Acta Scientific Orthopaedics (ISSN: 2581-8635)

Volume 5 Issue 12 December 2022

Review Article

How Common are Fungal Fracture Related Infections? A Literature Review of Fungal Fracture Related Infections

Dhanasekaraprabu Balasubramanian*, Alexis-Dimitris Iliadis, Alexandros Vris and Nima Heidari

Bone Infection and Limb reconstruction Service, Royal London Hospital, Barts Health NHS, UK

***Corresponding Author:** Dhanasekaraprabu Balasubramanian, Bone Infection and Limb reconstruction Service, Royal London Hospital, Barts Health NHS, UK.

Received: August 22, 2022

Published: November 08, 2022

Abstract

Infections following Fracture fixation is one of the dreaded complications in the setting of polytrauma. While bacteria seem to be the predominant pathogen in most of the Fractures related infections (FRI), Fracture related infections caused by fungus are quite severe and sometimes missed as they are not common. Also, the published literature on Fungal FRI's is few when compared to published reports of fungal prosthetic joint infection. Fracture related infections in the setting of polytrauma can be bacterial, fungal, or mixed. They pose several diagnostic and surgical challenges, but the principles of treatment and reconstruction include thorough debridement and appropriate antimicrobial therapy.

Keywords: Fractures related infections, Polytrauma

Introduction

Review of Fungal Fracture Related Infections

Fracture related Infection (FRI) is a major complication following orthopaedic trauma and results in significant costs to the patient and the healthcare system. A study looking into incidence of infection following intramedullary nailing of tibial shaft fractures concluded that it causes a substantial burden tothe healthcare system, leading to increased hospital stay, need for hospital readmission and reoperation, and increased use of primary care resources [1]. This can result in significant morbidity and loss of function in otherwise healthy patients. While several measures have been suggested to prevent infection including antibiotic prophylaxis, perioperative prevention measures, surgical technique [2] FRI still occurs in 1-2% of closed fractures and up to 30% in cases of open fractures [3].

Diagnosis of fracture related infection (FRI)

The diagnosis and management of FRI remains a huge challenge because of the myriad ways in which FRI can present in acute and chronic phases. During the early post-operative period, the signs of FRI like pain, redness and warmth can overlap with features of normal healing while in chronic phase the subtle signs make the diagnosis even more difficult [4]. There was a lack of consensus in the definition of FRI which made the diagnosis and management of these patients challenging. A systematic review showed that only a minority of the randomised controlled trials (2%) in fracture care use any kind of standardized definition of infection [5]. The development of diagnostic criteria for Prosthetic Joint Infection (PJI) has led to an improvement in diagnosis of PJI after hip and knee arthroplasty [6]. This further highlighted the need for uniform criteria for diagnosis of FRI. Hence the AO Foundation and the European Bone and Joint Infection Society (EBJIS) recently proposed a consensus

definition for FRI to standardize the diagnostic criteria and improve the quality of patient care and applicability of future studies regarding this condition [7].

Microbiology

Fracture related infections are usually caused by bacteria growing in biofilms on foreign material andin necrotic bone. Polymicrobial infections are linked to open fractures. Atypical organisms like nontuberculous mycobacterium and fungi are typically introduced via open wounds. The inoculated fungi then usually proliferate and invade surrounding tissue. The delays in diagnosis and management of post traumatic fungal infections and their aggressive nature led to poor outcomes in patients. While there is a lot of data available for prosthetic joint infections there remain significant gaps in literature when it comes to FRI and especially those caused by atypical organisms.

There is a number of studies reporting on organisms involved in bacterial FRI with Staphylococcus aureus being the most common organism causing fracture related infection, and Methicillin resistant S. aureus becoming much more common than Methicillin sensitive S. aureus in some areas. They canalso be caused by less virulent microorganisms like coagulase negative staphylococcus and 80-90%of these cases are methicillin resistant. Other less virulent organisms like Corynebacterium and Propionibacterium are increasingly identified. Gastrointestinal tract organisms including E Coli, Enterobacter, Enterococci, Klebsiella and Proteus are identified in FRI in sites near perineum. Gram negative Multi drug resistant Pseudomonas aeruginosa and Acinetobacter baumannii are also being increasingly identified. Pseudomonas infections are associated with higher recurrence rates whencompared to staphylococcus.

The incidence of Fungal FRI's and the organisms causing it is not clear because of lack of sufficient literature. However Fungal prosthetic joint infections are reported to be about 1-3% of reported PJI [8] and the most common organism in these cases is candida species with C. albicans being isolated in majority of cases [9]. Candida species also are the most common organisms causing septic arthritis and osteomyelitis [10]. Significant data for invasive fungal infections post trauma are usually from combat related injuries. The common organisms isolated in military patients are Mucorales, Aspergillus and Fusarium species [11].

Within the order of Mucorales, Mucor species are predominant organisms. Also rates of bacterial co-infection in cases of Mucor mycosis varies from 20-100% with involvement of diverse organisms like S aureus, E coli, Pseudomonas and Enterococci [12].

Diagnosis of fungal infections

The diagnosis of FRI and in particular Fungal FRI remains a challenge. In the presence of purulent discharge and wound breakdown or fistula it is straight forward but in chronic cases these may be absent. Serum inflammatory markers like leukocyte count, C-reactive protein and Erythrocyte sedimentation rate may provide some supplementary evidence. A systematic review looking into thediagnostic value of the inflammatory markers found that CRP was the most useful with sensitivity ranging from 60-100% and specificity ranging from 34.3 and 85.7% [13]. But most of the studies evaluating the serum inflammatory markers are based on bacterial FRI. The cut-off values for fungalFRI are not clear because of lack of literature. A Multicentre Fungal PJI study had reported an average ESR and CRP of 54mm/hour and 17.5mg respectively [14].

The intra operative samples from a suspected fungal FRI should be sent for microbiological analysis and culture. Identification of the fungal organism is essential for treatment. But as per literature available in setting of Fungal PJI, 46% of cases may be culture negative [15]. Also, Fungal cultures should be held for a minimum of 5-14 days [16] and ideally for 4 weeks given their indolent nature [14]. The use of selective fungal growth medium has been shown to increase culture sensitivity [14,16]. Theuse of molecular techniques like Polymerase chain reaction and next generation sequencing (NGS) toimprove organism yield to help with diagnosis is increasing. NGS is used to amplify microbial DNA using PCR and subsequent sequencing of all amplicons. The region of interest in the fungal genome is the internal transcribed spacer sequence which helps in identification of the fungal organism [17].

But the NGS data needs to be interpreted with caution as there has been reports of up to 40% falsepositive rate with fungal contaminants [17]. Histopathological analysis of specimens by specific staining techniques to confirm the presence of microorganisms and presence of acute inflammatorycell infiltrates can also be helpful.

While imaging in the setting of FRI can help with the confirming the presence or absence of infection,extent, presence of seques-

trum, cloaca, abscesses and show fracture healing and implant stability it is not specific for Fungal FRI

Treatment

The treatment of fungal FRI as with other cases of FRI's should be multidisciplinary where possible. As mentioned in a recent study the makeup of these teams should be based on international guidelines and should be flexible and adaptable to available resources and expertise [18]. The teams usually consist of orthopaedic trauma surgeons, Infectious disease specialists, microbiologists, plastic surgeons, musculoskeletal radiologists, Physiotherapists, and specialist nurses. Also, a comprehensive assessment of the patient factors such as pre-existing comorbidities, immunocompromised state, smoking should be done.

The surgical treatment of FRI is complicated by the presence of fracture. The stability of the fracture is essential not only for union but also in the treatment of infection. The surgical implants for stabilising the fracture can be removed after fracture healing, thereby removing the biofilm, and providing a chance at eradication of the infection. Based on these concepts two main strategies for treatment hasevolved. Debridement, antimicrobial therapy, and implant retention (DAIR) and Debridement, antimicrobial therapy and implant removal or implant exchange in one or multiple stages as necessaryif there is still non-union of the fracture. Also, in cases of extensive infection and poor host physiology other options like amputation and antibiotic suppression can be considered.

In surgical management of FRI's, after initial debridement the main issues are management of bone defects, dead space management and providing local antibiotic therapy. Local antibiotic therapy is especially useful in chronic cases where the delivery of systemic antibiotics is hampered because of the scarred tissue. The delivery of antibiotics locally is done commonly through polymethyl methacrylate (PMMA) beads, PMMA bone spacers or PMMA coated IM rods [19,20]. There also has been promising results for absorbable carriers for local antibiotic therapy [21]. These are usually impregnated with 10% antimicrobial concentration for infection treatment [22]. In Fungal FRI's amphotericin B is commonly used. Reports from PJI literature show amphotericin B eradicated infection at doses of 1.2gm per 40g of PMMA [23]. But amphotericin B forms covalent crosslinks with PMMA and elutes poorly. Cunningham., *et al.* reported that the phospholipids counteraction with PMMAin liposomal amphotericin B led to increased elution when compared to the standard form [24]. Other studies from PJI have also reported the use of fluconazole and voriconazole with PMMA for local antibiotic therapy [16,25]. But more in vivo studies are needed to determine their effectiveness.

Conclusion

Systemic antifungal therapy is also essential in the management of fungal FRI. There is a lot of debate on the duration of therapy, route of administration and choice of antifungal. The choice of antifungal depends on factors like susceptibility to specific pathogen, severity of systemic symptomsand side effect profile. Again, studies from fungal PJI have reported use of fluconazole and amphotericin B either in IV or oral form [16]. Other antifungals like 5-flucytosine, caspofungin, itraconazole, voriconazole, and ketoconazole have also been used [26]. Fluconazole is preferred because it is effective and has less side effects when compared to amphotericin B [27,28]. However,the duration of systemic antifungals following infections remains a matter of debate [14,28] and is usually a multidisciplinary decision depending on the specific organism, host status and degree ofinfection.

Bibliography

1. Galvain T., *et al.* "The economic burden ofinfections following intramedullary nailing for a tibial shaft fracture in England". *BMJ Open* 10.8 (2020): 1-11.

2. Metsemakers WJ., *et al.* "Prevention of fracture-related infection: a multidisciplinary care package". *International Orthopaedics* 41.12 (2017): 2457-2469.

3. Trampuz A and Zimmerli W. "Diagnosis and treatment of infections associated with fracture-fixationdevices". *Injury* 37.2 (2006): 59-66.

4. Govaert GAM., *et al.* "Diagnosing Fracture-Related Infection: Current Concepts and Recommendations". *Journal of Orthopaedic Trauma* 34.1 (2020): 8-17.

5. Metsemakers WJ., *et al.* "Definition ofinfection after fracture fixation: A systematic review of randomized controlled trials to evaluate current practice". *Injury* 49.3 (2018): 497-504.

6. Parvizi J., *et al.* "The 2018 Definition ofPeriprosthetic Hip and Knee Infection: An Evidence-Based and Validated Criteria". *Journal of Arthroplasty* 33.5 (2018): 1309-1314.e2.

7. Metsemakers WJ., *et al.* "Fracture-related infection: A consensus on definition from an international expert group". *Injury* 49.3 (2018): 505-510.

8. Gross CE., *et al.* "Fungal Periprosthetic Joint Infection: A Review of Demographics and Management". *The Journal of Arthroplasty* 36.5 (2021): 1758-1764.

9. BH H., *et al.* "Fungal peri-prosthetic joint infection after primary total knee replacement". *The Journal of Bone and Joint Surgery British* 94.5 (2012): 656-659.

10. JT B., *et al.* "Fungal osteomyelitis and septic arthritis. The Journal of the American Academy of Orthopaedic Surgeons 22.6 (2014): 390-401.

11. AC W., *et al.* "Combat trauma-associated invasive fungal wound infections: epidemiology and clinical classification". *Epidemiology and Infection* 143.1 (2015): 214-224.

12. Kronen R., *et al.* "Invasive Fungal Infections Secondary to Traumatic Injury". *International Journal of Infectious Diseases* 62 (2017): 102-111.

13. J Van Den K., *et al.* "Diagnostic accuracy of serum inflammatorymarkers in late fracture-related infection: a systematic review and meta-analysis". *The Bone and Joint Journal* 100-B.12 (2018): 1542-1550.

14. K A., *et al.* "Microbiological, clinical, and surgical features of fungal prosthetic joint infections: a multi-institutional experience". *The Journal of Bone and Joint Surgery American* 91.6 (2009): 142-149.

15. HK Y., *et al.* "A Review of the Literature on Culture-Negative Periprosthetic Joint Infection: Epidemiology, Diagnosis and Treatment". *Knee Surgery and Related Research* 29.3 (2017): 155-164.

16. O J., *et al.* "Fungal periprosthetic joint infection in total knee arthroplasty: a systematic review". *Orthopedic Reviews* 7.1 (2015).

17. M *et al.* "Can next generation sequencing play a role in detecting pathogens in synovial fluid?" The *Bone and Joint Journal* 100-B.2 (2018): 127-133.

18. Pulcini C., *et al.* "Developing core elementsand checklist items for global hospital antimicrobial stewardship programmes: a consensus approach". *Clinical Microbiology and Infection* 25.1 (2019): 20-25.

19. Ostermann PAW., *et al.* "Local antibiotic therapy for severe open fractures. Areview of 1085 consecutive cases". *Journal of Bone and Joint Surgery - Series B* 77.1 (1995): 93-97.

20. Lehner B., *et al.* "First experiences with negative pressure wound therapy and instillation in the treatment of infected orthopaedic implants: a clinical observational study". *International Orthopaedics* 35.9 (2011): 1415.

21. Morgenstern M., *et al.* "The effect of local antibiotic prophylaxis when treating open limb fractures: A systematic review and meta-analysis". *Bone and Joint Research* 7.7 (2018): 447-456.

22. Anagnostakos K., *et al.* "Fungal Periprosthetic Hip and Knee Joint Infections: Clinical Experience With a 2-Stage Treatment Protocol". *The Journal of Arthroplasty* 27.2 (2012): 293-298.

23. Ueng SWN., *et al.* "What Is the Success of Treatment of Hip and Knee Candidal Periprosthetic Joint Infection?" *Clinical Orthopaedics and Related Research* 471.9 (2013): 3002.

24. Cunningham B., et al. "Liposomal Formulation Increases Local Delivery of Amphotericin from Bone Cement: A Pilot Study". Clinical Orthopaedics and Related Research 470 (10 (2012): 2671.

25. Rouse MS., *et al.* "Are Anidulafungin or Voriconazole Released from Polymethylmethacrylate *In Vitro*?" *Clinical Orthopaedics and Related Research* 469.5 (2018): 1466.

26. Schoof B., *et al.* "Fungal Periprosthetic Joint Infection of the Hip: A Systematic Review". *Orthopedic Reviews* 7.1 (2015): 18-22.

27. Cobo F., *et al.* "Candida Prosthetic Joint Infection. A Review of Treatment Methods". *Journal of Bone and Joint Infection* 2.2 (2017): 114.

28. Kuiper JW., *et al.* "2-stage revision recommended for treatment of fungal hip and knee prosthetic joint infections: An analysis of 164 patients, 156 from the literature and 8 own cases". *Acta Orthopaedica* 84.6 (2013): 517.