and Anderson grading is 2–3% for grades I and II, and between 4 and 30% for grade III depending on severity of soft tissue damage.[20]

The prevalence of FRI increased by 0.28 from 8.4 cases per 100,000 inhabitants to 10.7 cases per 100,000 inhabitants between 2008 to 2018 in a German population-based study.[21] The biggest increase was in the elderly group, thought to be due to confounding comorbidities, poorer local blood supply and ability to regenerate. In a multicentre study out of China,[22] they found an incidence of FRI in 1.5% of patients, of which 65% were open fractures.

Walter et al.[21] used ICD-10 diagnostic codes to bring up cases from the Federal Statistical Office of Germany. The ICD-10 code for "T84.6, infection and inflammatory reaction due to internal fixation device" was used to identify patients ages 20 years or older with a fracture related infection. Prevalence was then compared to number of fractures per anatomical region as well as population data. There is no mention of any other inclusion or exclusion criteria.

Wang et al.[22] describe clearly their methods and data collection. Their inclusion criteria included patients eligible for diagnosis of FRI. This was based of the Metsemakers et al.[13] paper from Injury Journal around the consensus definition of FRI using confirmatory and suggestive criterion. The exclusion criteria included incomplete medical records, multi-site infection, pathological fracture such as bone tuberculosis and bone tumour, periprosthetic infection and infections of the skull, sternum and the ribs.

This highlights the importance of using a uniformed diagnostic criterion in future research to be able to accurately understand the significance and burden of FRI.

Infection poses a huge burden following orthopaedic and trauma surgery. These effects are felt by patients, treating teams and the healthcare system. They can result in long treatment cycles, high treatment costs, poor prognosis and significant physical and mental harm to patients.[22] The total medical cost of FRI after a tibia fracture is 6.5 times that of non-infected patients, hospital stay is 7.7 times that of non-

infected patients and antibiotic treatment time is 11 times longer.[23]

Clinically pragmatic scenarios: surgically managed closed fracture, open fractures, polytrauma patients

Orthopaedic Trauma surgery is around the clock urgent care provided to patients who suffer from a wide range of injuries from closed isolated fractures managed non-operatively to open fractures to polytrauma patients with life threatening time critical injuries. Each patient should be treated individually considering factors such as fracture configuration, soft tissue component to the injury, contamination, available resources and patient factors.

Primary preventative measures regarding infection are routinely implemented for most orthopaedic trauma surgery. Hair removal is associated with a higher prevalence of SSI, therefore hair should not be removed.[24] However, if it is required this should be performed with a clipper. Hand hygiene is very important in infection control.[2] Pre-operative skin preparation is an important measure to reduce the number of microorganisms at the incision site.[25] The use of sterile adhesive drapes in all three scenarios reduces bacterial load at the surgical site.[26] Pre-operative and correctly timed antimicrobial prophylaxis are an important intervention in the prevention of infectious complications in trauma patients.

Closed fracture infections are most commonly caused by normal skin flora or from hospital acquired sources like any other surgical site infection. The prevalence is well known at 1–2%.[27] The primary preventative measures mentioned above should be implemented as with all trauma surgery, with the difference being the need to take into consideration the significant variability of concurrent injuries in our patients.

Open fractures possess a higher risk of FRI.[27] The higher energy mechanism with resultant soft tissue damage and poor blood supply contribute to a greater risk.[28] In addition to the normal skin flora risk with orthopaedic trauma surgical management, there is the additional risk of contamination from external sources in the wounds as well as hospital acquired infections. Degree and type of contamination play an important role in surgical management for both osteosynthesis and soft tissue management as well as use of antibiotics.

Polytrauma patients are fighting on a number of fronts and often have severe associated soft tissue injuries, as such they are at an increased risk of infection. Severe polytrauma patients pose their own complex unique risks. Rare and or multiresistant pathogens are identified and add to the care required for these patients. Haematogenic spread is more common, with the addition of potential hospital equipment sources, such as ventilators and peripheral or central access lines.

Fracture related infection are different to prosthetic joint infections. They have unique features of fracture, bone healing and soft tissue injuries that need to be considered. Longer term in contrast to PJI, fracture fixation devices can be removed once healing has occurred and therefore a higher long-term chance of healing the infection.

Antimicrobial prophylaxis is known to reduce SSI.[29] Timing is key and in trauma should be aimed between 15–60 min before incision. The correct prophylactic antibiotic choice is also important. In closed fractures requiring hardware, antibiotics should be continued for at least 24 h post operatively and in open fractures or polytrauma patients' antibiotics should continue as per local guidelines and individual cases. In closed fractures, *staphylococcus* and *streptococcus* are the most common infective organisms.

In open fractures, the risk of infection is profoundly increased when the administration of prophylactic antibiotics is delayed for more than 6 h.[30] In open fractures, a minor delay in initial surgical debridement of more than 6 h is not associated with a significantly higher risk.[31] Antibiotics should be guided based on mechanism of injury and adjusted for water contamination as well as heavily contaminated wounds with material embedded in bone or soft tissues such as agricultural injuries or injuries involving sewage. Adjustment to antibiotic prophylactic regimes should be determined by such recommendations as the EAST guidelines and adjusting to local guidelines and practice that adheres to local antibiotic stewardship. EAST[32] below state systemic antibiotic coverage directed at gram positive organisms should be initiated as soon as possible after injury, additional gram negative cover should be added for type III Gustilo and Anderson fractures,[33] high dose penicillin should be added in the presence of faecal or potential *clostridium* contamination, in type III fractures antibiotics should continue for 72 h after injury or 24 h after soft tissue coverage and that once daily aminoglycoside dosing is safe and effective for type II and III fractures.

Debridement remains an important surgical tool in all trauma patients and should include excision of all necrotic bone or tissue, excision of poorly perfused tissue (as this will not contribute to healing and antibiotic delivery) and removal of all non-essential foreign material (hardware and suture material).[7] Irrigation is used which aims at decreasing bacterial load and removal of loose debris. Soft tissue management has limited data regarding optimal timing but decisions should be made with our plastic and reconstructive colleagues. The British Association of Plastic, Reconstructive and Aesthetic surgeons' guidelines recommend open fractures should be covered within 5–7 days after injury.[34] If unable to be closed, negative pressure

wound therapy can be utilised and timing of coverage after open fractures should be done within 7 days[35] and early after definitive skeletal fixation method is performed.

Confirmation of infection is achieved by culture of organisms from intraoperative deep tissue samples, metal implants or histological evaluation of deep tissue. Preferably five tissue samples should be obtained using separate instruments, from sites around the fracture or defect and surrounding tissue.[7] The combination of microbiology and histology has been shown to improve the accuracy of diagnosis.[36]

Dudareva et al.[36] compared sonication versus tissue sampling diagnosis of prosthetic joint and other orthopaedic device related infections. They measured 505 procedures on 463 patients and found that the combined sensitivity of tissue and sonication culture was higher than that for any method alone and increased with the number of tissue samples maintained. There were still 76 cases (15.0%) with discordant results, of which 48 (63.1%) showed histological evidence of infection.

Spectrum of pathogens

A number of studies have demonstrated a number of microorganisms that are involved in fracture related infections.[37,38] Detailed and contemporary knowledge of pathogens responsible for FRI is necessary in the formulation of local guidelines for antibiotic prophylaxis.

Staphylococcus aureus is the most common pathogen of skin, soft tissue infections and surgical site infections.[39] Eisner et al.[40] measured 438 pathogens in a level one trauma centre and found the most frequent pathogens being *Staphylococcus aureus* (27.1%), *Staphylococcus epidermis* (20.6%), *Enterococcus faecalis* (13.6%) and *Escherichia coli* (5.1%). 29.4% of all bacteria were found to be multidrug resistant. Of the *Staphylococcus epidermis* isolates, 79.8% were resistant against beta-lactam antibiotic agents. Altogether, only 44% of the infecting organisms were susceptible to cefuroxime.

Worth et al.[41] compared time trends, pathogens and resistance patterns for surgical site infections over 81 Australian hospitals, and compared results from 2002 to 2013. In the timeframe, 183,625 patients were observed with a 2.8% rate of SSIs (64.8% of which were microbiologically confirmed). Across all procedures, every 1-year increase across the observation period was associated with a 9% decrease in the risk of SSI. *Staphylococcus* was the most frequently identified pathogen (46%). For SSIs following orthopaedic procedures, *pseudomonas* species (11.9%) was the second most and coagulase negative staphylococci (CNS) (8.9%) third. This is no surprise as infections from trauma and fractures are typically caused by skin flora (*Staphylococcus aureus* and Coagulase negative staphylococci). However, open fractures with gross contamination showed an array of environmental organisms including gram negatives (*Pseudomonas aeruginosa*, *Enterobacter cloacae*, *Escherichia coli*), other gram positives, anaerobes and mycobacteria.[16] Moreover, patients with high grade open fractures and extensive soft tissue damage are at enhanced risk of nosocomial infections with resistant pathogens, possibly due to the propensity for delayed wound closure, impairment of protective skin barrier and operative fixation.[42]

Sheehy et al.[38] based in Oxford studied 166 patients in a prospective series of chronic osteomyelitis and found *Staphylococcus aureus* to be the most common cause (32%) but also showed a high proportion of poly microbial (29%) and culture negative samples (28%). Many isolates were found to be resistant to commonly used antimicrobial regimens. Narrow spectrum antibiotics (e.g., flucloxacillin) would have only treated 29% of their isolates.

The predominance of *Staphylococcus aureus* as an etiological agent of osteomyelitis is likely driven by two factors. First, approximately 25–30% of the global population is thought to be colonised with *Staphylococcus aureus*, with estimates reaching 50–70% when considering health care workers and transient colonisation.[43] Second, staphylococci produced many virulence factors, including adhesins, cytolytic toxins, immuno-evasion factors, superantigens and antioxidant systems.[44]

What has changed during the last two decades?

The emergence and spread of drug resistant pathogens that have acquired new resistance mechanisms has led to antimicrobial resistance, which continues to threaten our ability to treat common infections.[45] Especially alarming is the rapid and global spread of multi-resistant bacteria (superbugs) that cause infections that are not treatable with existing antimicrobial medications.[45] It is widely accepted by the CDC that one of the leading causes of antibiotic resistance is due to over prescribing of these agents.[46] Bacterial species prevalence have changed significantly during the last 25 years.[40] Infections caused by multi-drug resistant and biofilm producing species like *Staphylococcus aureus*, *Staphylococcus* Epidermidis and *Enterococcus faecalis* are on the rise.

Empiric therapy decisions for infection have been heavily influenced by the emergence of community acquired methicillin sensitive *Staphylococcus aureus* (MSSA) and are also shaped by local antibiograms, patient history and disease severity. Recent antibiotic susceptibility trends in *Staphylococcus aureus* isolates indicate an overall increase in methicillin sensitive *Staphylococcus aureus* (MSSA) relative to methicillin resistant *Staphylococcus aureus* (MRSA).[47] Hence, it is common practice to target

both MSSA and MRSA in empiric therapy for FRI.[16] Pathogens responsible for SSIs that showed clinically relevant resistance patterns displayed significant trends over time with a reduction in rates of MRSA. In Europe and North America, the incidence of MRSA has shown a slow and steady decline in the last 10 years. From 2007 to 2015, Europe and Canada have shown an 18% and 16% reduction of MRSA infections respectively, with the US showing a 44% decrease in that time frame.[46,48,49] The factors contributing to a reduction in MRSA FRI are related to antimicrobial stewardship programs.

Dudareva et al.[50] compared the microbiology of chronic osteomyelitis and its changes over a 10-year period comparing 2001–2004 cohort to 2013–2017. They found a similar proportion of *Staphylococcus aureus* in both cohorts and the rate or MRSA lower in the 2013–17 (11.4% vs 30.8%). This reduction could be attributed to improved hospital infection prevention practices including preoperative decolonisation therapy in orthopaedic surgery. However, the proportion of MDR infection was similar in both cohorts (15.2% vs 17.2%). High incidence of *Staphylococcus aureus* in surgical patients has led to vigorous efforts to develop specific preventative and therapeutic measures directed against the pathogen.[39] This includes infection control practices, liberal use of topical antiseptics and specific systemic antibiotics. Despite these efforts, prevention has remained elusive and management of confirmed infections remains difficult. An important key that has led to suboptimal prevention and treatment of *Staphylococcus aureus* infections has been the rapid evolution of resistance to antimicrobial agents and the development of new virulence factors.

Baym et al.[51] showed the speed at which a common microbe can mutate and acclimate to gradually increasing antibiotic concentrations. They showed that *Escherichia coli* could become resistant to an antibiotic it was usually sensitive to in a very short time. They found that with gradual 10-fold increases in antibiotic concentration across a linear agar medium, these bacteria could gain resistance to a 1000-fold increase in antibiotic concentration over a matter of only 11 days.

Not only are bacteria able to adapt and evade the hosts immune system, they also have acquired resistance mechanisms to survive a plethora of antibiotic treatments available today. Microbiologists investigated the mechanisms of increased virulence, biofilm formation and distribution of resistance mechanisms. There are three main mechanisms by which bacteria confer resistance. These include changing the membrane permeability to the antimicrobial, destroying the antimicrobial compound and altering the bacterial component which is a target of the antimicrobial.[52]

In terms of management, preoperative and correctly timed prophylactic antibiotic intervention is mandatory for a majority of orthopaedic procedures. Surgical antimicrobial prophylaxis with a beta lactam antimicrobial such as cefazolin is the mainstay of SSI prevention. However, current guidelines are informed by research undertaken over 30 years ago when methicillin sensitive *Staphylococcus aureus* was the predominant organism. Over time with the increased incidence of antimicrobial resistance, this data is no longer representative of the current ecology.

The 2013 Cochrane review of chronic osteomyelitis examined all randomised control trials of different antibiotic regimes given after surgical debridement of chronic osteomyelitis and found only eight small applicable trials with a total of 282 patients.[53] Most papers were over 20 years old and do not reflect the emerging prevalence of antimicrobial resistance patterns. The level of evidence for treating acute osteomyelitis in adults is even worse and largely based on local guidelines and expert opinion.

Potential reasons for change

Orthopaedic trauma surgical practice, the epidemiology of injuries and the demographics of the injured are constantly changing. There has been an increase in rates of operative management of fractures and as a consequence we will see more infections. Furthermore, immunocompromised polytrauma patients are surviving and therefore need management of injuries they would have previously succumbed to. This is evident with a mortality rate of only 7.5% (average ISS 20) in a busy level 1 trauma centre.[54] Globally, there is an ageing population and inherently this group have a higher infection rate.[21] In other areas of the globe, the concept of open reduction and internal fixation using implants is a newly introduced concept. The widespread and frequently questionable practice of using antibiotics in all areas of medicine, veterinary practice and the food industry has also caused major problems[45] such as:

Biofilm

Biofilm is a virulence factor that is a secreted product that is also part of the staphylococcal cell structure. Biofilm is produced by several bacterial species after adherence of the bacterial cell to a foreign structure.[39] Biofilm encases a community of cells and changes the phenotype from planktonic to dormancy, offering barrier protection from host defences and imperviousness to antibiotics.[55] The presence of biofilms has been suggested as the main cause of clinical dormancy of chronic osteomyelitis. They provide protection against antimicrobials, the host immune response and shear stresses.[15] Biofilms further enhance the survival of the staphylococci residing within them by functioning to obtain and concentrate important environmental nutrients.[56] Biofilm begins to form following invasion of a microbial colony into a host where the bacteria attempt to adhere to a

site. Ideally for a microbe, the site has limited to no viability (devitalised tissue or bone or prosthetic material). At that stage, the microbial cells are in the planktonic phase, where they are rapidly dividing with a short generational cycle. This is the cell cycle which is susceptible to systemic concentrations of antibiotics, hence the importance of early antibiotic administration. It is still not known how long until a mature biofilm forms. The reason that single culture positive infections show high rates of *Staphylococcus aureus* is thought to be due to its biofilm. It is thought the biofilm inhibits growth inhibition of other species.[57] The increasing use of implants allow for biofilm producing bacteria such as *Staphylococcus aureus* and *Staphylococcus* Epidermidis to evade more often nonspecific immune systems as well as to escape antimicrobial agent effects.[58]

Virulence

Microbial virulence factors for *Staphylococcus aureus* have been divided into bacterial structural factors (polysaccharide capsule), secreted bacterial products and enzymes and resistance mechanisms to anti-microbial agents. The surface adhesion proteins of the cell wall are referred to collectively as microbial surface components recognising adhesive matrix molecules (MSCRAMMs).[59] Once the MSCRAMMs have colonised the *staphylococcus* onto the bone, the staphylococci can produce a biofilm which facilitates persistence of the infection.

SERAMs

SERAMs (Secretable expanded repertoire adhesive molecules) are a group of secreted proteins that have duplicate functions of the MSCRAMMs except that they are secreted and not attached to the cell wall.[60] A SERAM of considerable interest is coagulase, which targets prothrombin and fibrinogen. The result is generation of a matrix and creation of a local environment that facilitates microbial adherence to tissue and a protected environment against host defence mechanisms and antimicrobial therapy.[60] Exotoxins are secreted products that are cytotoxic to host cells. The cytokine of greatest interest has been the Panton-Valentine leucocidin (PVL).[61] It has been particularly associated with community acquired MRSA and has been implicated in the increased virulence of the community acquired versus the healthcare acquired infections.

Antimicrobial resistant organisms are found in people, animals, food and the environment.[45] AMR occurs naturally over time. Misuse and overuse of antimicrobials are the main drivers in the development of drug resistant pathogens. In developing countries, lack of clean water and sanitation and inadequate infection prevention and control promotes the spread of microbes, some of which can be resistant to antimicrobial treatment.[45] Other reasons include affordable medications, vaccines and diagnostics, lack of awareness and knowledge and lack of enforcement of legislation.[45]

There are a number of known risk factors associated with infection. Patient or host factors are well established and comprise factors such as increasing age, obesity, smoking status, involvement of metalware, immunosuppression, dialysis dependence, diabetes mellitus, cancer, intravenous drug use, alcohol abuse, poor nutritional status and recent surgery. Therefore, identification of patient factors is important in prevention of colonisation of those at high risk.[62,63]

With our better understanding of how microbes gain attachment to sites in our body and morph from a planktonic state to the slow growing sessile phase of growth, combined with their formation of a highly structured biofilm, we need to realise that we must resort to other forms of treatment.

"Beyond bacteria"

Although rare, there have been reports of fungal fracture related infections. A systematic review in 2021[64] reported 5 cases of *candida* grown on samples from FRI. Risk factors for fungal infection included open wounds, prolonged antibiotic therapy and immunodeficiency. The reoperation rate was 33% and prolonged antifungal therapy was required (mean time 8.8 weeks).

Outcomes

Depending on injury severity, success rates vary between 70–90% of cure with a recurrence of disease in 6–9% of the patients.[27,65] Healing of fractures is much slower in the context of FRI. Several limitations such as immobility, amputations, prolonged hospital stays, multiple surgeries, long term medication with associated side effects and further socioeconomic issues such as job loss are often unavoidable.[66] There is a large psychological burden on patients in addition to their physical injuries. Walter et al.,[67] 37 patients with successfully treated FRIs were assessed with patient questionnaires (EQ-5D, SF-36 and ISR). After a mean follow-up of 4.2 years, patients who suffered from FRI scored significantly lower on quality of life than a German reference population. The ISR (WHO ICD-10 based symptom rating) which is highly correlated with the Beck-Depression-Inventory-II (BDI-II) revealed that 21.6% of individuals showed moderate to severe impairments.

A systematic literature review of treatment and outcomes in fracture related infection was performed in 2018.[65] 93 studies were suitable including 3701 patients with complex FRI. The population group was predominantly male (77%), with a mean infective duration of 28 months and a mean follow up on 42 months. Mean length of hospital stay was 1.4 months and bone healing was achieved in a mean time of 7 months. The majority (68%) of fractures

involved the tibia. The most common clinical signs were wound discharge, pain and swelling. Radiologically there were signs of osteomyelitis in 67% of cases and evidence of non-union in 37%. Eradication of infection without recurrence was reported in 85% of cases and 93% if amputation occurred. In total, 3% of patients required amputation.

Studies and data on long term patient outcomes following FRI are rare. Walter et al.[67] investigated whether FRI patients return to a quality of life state comparable to normative data after successful surgical treatment. They reviewed 37 patients and used both physical and psychological quality of life health outcome measures to quantify their results. They found with a mean follow up of 4.19 years in successfully treated FRI, patients reported significant lower quality of life in both aspects, but especially in the physical health component. Moderate to severe psychological symptoms was found in 21.6% of patients.

Osteomyelitis is a feared complication of trauma and FRI, affecting up to one third of patients who present with severe limb injury or open fracture.[37,68] It is most commonly caused by opportunistic Gram-positive cocci (75%).[15]

In regards to long term treatment, multi-drug resistant patterns are evolving and ever changing due to the increased use of antimicrobial agents and so the epidemiology and resistance patterns need to be reviewed periodically.

Future Directions

Fracture related infection is one of the most challenging complications in orthopaedic trauma surgery. The goal of the treatment in FRI is to achieve eradication of infection and the bony union of the fracture. Regular follow up is needed to monitor therapy, identify complications early and to maximise functional outcomes.[7]

Further studies of FRI in orthopaedic trauma patients should utilise and consistently apply the novel consensus definition of FRI. It is important to standardise sampling and culturing techniques in order to maximise the reporting of detailed microbiology of FRI.

Govaert et al.,[14] using the consensus definition for FRI[13] outline the diagnostic value of clinical parameters, serum inflammatory markers, imaging modalities, tissue and sonication fluid sampling, molecular biology techniques and histopathological examination.

Clinical investigation includes wound breakdown, fistula or sinus formation and purulent drainage. Inflammatory markers include WCC, leukocyte count, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR).

Imaging modalities need to consider resources available to the treating team. They can include plain film radiography, computed tomography (CT), magnetic resonance imaging (MRI), 3-phase bone scan, fluorodeoxyglucose positron emission tomography (FDG-PET) and white cell labelled scintigraphy.

Sampling should aim for confirmatory criteria of FRI. This involves at least two deep tissue/implant specimens of a distinct pathogen. Preferably, five or more deep tissue or fluid samples should be collected using a no touch technique. Polymerase chain reaction (PCR) can be used to amplify bacterial DNA. In regards to histopathology and FRI consensus definition, the presence of visible microorganisms in deep tissue specimens using specific staining techniques for bacteria and fungi is regarded as a confirmatory sign.

Local knowledge of bacterial strains causing infection and antimicrobial resistance is the prerequisite for sufficient antimicrobial prophylaxis. Future directions require urgent multisectoral action in order to achieve the sustainable development goals of the WHO.[45] Continuous surveillance and permanent hand hygiene standards[69] may reduce the use of broad spectrum antimicrobial agents and prevent outbreaks of highly resistant strains.[70] The current pipeline of new antimicrobials is limited. In 2019, WHO[45] identified 32 antibiotics in clinical development that address the list of priority pathogens, of which only six were classified as innovative. A lack of access to antimicrobials remains a major issue. Antibiotic shortages are affecting countries of all levels of development. Without a radical change in how antibiotics are used, new antibiotics will suffer the same fate as the current ones.

Optimisation of timing of definitive internal fixation for polytrauma patients needs to balance early systemic hyperinflammation related immunoparalysis against longer ICU stay and its associated colonisation and bacteraemia in order to minimise the morbidity and mortality associated with FRI. We need international collaboratives to perform prospective epidemiological studies as foundations for interventional studies to improve practice in the field.

Further clinical and experimental research is needed to understand FRI and comprehend the development of virulence in certain species as well as to design colonisation-inhibiting medical implants to make a targeted antimicrobial prophylaxis possible. Although work is being pursued with novel antimicrobial molecules, other tactics being investigated include phage therapy, molecules aimed at blocking regulation of virulence determinants and surface adhesions, and vaccination.[39] New imaging and molecular technologies are also developing rapidly and as such, improvement in the diagnostic accuracy in being able to identify FRI and treat rapidly has promise. Global education remains vital to the management and prevention of FRI.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

David Graan https://orcid.org/0000-0001-8410-2597

References

1. Sliepen J, Onsea J, Zalavras CG, et al. What is the diagnostic value of the Centers for Disease Control and Prevention criteria for surgical site infection in fracture-related infection? *Injury* 2021; 52: 2879–2885. DOI: 10.1016/j.injury.2021.08.009.
2. Metsemakers WJ, Onsea J, Neutjens E, et al. Prevention of fracture-related infection: a multidisciplinary care package. *Int Orthop* 2017; 41: 2457–2469. DOI: 10.1007/s00264-017-3607-y.
3. Turner MC and Migaly J. Surgical Site Infection: The Clinical and Economic Impact. *Clin Colon Rectal Surg* 2019; 32: 157–165. DOI: 10.1055/s-0038-1677002.
4. Hwabejire JO, Kaafarani HM, Imam AM, et al. Excessively long hospital stays after trauma are not related to the severity of illness: let's aim to the right target. *JAMA Surg* 2013; 148: 956–961. DOI: 10.1001/jamasurg.2013.2148.
5. Urban JA. Cost analysis of surgical site infections. *Surg Infect (Larchmt)* 2006; 7(Suppl 1): S19–S22. DOI: 10.1089/sur.2006.7.s1-19.
6. Whitehouse JD, Friedman ND, Kirkland KB, et al. The impact of surgical-site infections following orthopedic surgery at a community hospital and a university hospital: adverse quality of life, excess length of stay, and extra cost. *Infect Control Hosp Epidemiol* 2002; 23: 183–189. DOI: 10.1086/502033.
7. Metsemakers WJ, Morgenstern M, Senneville E, et al. General treatment principles for fracture-related infection: recommendations from an international expert group. *Arch Orthop Trauma Surg* 2020; 140: 1013–1027. DOI: 10.1007/s00402-019-03287-4.
8. World Health O. *Antimicrobial Resistance: Global Report on Surveillance*. Geneva, Switzerland: World Health Organization, 2014.
9. Geubbels EL, Nagelkerke NJ, Mintjes-De Groot AJ, et al. Reduced risk of surgical site infections through surveillance in a network. *Int J Qual Health Care* 2006; 18: 127–133. DOI: 10.1093/intqhc/mzi103.
10. Brandt C, Sohr D, Behnke M, et al. Reduction of surgical site infection rates associated with active surveillance. *Infect Control Hosp Epidemiol* 2006; 27: 1347–1351. DOI: 10.1086/509843.
11. Antibiotic Expert Group. *Therapeutic Guidelines: Antibiotic*. 16th ed. Melbourne, VIC: TGL, 2020.
12. CDC. Surgical site infection, https://www.cdc.gov/nhsn/pdfs/pscmanual/9pscSSIcurrent.pdf (2022.
13. Metsemakers WJ, Morgenstern M, McNally MA, et al. Fracture-related infection: A consensus on definition from an international expert group. *Injury* 2018; 49: 505–510. DOI: 10.1016/j.injury.2017.08.040.
14. Govaert GAM, Kuehl R, Atkins BL, et al. Diagnosing fracture-related infection: Current concepts and recommendations. *J Orthop Trauma* 2020; 34: 8–17. DOI: 10.1097/BOT.0000000000001614.
15. Kavanagh N, Ryan EJ, Widaa A, et al. Staphylococcal osteomyelitis: disease progression, treatment challenges, and future directions. *Clin Microbiol Rev* 2018; 31: e00084–e000117. DOI: 10.1128/CMR.00084-17.
16. Urish KL and Cassat JE. Staphylococcus aureus Osteomyelitis: bone, bugs, and surgery. *Infect Immun* 2020; 88: e00932–e001119. DOI: 10.1128/IAI.00932-19.
17. Dadgostar P. Antimicrobial resistance: implications and costs. *Infect Drug Resist* 2019; 12: 3903–3910. DOI: 10.2147/IDR.S234610.
18. Trampuz A and Zimmerli W. Diagnosis and treatment of infections associated with fracture-fixation devices. *Injury* 2006; 37(Suppl 2): S59–S66. DOI: 10.1016/j.injury.2006.04.010.
19. Ktistakis I, Giannoudi M and Giannoudis PV. Infection rates after open tibial fractures: are they decreasing? *Injury* 2014; 45: 1025–1027. DOI: 10.1016/j.injury.2014.03.022.
20. Fang C, Wong TM, Lau TW, et al. Infection after fracture osteosynthesis - Part I. *J Orthop Surg (Hong Kong)* 2017; 25: 2309499017692712. DOI: 10.1177/2309499017692712.
21. Walter N, Rupp M, Lang S, et al. The epidemiology of fracture-related infections in Germany. *Sci Rep* 2021; 11: 10443. DOI: 10.1038/s41598-021-90008-w.
22. Wang B, Xiao X, Zhang J, et al. Epidemiology and microbiology of fracture-related infection: a multicenter study in Northeast China. *J Orthop Surg Res* 2021; 16: 490. DOI: 10.1186/s13018-021-02629-6.
23. Metsemakers WJ, Smeets B, Nijs S, et al. Infection after fracture fixation of the tibia: analysis of healthcare utilization and related costs. *Injury* 2017; 48: 1204–1210. DOI: 10.1016/j.injury.2017.03.030.
24. Tanner J, Norrie P and Melen K. Preoperative hair removal to reduce surgical site infection. *Cochrane Database Syst Rev* 2011: CD004122. DOI: 10.1002/14651858.CD004122.pub4.
25. Greene LR. Guide to the elimination of orthopedic surgery surgical site infections: an executive summary of the association for professionals in infection control and epidemiology elimination guide. *Am J Infect Control* 2012; 40: 384–386. DOI: 10.1016/j.ajic.2011.05.011.
26. Chiu KY, Lau SK, Fung B, et al. Plastic adhesive drapes and wound infection after hip fracture surgery. *Aust N Z J Surg* 1993; 63: 798–801. DOI: 10.1111/j.1445-2197.1993.tb00343.x.
27. Metsemakers WJ, Kuehl R, Moriarty TF, et al. Infection after fracture fixation: Current surgical and microbiological concepts. *Injury* 2018; 49: 511–522. DOI: 10.1016/j.injury.2016.09.019.

28. Bai Y, Zhang X, Tian Y, et al. Incidence of surgical-site infection following open reduction and internal fixation of a distal femur fracture: An observational case-control study. *Medicine (Baltimore)* 2019; 98: e14547. DOI: 10.1097/MD.0000000000014547.
29. Uckay I, Hoffmeyer P, Lew D, et al. Prevention of surgical site infections in orthopaedic surgery and bone trauma: state-of-the-art update. *J Hosp Infect* 2013; 84: 5–12. DOI: 10.1016/j.jhin.2012.12.014.
30. Penn-Barwell JG, Murray CK and Wenke JC. Early antibiotics and debridement independently reduce infection in an open fracture model. *J Bone Jt Surg Br* 2012; 94: 107–112. DOI: 10.1302/0301-620X.94B1.27026.
31. Khatod M, Botte MJ, Hoyt DB, et al. Outcomes in open tibia fractures: relationship between delay in treatment and infection. *J Trauma* 2003; 55: 949–954. DOI: 10.1097/01.TA.0000092685.80435.63.
32. Hoff WS, Bonadies JA, Cachecho R, et al. East practice management guidelines work group: update to practice management guidelines for prophylactic antibiotic use in open fractures. *J Trauma* 2011; 70: 751–754. DOI: 10.1097/TA.0b013e31820930e5.
33. Gustilo RB and Anderson JT. Prevention of infection in the treatment of one thousand and twenty-five open fractures of long bones: retrospective and prospective analyses. *J Bone Jt Surg Am* 1976; 58: 453–458.
34. Trickett RW, Rahman S, Page P, et al. From guidelines to standards of care for open tibial fractures. *Ann R Coll Surg Engl* 2015; 97: 469–475. DOI: 10.1308/rcsann.2015.0020.
35. Pincus D, Byrne JP, Nathens AB, et al. Delay in flap coverage past 7 days increases complications for open tibia fractures: a cohort study of 140 North American trauma centers. *J Orthop Trauma* 2019; 33: 161–168. DOI: 10.1097/BOT.0000000000001434.
36. Dudareva M, Barrett L, Figtree M, et al. Sonication versus Tissue sampling for diagnosis of prosthetic joint and other orthopedic device-related infections. *J Clin Microbiol* 2018; 56: e00688–e00718. DOI: 10.1128/JCM.00688-18.
37. Gustilo RB and Anderson JT. JSBS classics. Prevention of infection in the treatment of one thousand and twenty-five open fractures of long bones. Retrospective and prospective analyses. *J Bone Jt Surg Am* 2002; 84: 682. DOI: 10.2106/00004623-200204000-00029.
38. Sheehy SH, Atkins BA, Bejon P, et al. The microbiology of chronic osteomyelitis: prevalence of resistance to common empirical anti-microbial regimens. *J Infect* 2010; 60: 338–343. DOI: 10.1016/j.jinf.2010.03.006.
39. Fry DE and Barie PS. The changing face of Staphylococcus aureus: a continuing surgical challenge. *Surg Infect (Larchmt)* 2011; 12: 191–203. DOI: 10.1089/sur.2011.068.
40. Eisner R, Lippmann N, Josten C, et al. Development of the bacterial spectrum and antimicrobial resistance in surgical site infections of trauma patients. *Surg Infect (Larchmt)* 2020; 21: 684–693. DOI: 10.1089/sur.2019.158.
41. Worth LJ, Bull AL, Spelman T, et al. Diminishing surgical site infections in Australia: time trends in infection rates, pathogens and antimicrobial resistance using a comprehensive Victorian surveillance program, 2002-2013. *Infect Control Hosp Epidemiol* 2015; 36: 409–416. DOI: 10.1017/ice.2014.70.
42. Burns TC, Stinner DJ, Mack AW, et al. Microbiology and injury characteristics in severe open tibia fractures from combat. *J Trauma Acute Care Surg* 2012; 72: 1062–1067. DOI: 10.1097/TA.0b013e318241f534.
43. Laux C, Peschel A and Krismer B. Staphylococcus aureus colonization of the human nose and interaction with other microbiome members. *Microbiol Spectr* 2019; 7. DOI: 10.1128/microbiolspec.GPP3-0029-2018.
44. Tam K and Torres VJ. Staphylococcus aureus secreted toxins and extracellular enzymes. *Microbiol Spectr* 2019; 7. DOI: 10.1128/microbiolspec.GPP3-0039-2018.
45. World Health Organisation. W. Antimicrobial Resistance. https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance. 2020.
46. Centre for Disease Dynamics. *Economics and Policy. State of the World's Antibiotics*. Washington, DC: CDDEP, 2015.
47. Sutter DE, Milburn E, Chukwuma U, et al. Changing Susceptibility of Staphylococcus aureus in a US Pediatric Population. *Pediatrics* 2016; 137: e20153099. DOI: 10.1542/peds.2015-3099.
48. Public Health Agency of Canada. Canadian antimicrobial resistance surveillance system report. 2015 Ottawa.
49. European antimicrobial resistance surveillance network. EARS - Net Report. Dublin. 2014.
50. Dudareva M, Hotchen AJ, Ferguson J, et al. The microbiology of chronic osteomyelitis: Changes over ten years. *J Infect* 2019; 79: 189–198. DOI: 10.1016/j.jinf.2019.07.006.
51. Baym M, Lieberman TD, Kelsic ED, et al. Spatiotemporal microbial evolution on antibiotic landscapes. *Science* 2016; 353: 1147–1151. DOI: 10.1126/science.aag0822.
52. Blair JM, Webber MA, Baylay AJ, et al. Molecular mechanisms of antibiotic resistance. *Nat Rev Microbiol* 2015; 13: 42–51. DOI: 10.1038/nrmicro3380.
53. Conterno LO and Turchi MD. Antibiotics for treating chronic osteomyelitis in adults. *Cochrane Database Syst Rev* 2013: CD004439. DOI: 10.1002/14651858.CD004439.pub3.
54. NSW Trauma Registry. Major Trauma in NSW -NAfCI.
55. Weigel LM, Donlan RM, Shin DH, et al. High-level vancomycin-resistant Staphylococcus aureus isolates associated with a polymicrobial biofilm. *Antimicrob Agents Chemother* 2007; 51: 231–238. DOI: 10.1128/AAC.00576-06.
56. Brady RA, Leid JG, Calhoun JH, et al. Osteomyelitis and the role of biofilms in chronic infection. *FEMS Immunol Med Microbiol* 2008; 52: 13–22. DOI: 10.1111/j.1574-695X.2007.00357.x.
57. Malic S, Hill KE, Playle R, et al. In vitro interaction of chronic wound bacteria in biofilms. *J Wound Care* 2011; 20572: 569574–570567. DOI: 10.12968/jowc.2011.20.12.569.

58. Namvar AE, Bastarahang S, Abbasi N, et al. Clinical characteristics of Staphylococcus epidermidis: a systematic review. *GMS Hyg Infect Control* 2014; 9: Doc23. DOI: 10.3205/dgkh000243.
59. Plata K, Rosato AE and Wegrzyn G. Staphylococcus aureus as an infectious agent: overview of biochemistry and molecular genetics of its pathogenicity. *Acta Biochim Pol* 2009; 56: 597–612.
60. Chavakis T, Wiechmann K, Preissner KT, et al. Staphylococcus aureus interactions with the endothelium: the role of bacterial "secretable expanded repertoire adhesive molecules" (SERAM) in disturbing host defense systems. *Thromb Haemost* 2005; 94: 278–285. DOI: 10.1160/TH05-05-0306.
61. Otto M. Basis of virulence in community-associated methicillin-resistant Staphylococcus aureus. *Annu Rev Microbiol* 2010; 64: 143–162. DOI: 10.1146/annurev.micro.112408.134309.
62. Jacobsson G, Dashti S, Wahlberg T, et al. The epidemiology of and risk factors for invasive Staphylococcus aureus infections in western Sweden. *Scand J Infect Dis* 2007; 39: 6–13. DOI: 10.1080/00365540600810026.
63. Calhoun JH, Manring MM and Shirtliff M. Osteomyelitis of the long bones. *Semin Plast Surg* 2009; 23: 59–72. DOI: 10.1055/s-0029-1214158.
64. De Meo D, Cera G, Ceccarelli G, et al. Candida fracture-related infection: a systematic review. *J Bone Jt Infect* 2021; 6: 321–328. DOI: 10.5194/jbji-6-321-2021.
65. Bezstarosti H, Van Lieshout EMM, Voskamp LW, et al. Insights into treatment and outcome of fracture-related infection: a systematic literature review. *Arch Orthop Trauma Surg* 2019; 139: 61–72. DOI: 10.1007/s00402-018-3048-0.
66. Alt V and Giannoudis PV. Musculoskeletal infections - A global burden and a new subsection in Injury. *Injury* 2019; 50: 2152–2153. DOI: 10.1016/j.injury.2019.11.001.
67. Walter N, Rupp M, Hierl K, et al. Long-term patient-related quality of life after fracture-related infections of the long bones. *Bone Jt Res* 2021; 10: 321–327. DOI: 10.1302/2046-3758.105.BJR-2020-0532.
68. Harris AM, Althausen PL, Kellam J, et al. Complications following limb-threatening lower extremity trauma. *J Orthop Trauma* 2009; 23: 1–6. DOI: 10.1097/BOT.0b013e31818e43dd.
69. Dancer SJ. Controlling hospital-acquired infection: focus on the role of the environment and new technologies for decontamination. *Clin Microbiol Rev* 2014; 27: 665–690. DOI: 10.1128/CMR.00020-14.
70. Bucher BT, Warner BW and Dillon PA. Antibiotic prophylaxis and the prevention of surgical site infection. *Curr Opin Pediatr* 2011; 23: 334–338. DOI: 10.1097/MOP.0b013e3283464a75.