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Review Article

Open Tibial Shaft Fracture Related Infections: Review of Presentation, Diagnosis, and Treatment

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Infections are a relatively common complication following open tibial shaft fractures. The tibia is an important bone for weight bearing and has important neurovascular structures in close proximity. Patients typically present following an open tibial shaft fracture, mostly common which resulted from high energy trauma. Diagnosis can be made by meeting certain criteria and employing various testing and imaging modalities. Treatment options for tibial shaft fracture related infection (FRI) include various combinations of antibiotic medications and surgical interventions. Long term complications of this condition are numerous. This review article will dive deeper into the relevant information regarding anatomy, presentation and diagnosis, treatment, and complications of tibial shaft FRI.

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INTRODUCTION

In the context of orthopedic surgery, the term infection is nebulous due it being broadly inclusive. Variants of the term include osteomyelitis, osteitis, superficial infection, deep infection, or surgical site infection. Recently, the term "fracture-related infection (FRI)" was proposed to encompass the aforementioned terms to simplify diagnosis and the description of orthopedic fracture related infections. It should be noted that FRI is distinctly different from intra-articular or prosthetic joint infection (PJI), which is infection involving a native or total joint arthroplasty, respectively, as that topic has been studied to a greater extent (Metsemakers, Morgenstern, et al. 2018). FRI rates have ranged from 1% after operative fixation of closed low energy fractures to over 30% in open tibia fractures. Additionally, there has been a decline in infection rates over the past decades (Metsemakers, Kuehl, et al. 2018).

A paper by Metsemakers et al. recently presented an unambiguous definition of the condition. This paper presented 4 confirmatory criteria: fistula, sinus, or wound breakdown with connection to the implant, purulent drainage from the wound or pus during surgery, phenotypically indistinguishable pathogens identified from at least two separate deep tissue samples, or presence of microorganisms in deep tissue taken during an operation, confirmed by histopathology and specific staining. The presence of any of these indicators is pathognomonic of FRI. There are also suggestive criteria: clinic signs, which include any one of pain, redness, swelling, increased local temperature, and fever, radiologic sign which include any one of bone lysis, implant loosening, sequestration, nonunion, periosteal bone formation, pathogen identified from a single deep tissue sample, elevated inflammatory markers (Erythrocyte sedimentation rate (ESR), White blood cell count (WBC), C-reactive protein (CRP)), persistent wound drainage beyond the few days postoperatively, and new onset joint effusion (Metsemakers, Morgenstern, et al. 2018).

Generally, FRI results from bacterial invasion, but can also occur due to fungal pathogens (Metsemakers, Morgenstern, et al. 2018) The formation of a biofilm on implanted hardware is crucial to the development of FRI, as it enables microorganisms to survive at much higher concentrations of antibiotics. Management of FRI, as a result, involves a combination of surgical intervention and antimicrobial treatment (Depypere et al. 2020).

Depypere et al. demonstrated that the most common microorganism isolated from FRI is Staphylococcus aureus (31.4%). S. epidermidis was the second most common at 25.8%. Non-epidermidis coagulase-negative staphylococci were present 18.0% of the time. Monomicrobial infections (71.1%) were more common than polymicrobial infections (25.3%) (Depypere et al. 2022).

Tibial shaft fractures are fractures of the diaphysis of the tibia and exclude intra-articular fractures or fractures within 5 cm of the proximal and distal ends of the bone. They can also be divided into proximal, middle, and distal one-third fractures (Court-Brown and McBirnie 1995). Tibial shaft fractures can be a result of low or high energy trauma. Low energy fracture patterns are generally rotational, resulting in spiral fractures. High energy fractures are a result of direct force and cause wedge or oblique fracture patterns (Bourne, Sinkler, and Murphy 2023). Generally, treatment options include nonoperatively management with immobilization, intramedullary nailing, plate fixation, external fixation, and rarely amputation (Wennergren et al. 2021).

ANATOMY

The tibia is the second largest bone in the body and supports the majority of weight bearing in the leg. Proximally, the medial and lateral tibial plateau form the inferior articular surface of the knee. The tibial tubercle lies distal and is the insertion of the patellar tendon on the anterior surface of the tibia. The diaphysis of the tibia is triangular in cross section, with the tibial crest anteriorly (Cantrell, Imonugo, and Varacallo 2023) Due to the anteromedial surface being directly subcutaneous, these fractures are more likely to be open than other long bone fractures (Bourne, Sinkler, and Murphy 2023). Open tibia fractures are associated with 18% infection rate in low-middle income countries and 17.9% infection rate in high income countries, indicating a steady infection rate across the world (Schade et al. 2021). The most distal aspect of the tibia is the medial malleolus. The interosseous membrane, connecting the tibia and fibula, is important for ankle stability and mobility (Cantrell, Imonugo, and Varacallo 2023).

The leg, the anatomical region between the knee and ankle joints, is divided into four fascial compartments: anterior, lateral, deep posterior, and superficial posterior. The anterior compartment contains the tibialis anterior, extensor hallucis longus, extensor digitorum longus, and fibularis tertius muscles. Blood is supplied by the anterior tibial artery and innervation is provided by the deep peroneal nerve (Lezak and Summers 2023). The lateral compartment, which consists of the fibularis longus and brevis muscles, is perfused by the anterior tibial artery and fibular artery and innervated by the superficial peroneal nerve (Khan et al. 2023). The posterior compartment of the leg is divided into superficial and deep aspects but shares a common blood supply and innervation: the posterior tibial artery and tibial nerve respectively. The superficial muscles are the gastrocnemius, soleus, and plantaris while the deep muscles are the popliteus, flexor hallucis longus, flexor digitorum longus, and tibialis posterior (Mostafa, Graefe, and Varacallo 2023).

PRESENTATION AND DIAGNOSIS

Open tibial shaft fractures are often caused by some high energy trauma, with motor vehicle crashes (63%) being the most common etiology (Figure 1). Other mechanisms of injury include assault (18%), falls (17%), and industrial accidents (2%). Additionally, 26.7% of open tibial shaft fractures developed an infection and 68.3% were Gustilo-Anderson grade II or III injuries. The most common complication following open fractures is infection (Mwafulirwa et al. 2022).

FRI of tibial shaft fractures arises after operative fixation of these injuries, and patient presentation can vary widely. Timing of debridement is of the utmost importance, with most sources emphasizing early debridement within the first 24 hours (Rupp, Popp, and Alt 2020) In the early postoperative period, many signs of infection overlap with signs of bone healing, including pain, redness, warmth, and swelling. In the proceeding course of the condition, FRI can present as fracture nonunion or persistent pain, both of which can be due to infectious or noninfectious causes (Govaert et al. 2020). All of this is to say that diagnosing FRI is a challenge.

Clinical signs are the most basic tools clinicians can use to establish an accurate diagnosis. Studies have shown that the only two undisputed clinical criteria for infection are purulent drainage and wound dehiscence and breakdown, which corresponds with the criteria set forth by Metsemakers et al. Other clinical signs that can be used, but are not pathognomonic of FRI include local redness, swelling, warmth, and fever (Govaert et al. 2020). The presence of these signs warrant further investigation by the physician.

Serum inflammatory markers such as erythrocyte sedimentation rate (ESR), white blood cell count (WBC), and C-reactive protein (CRP) are another tool that can be employed in FRI diagnosis. However, these values rise in response to trauma and surgery, both of which the patient is likely to have sustained recently, reducing certainly in diagnosis of FRI. Though, this is in line with the consensus definition, which marks these values as merely suggestive (Govaert et al. 2020). A recent meta-analysis gave sensitivity and specificity values for CRP, WBC, and ESR in diagnosing FRI. Sensitivity and specificity for CRP was 77.0% and 67.9%, respectively. For WBC, sensitivity and specificity was 51.7% and 67.1% specificity. Lastly, for ESR, sensitivity and specificity were 45.1% and 79.3%, respectively. The authors note that these values are suggestive, and, used without additional information, are insufficient to diagnose FRI accurately (van den Kieboom et al. 2018). A secondary rise after initial decrease for these values, however, should increase suspicion (Depypere et al. 2020). Recent studies have shown that elevated IL-6 can be a marker for infection and may be more sensitive than the other forementioned inflammatory markers (Tanaka, Narazaki, and Kishimoto 2014), as it is a key regulator of inflammatory cells such as CD4+ and T helper Cells. Once again this value must be evaluated with caution as it can be elevated with acute trauma, but even more so in the face of viral infection over bacterial (Tanaka, Narazaki, and Kishimoto 2014).

Potential imaging methods for FRI include standard radiography (Figure 2), computed tomography (CT) scanning, magnetic resonance imaging (MRI), 3-phase bone scans, fluorodeoxyglucose positron emission tomography (FDG-PET), and white blood cell scintigraphy. Traditional radiography is the mainstay of traditional imaging modalities for FRI identification. While the diagnostic value of radiography for FRI has not been studied, it is easy, available, quick, has low radiation exposure, and gives baseline information about the position of the fracture and stability and integrity of any orthopedic implants. CT scans can provide better detail but lack sensitivity and specificity. Signs of FRI on CT scans include implant loosening, bone lysis, nonunion, sequestration, and periosteal bone formation. MRI can be useful for investigating soft tissue pathology and morphological bone changes but is difficult to use in differentiating the causes of these changes (Govaert et al. 2020). Nuclear imaging has varying degrees of diagnostic capability and is often unavailable. It has not proved to be any more effective than other imaging modalities in establishing the presence of FRI, so it is seldom employed (Depypere et al. 2020).

Bone and tissue culture is the mainstay to diagnosis. Culture allows for identification of FRI and determination of antibiotic sensitivities. When taking deep tissue samples, it is recommended that at least five samples be taken with different instruments from sites around the fracture and adjacent to implants. Antibiotics should be stopped at least 2 weeks before taking samples to avoid false-negative cultures and be restarted immediately after sampling. Visible microorganisms in deep tissue samples using various staining techniques for bacteria and fungi are pathognomonic for FRI. Biofilms should be disrupted by homogenization during processing, via vortexing, sonication, or beadmill processing. Enrichment broth cultures can also be helpful in the case of slow growing or sparely concentrated organisms (Depypere et al. 2020).

Histopathology is another method of investigating FRI. A recent study by Morgenstern et al. showed that complete absence of polymorphonuclear (PMN) cells was highly correlated with lack of infection (98% specificity, 98% positive predictive value). Additionally, >5 PMNs per high power field was always associated with infection (100% specificity, 100% positive predictive value) (Morgenstern, Athanasou, et al. 2018).

The use of molecular techniques, such as real-time polymerase chain reaction (PCR), is limited because there is scarce evidence of its diagnostic value. Also, as is the case in open fractures, PCR cannot reliably differentiate species of microorganisms present within a biofilm (Morgenstern, Kühl, et al. 2018).

TREATMENT

Treatment for tibial FRI is varied and entirely dependent on the severity of infection, which is often correlated with the time frame in which infection is detected. Infection prevention is of the utmost importance and guidelines are constantly evolving. Prophylactic antibiotics are administered in the case of open fractures to mitigate the risk of infection; although, the specific blend of drugs used is contingent on the fracture type (Isaac et al. 2016). Antibiotic treatment has been shown to be quite effective; Morgenstern et al conducted a meta-analysis and found local antibiotic therapy to be an effective deterrent of infection in open fractures, observing an 11.9% reduction (Hoit, Bonyun, and Nauth 2020a). Further steps can be taken to mitigate the risk of infection, including thorough irrigation in the emergency department with 1L of normal saline with

Table 1. Characteristics of various acute phase reactants in the diagnosis of infection

Name	Time to Rise	Time to Peak	Normal Values	Sensitivity	Specificity	Increased or decreased during infection
White Blood Cell (WBC)	8-20 hours	24-48 hours	5,000-10,000mcL	Low	High	Increased
Erythrocyte Sedimentation Rate (ESR)	24-48 hours	Variable	≤ 20mm/hr	High	Low	Increased
C-Reactive Protein (CRP)	12-24 hours	2-3 days	2-10mg/L	High	Low	Increased
Interluekin-6 (IL-6)	1-2 hours	12 hours	1.25-2.25 pg/ml	High	High	Increased
Fibrinogen	1-2 days	3-4 days		High	High	Increased
Procalcitonin	3-4 hours	6-24 hours	0.5-1.99 ng/L	High	Low	Increased

betadine, and proper sterile coverage of the wound. Some districts have advocated for this from the pre-hospital response team. During the index procedure, sharp debridement of necrotic tissue can de decrease surface area and reduce medium that would otherwise attract bacteria. Furthermore, topical gel or powder antibiotics are often used at the time of the index surgery, directly on the wound. It has been found that Vancomycin powder administered directly into an open wound decreases the risk of infection with gram-positive bacteria (O'Toole et al. 2017), and addition of an aqueous aminoglycoside is an independent predictor of superficial and deep infection with gram-negative bacteria (Lawing, Lin, and Dahners 2015).

Intraoperatively, open fractures are based on the Gustillo-Anderson Classification, with each Grade carrying a higher probability of infection. Infection rates vary throughout the literature, with findings of 1.8% in Gustillo-Anderson Grade I compared with 42.9% in type IIIb (Rupp, Popp, and Alt 2020). For all open fractures, initiation of intravenous antibiotic therapy as soon as possible with broad spectrum antibiotics is recommend. For Gustillo type I and II open fractures, broad spectrum coverage such as cefazolin is often use, with the addition of aminoglycosides for type III fractures. Antibiotic therapy can be tailored to the type of contamination, such as Penicillin for soil-contaminated wounds and fluoroquinolones wounds involving water sources (Rupp, Popp, and Alt 2020). It would seem the timing of antibiotic administration is more important than the duration, as Rupp et al. found no benefit to intravenous antibiotics past 72 hours, unless the wound had not been definitively closed yet (Rupp, Popp, and Alt 2020).

Once infection is detected, antibiotic treatment is tailored to pathogens detected via culture (Concia et al. 2006). The standard course for antibiotic treatment of FRI is four to six weeks. This can be abbreviated to 10 days in the event of resection of the infected bone tissue (Lázaro-Martínez, Aragón-Sánchez, and García-Morales 2014). Various oral antibiotics have proven to be effective; however, the effectiveness of antibiotics is reduced once the infection acquires resistance (Zimmerli 1998).

Surgical treatment becomes viable in the context of stages 3 and 4 Cierny-Mader infection, which is a localized lesion that implicates both cortical and medullary and is mechanically stable post debridement, whereas stages 1 and 2 do not warrant this type of intervention (Paluska 2004). The purpose of operative treatment is resection and debridement of necrotic tissue, which is achieved through a variety of techniques. Extensive bone debridement is crucial as the excision of necrotic tissue ensures a reduced risk of recurrent infection (Calhoun and Manring 2005). The management of dead space, or tissue deformity after debridement, is typically done by inserting vascularized tissue to ensure proper perfusion to mitigate persistent infection. Antibiotic-impregnated polymethylmethacrylate (PMMA) cement is an alternative method of addressing dead space with a storied clinical history (Mifsud and McNally 2019).

Infection induced nonunions can go on to incur tertiary complications; in the event of nonunions that require exchange nailing, the risk of infection indicates detrital hardware removal such as screw fragments should be removed (VanderWilde, Lewallen, and Papagelopoulos 1992). Further, infection can contraindicate subsequent internal fixation, complicating surgical revision. Although there remains no clear treatment consensus for tibial nonunions, various techniques have been shown to be selectively effective (Tong et al. 2017).

Further intramedullary fixation after the index procedure is often debated in the literature. Antibiotic coated nails can be used to provide stability while also combating infection (Figure 3). In their review of 28 articles concerning treatment of long bone fracture infections via intramedullary nailing, Makridis et al. found antibiotic coated nails to be effective in addressing stage II (delayed) infections in particular (Makridis, Tosounidis, and Giannoudis 2013). Alternatively, stage III infections may also be treated via exchange nailing wherein the previous nail is removed and replaced with a large diameter nail, usually 1-4mm larger than the extracted nail. This may allow nails to achieve occupancy of more than 90% of the cortex, significantly increasing union rates (Millar et al. 2018). This needs to be taken into account for antibiotic nail placement, as equivalent sized nails or even slight downsizing of nails are used to accommodate for the antibiotic cement, which may sacrifice some stability of the construct. Though the union rate for a single exchange nailing is 63%, the efficacy jumps to 93% in cases requiring up to five exchange nailings (Lam et al. 2010). Moreover, alternative nailing techniques are utilized depending on the type of nonunion. Hypertrophic nonunions are typically treated via reamed exchange nailing as the stability of the construct is the greatest priority (Rupp et al. 2017). In atrophic nonunions however, dynamization has been shown to be comparable to reamed exchange nailing in the event of minimal bone loss (Court-Brown et al. 1995). It must be noted that caution should be taken with reamed exchange nailing for a septic nonunion in type IIIb open wounds, as there may be lack of clearance and continued infection at the site. Templeman et. Al advised the use of plate augmentation and bone grafting instead of exchange nailing when dealing with type IIIb fractures (Templeman et al. 1995). There does not seem to be a consensus in the literature of timing of exchange intramedullary nailing and antibiotic nail placement, as open tibia shaft fractures are notoriously slow to heal. Radiographic, clinical, and inflammatory workup often guide the need for re-operation on a case-by-case basis.

Although, hardware removal is indicated in the event of infection of extremely resistant organisms; if the target components are structural, the Ilizarov technique, a method used to straighten and lengthen bone via an eponymous circular external fixator, can be used to achieve stability via external fixation as well as promoting bone growth via osteogenic distraction (Gateley et al. 1996). In terms of non and malunion, medial plating may also be employed, with the added benefit of having less malignment than intramedullary nailing (IM) (Mukherjee et al. 2017). For the distal third of the tibia in particular, IM is considered inferior to minimally invasive plate osteosynthesis (MIPO) (Paluvadi et al. 2014). There are other plating variants including the modified Judet's osteoperiosteal technique with buttress plating, which may also be utilized (Binod et al. 2016). Granted, infections often lead to delayed nonunion which can fatigue plates (Bilat, Leutenegger, and Rüedi 1994). In the event that all of the aforementioned techniques fail and the infection progresses, amputation becomes a viable option (Compton et al. 2019).

For any major fracture, mobilizing in the coming months to even years may be a potential issue. Physical therapy will be of the utmost importance in recovery and regaining as much function as possible. This need will be increased if multiple procedures are undergone. Physical therapy, along with icing, elevation, and pain control, will help combat swelling and stiffness that can be barriers to recovery.

COMPLICATIONS

There are numerous complications stemming from tibial shaft infection. Chronic osteomyelitis, for instance, has been known to initiate malignant transformation resulting in a neoplasm dubbed Marjolin's ulcer (Panteli et al. 2014). This incidence of Marjolin's ulcer is anywhere from 1.6-23% in all patients with chronic osteomyelitis. Moreover, the incidence of recurrent infection is quite high, with certain at-risk populations such as the elderly having a 20-30% rate of recurrence (Huang et al. 2016).

Although rare, posttraumatic cellulitis induced compartment syndrome has also been observed. This tertiary, atraumatic variant of compartment syndrome is particularly notable as it is highly irregular, exacerbating the already emergent nature of the condition (Robinson, Kellar, and Stehr 2021). Similarly, another more severe complication is necrotizing fasciitis, which is caused by a combination of aerobic and/or anaerobic organisms, and is distinguished by vascular thrombosis and cutaneous gangrene. It often precipitates severe systemic toxicosis such as hemorrhagic bullae consisting of toxic-epidermal necrolysis, septic toxic shock and progressive multiple, organ failure (Wallace and Perera 2023).

In the context of implants, FRI's may also cause osteolysis, hardware loosening, and periosteal reaction (Hoit, Bonyun, and Nauth 2020b). Peri-implant infection, therefore, has been implicated as a cause in as many as 38% of cases in one study. In addition to bone nonunion and systemic infection, Infection can also induce various chronic issues such as drainage, pain, and stiffness, which may emerge post infection (Mills et al. 2016).

An expected outcome of orthopedic procedures is swelling and stiffness, which will likely be exacerbated if multiple procedures are undertaken over the course of months. There are a myriad of confounding variables that would lead a patient to not mobilizing or participating in their daily activities of living. This can lead to decreased range of motion at joints, especially the knee and ankle. This can cause pain at other musculoskeletal locations including the spine, pelvis, and hip due to change of gait mechanics. Furthermore, a lack of mobilization and weight-bearing can lead to osteopenia and increased risk of future fracture.

Lastly, with any fracture, there is a risk of fracture shortening and a leg length discrepancy. This risk is increased with open fractures where this is an increased risk of bone loss. As subsequent procedures are undertaken and more bone will be debrided, the patient should be counseled on the possibility of a small leg length discrepancy.

CONCLUSION

Tibial shaft FRI are a broad category of infection typically caused by bacterial or fungal agents with varying degrees of severity. Given that the tibia undergoes tremendous weight bearing, it is essential for ambulation. Thus, effective treatment of tibial shaft FRI is essential for ensuring patients' holistic health outcomes. This can be managed via several methods including antibiotics, surgical debridement, dead space management, hardware removal, antibiotic cement replacements, and amputation. While complications are similar to those of any osteolytic variant, FRI display a particular risk of developing malignant neoplasms such as

Marjolin's ulcer in the event of chronic osteomyelitis as well as recurrent infection and sepsis.

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