CLINICAL AND MICROBIOLOGICAL PROFILING OF INFECTIONS IN OPEN TIBIA FRACTURES AT MUHIMBILI ORTHOPAEDIC INSTITUTE

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ABSTRACT

Background: Fracture-Related Infection (FRI) is a challenging complication after surgical fracture treatment. Consequences include reoperations, increased medical costs, loss of function and even amputation.

Objectives: This study aimed to analyze the rate, predictors of infection, clinical-radiological presentation and microbial profiles of open tibia FRI.

Methods: Between January 2022 and June 2022, a descriptive cross-sectional observational study was conducted at Muhimbili Orthopaedic Institute (MOI) involving patients aged 18 years and above with surgically managed open tibial shaft fractures in the preceding 12 months. Microbiological culture of three intraoperative tissue and bone specimens were taken by sterile techniques using separate and sterile instruments.

Results: There were 190 patients between 18-72 years with a mean age of 35.6 ±10 years. After surgical debridement, all 190 (100%) were managed with either an external fixator or an intramedullary nail. It was found, 49 (25.8%) patients had FRI. A smoking history was identified as a predictor of infection (AOR= 2.21 95% CI 0.84-5.59, P value 0.108). Delayed union was a complication found in 70.3% of patients with infection attending 12th week follow-up and beyond. Almost all (96.5%) intraoperative tissue samples were culture positive, yielding most isolates as polymicrobial (57.9%) and the predominant pathogen identified being Gram-negative bacteria in delayed and late infections.

Conclusion: About one-quarter of open tibial shaft fractures are at risk of FRI. The risk is higher among smokers. Intraoperative tissue sampling provides significant cultural yield with predominant gram-negative infection in delayed and late presentation.

Key words: Open tibia, Fracture-related infection, Tissue samples, Microbiological

INTRODUCTION

Fracture-Related Infection (FRI) is a challenging complication after surgical fracture treatment. Consequences include reoperations, prolonged treatment with antibiotics, prolonged immobilization, inability to participate in social and work-related activities, increased medical costs, loss of function and even amputation (1,2).

In 2017 a consensus definition including diagnostic criteria was proposed by a group of experts representing the Association for the Study of Internal Fixation (*Arbeitsgemeinschaft für Osteosynthesefragen*, AO), the European Bone and Joint Infection Society (EBJIS), and prominent orthopaedic trauma hospitals and academic centres. The definition of FRI definition was published in 2018. From that publication onwards, this encompasses the complete spectrum of infections (e.g. acute or chronic, superficial or deep, with or without bone involvement, with or without implants *in situ*) following surgical fixation of a closed or open fracture. Two levels of certainty were defined around the diagnostic features of FRI. Criteria could be confirmatory (infection definitely present) or suggestive (infection possibly present) (3).

A retrospective cohort study by Chen *et al.* (4) at the University of Pittsburgh Medical Centre PA, USA, involving 189 patients with 202 open tibia fractures treated surgically from 2009 to 2010 found 20 (10%) of the open fractures had infection, whereas in another study by Jyc *et al.* (5) in Singapore carried out over a five year period; from 2006 to 2011 identified 173 patients who had open tibia fractures and underwent operative treatment at a single institution over a five year period, the rate of infection was found to be 21.4%. Another retrospective study involving 103 open tibia fractures done in Wellington Public Hospital in New Zealand over a three-month period in 2011, found 12 cases (11.6%) infection rate (6).

In Nigeria, a study by Cent (7) found a 22.3% incidence of infection in 197 patients over 3 years. In that study, most open fractures (71.7%) were treated by debridement and application of Plaster of Paris (POP), while 17.3% had internal fixation with either plates and screws or interlocking nails. External fixation was applied in 10.2% of patients.

In a randomized control trial at the study setting, conducted by Haonga *et al*. (8) with regard to use of intramedullary nailing and external fixation in the surgical management of open tibia shaft fractures and published in 2020 found the overall rate of deep infection in open fractures by clinical features was found to be to be 12.7% (13.5% in intramedullary nailing group versus 11.8% in the external fixation group) and there was no significant difference between the two groups.

A recent systematic review and meta-analysis in sub–Saharan African countries on treatment of open tibia fractures by Kouassi *et al*. (9) involving eight prospective studies found the most common treatment was non-operative management of open tibial shaft fracture with cast immobilization (67%). Gustilo II and III fractures were associated with higher risk of complications and the overall rate of infection was 30%. Malunion, chronic osteomyelitis and nonunion were observed in 14.5%, 12.3% and 7% of the cases, respectively (9).

A systematic review and meta-analysis by Kortram *et al.* (10) identified male gender, diabetes mellitus, smoking, lower extremity fracture, Gustilo-Anderson grade 3 open fracture, contaminated fracture and polytrauma conditions to be associated with fracture-related infections. Another systematic review by Henkelmann *et al.* (11), involving 32 studies with 2063 patients, evaluated the incidence and outcome of infection following fixation of proximal tibia fractures. The average reoperations in infection were between 2.1 and 5 reoperations per patient, 15.3% nonunion or pseudoarthrosis, and a worst-case amputation rate of 5.4% among patients who had a deep infection.

MATERIALS AND METHODS

Study design and site

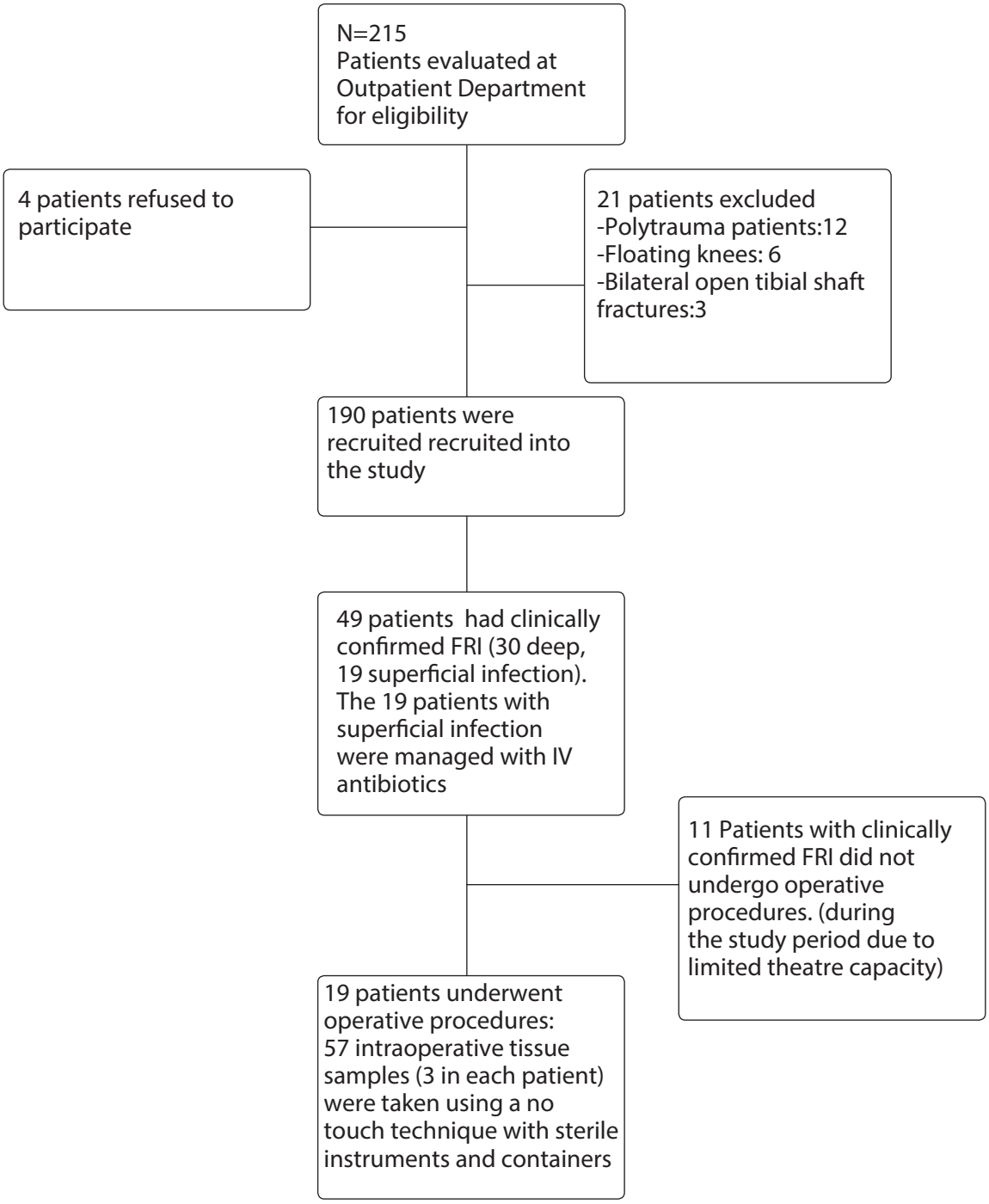
This was a descriptive cross sectional observational study that involved patients with open shaft fracture of tibia (AO 42) aged 18 years and above and managed surgically within the preceding 12 months. Between January 2022 and June 2022, patients were recruited in trauma clinics at a tertiary and national orthopaedic centre; Muhimbili Orthopaedic Institute. Interviews were carried out and clinical data extracted from medical records with regard to the duration and mechanism of injury, and administration of perioperative antibiotics using a structured questionnaire in Research Electronic Data Capture (REDCAP) (12). Antibiotics were avoided during or prior to the sampling, preferably for at least two weeks prior to operation. Three intraoperative tissue samples were taken from each patient with deep infection as scheduled by the attending surgeon. The tissues were aseptically obtained using separate containers for superficial, deep and bone tissue. They were transported using Tryptic Soy Broth (TSB) transport media and incubated on arrival at MUHAS microbiology laboratory at 37^{o}C for 18-24 hours. Isolates were then subcultured on Nutrient agar (Oxoid, UK) and incubated at 37^{o}C for another 18-24 hours. Biochemical identification was carried for Gram positive and negative bacteria.

Sample size estimation and sampling technique

From the study by Haonga *et al.* (8) rate of deep infection in open tibia shaft fractures is 12.7%. Taking this into consideration and maximum marginal error that can be encountered is 5%, non-response rate estimated at 10%. The sample size was calculated to be 187 patients, obtained through convenient sampling technique. Patients with mental illness, polytrauma severe head injury, chest or other extremity injuries, spinal cord injury, burn injury, were excluded.

Figure 1

Patient assessment and recruitment



Statistical analysis

These data were integrated to SPSS version 24. Data entry from REDCAP was exported to SPSS program version 24 and analyzed accordingly.

Ethical clearance

The study was conducted in accordance to existing ethical guidelines. Ethical clearance was sought from MUHAS ethical committee with reference MUHAS-REC-07-2021-750. Written informed consent including details for the examination of their tissue or bone samples were available for patients enrolled in the study.

RESULTS

A total of 215 patients with open tibial shaft fractures attending trauma clinics for follow up were screened during the study period. Out of

these, 21 patients were excluded and 4 patients declined further participation making a total of 190 patients as study participants who were analysed. The age range was 18-72 years with mean age of 35.6 ±10 years, 159 (83.7%) were males and 172 (90.5%) sustained the injury in motor traffic crash (Table 1).

Out of 190 patients recruited, 49 (25.8%) patients were found to have fracture-related infection. Thirty (15.8%) patients had deep infection and surgical treatment was indicated. Nineteen (10%) patients had superficial infection that were managed with IV antibiotics for one week and subsequent oral equivalents for 3 - 6 weeks. There was a higher rate of infection in patients who had open tibial shaft fractures managed with an external fixator 35 (18.4%) as compared to an intramedullary nailing 14 (7.4%). Patients were either managed with an external fixator 135 (71.1%) or an intramedullary nailing 55 (28.9%.). However, some patients managed with external fixators were converted into a cast after a duration of period as decided by the attending clinician.

Table 1

Characteristics of study participants (n=190)

Demographic characteristics	n (%)
Age (years)	35.6 ± 10.6
Sex	
Male	159 (83.7%)
Female	31 (16.3%)
Cause of injury	
Motor traffic crash	172 (90.5%)
Fall from height.	14 (7.4%)
Assault	4 (2.1%)
Level of education	
No formal education.	5 (2.6%)
Primary school education	99 (52.1%)
Secondary school education	63(33.2%)
College/University Education	23(12.1%)
Gustillo-Anderson Grade of Open Fracture	
Grade I.	5 (2.6%)
Grade II.	37 (19.5%)
Grade IIIA	148 (77.9%)
Present comorbidities	4 (2.1%)
Hypertension	
Diabetes mellitus	2 (1.1%)
No known comorbidities	184 (96.8%)
History of smoking	20 (10.5%)
History of alcohol use	71 (37.4%)
Treatment modality	
External fixation	135 (71.1%)
Intramedullary nail	55 (28.9%)
Received perioperative blood transfusion	84 (44.2%)
Not received preoperative antibiotics	20 (10.5%)
Hospital stay beyond 5 days from admission	71 (37.4%)

Out of ten predictors; only two factors; history of smoking and preoperative antibiotics administration were found to have Combined Odd Ratios (COR) of 2.098 and 0.480 respectively and a P value of 0.131 and 0.135 respectively in a bivariate logistic regression analysis. Upon multivariable analysis only smoking revealed a statistically sounding odds ratio (AOR) of 2.218(95% CI 0.841-5.585), although the association was not statistically significant (P value > 0.05) (Table 2).

Table 2

Analysis of predictors of open tibial Fracture Related Infection (FRI) (n=190) using a bivariate and multivariate analysis (n=190)

	Bivariate models			Multivariate models		
Predictor	Combined Odds Ratio (OR)	95% CI	P-value	Adjusted OR(AOR)	95% CI	P-value
Mechanism of injury	0.854	0.481-1.517	0.590			
Gustillo-Anderson Grade of injury	0.986	0.506-1.922	0.967			
Sex	0.683	0.296-1.573	0.370			
Modality of fixation	1.025	0.500-2.103	0.946			
Received Perioperative blood transfusion	0.985	0.532-1.827	0.963			
History of alcohol use	1.209	0.780-1.874	0.396			
Hospital stay beyond 5 days	0.981	0.882-1.092	0.724			
History of smoking	2.098	0.802-5.484	0.131	2.218	0.841-5.585	0.108
Preoperative antibiotics administration	0.480	0.184-1.256	0.135	0.45	0.171-1.189	0.108
Presence of comorbidities	1.060	0.707-1.588	0.779			

Clinical-radiological profiling of a subset of patients (n=49) with fracture-related infection was assessed using the confirmatory and suggestive criteria along with a Modified RUST (mRUST) score. Most patients, 32 (65.3%), had late presentation as compared to 16 (32.7%) with delayed presentation, and only one patient had early FRI that necessitated surgical management. Out of 49 patients with FRI, 37 were evaluated while attending a 12th-week follow-up. Radiographs of such patients (at 12 weeks and beyond) were evaluated to assess healing and 26 (70.3%) had a mRUST score below 13 signifying a delayed union. Three intraoperative tissue or bone samples were taken for each patient, totalling 57 samples submitted to undergo microbiological profiling. Almost all samples, 55 (96.5%), were culture-positive, and 73 bacterial isolates were identified. From the cultured samples, 33 (57.9%) samples yielded polymicrobial isolates, and 56 (76.7%) isolates were comprised of Gram-negative bacteria. *Staphylococci* were the only Gram-positive bacteria isolated in which 17 (23.3%) isolates comprised of 14 (19.2%) *Staphylococcus aureus* and 3 (4.1%) isolates were *Coagulase negative Staphylococci* (CoNS) (Table 3).

Table 3

Spectrum of bacterial isolates (57 tissue samples, n=73 bacterial isolates)

Bacterial growth	% of isolates
Types of isolate morphotypes (n=73)	
Gram-negative bacteria	56 (76.7%)
Gram-positive bacteria	17 (23.3%)
Nature of isolates (n=57)	
Mono isolates	24 (42.1%)
Polymicrobial	33 (57.9%
Types of bacteria (n=73)	
Staphylococcus aureus	14 (19.2%)
Coagulase negative staphylococci	3 (4.1%)
Proteus spp	13 (17.8%)
Pseudomonas aureginosa	9 (12.3%)
E. Coli	9 (12.3%)
Klebsiella pneumoniae	8 (11.0%)
Enterobacter spp	3 (4.1%)
Providencia Spp.	2 (2.7%)
Citrobacter spp	1 (1.4%)
Serratia marcescens	1 (1.4%)
Unidenitifed Gram-negative Rods (UGNR)	10(13.7%)
Phenotypic resistance characteristics n (=73)	
Methicilin Resistant Staphylococci Aureus (MRSA)	12(16.4%)
Methicilin Susceptible Staphylococci Aureus (MSSA)	2(2.7%)
MRSA in Staphylococci aureus isolates (n=14)	12(85.7%)
Extended Spectrum Beta Lactamase (ESBL) producing microbes (n=56)	30 (53.6%)
Inducible Clindamycin Resistance (ICR) (n=14)	8 (57.1%)

DISCUSSION

This study found a 25.8% overall rate of fracture-related infection in open tibial shaft fractures and 15.8% rate of deep infection. The deep infection rate is slightly higher than that found by Haonga *et al.* (8) at the same sitting in which the rate was 12.7%. The overall rate is however consistent to what other studies found in other African settings including the study conducted in Ethiopia by Abraham *et al*. (13) in which the rate was 27.5% and this rate, is relatively lower as compared to the 30% rate of infection in open tibia fractures published in a recent systematic review involving eight studies in the sub-Saharan African countries (9). However the rate is higher as compared to those conducted by Cent (7) in Nigeria (22.3%) and Jyc *et al.* (5) in Singapore (21.4%) and more than twice as much the rate in studies conducted in the USA by Chen *et al.* (4) (10%) and in New Zealand in which the rate was 11.6% (14)

It's interesting to point out that contrary to the study by Cent (7) in Nigeria that indicated 71.7% of open tibial shaft fractures were managed non-operatively with a cast after debridement and in a systematic review and meta-analysis publication in sub Saharan Africa countries that indicates 67% of open tibial shaft fractures are

managed with a cast (9), the present study found 100% of open tibial shaft fractures in the study population were managed with either external fixators or interlocking intramedullary nails. This is striking in view of known complications with cast immobilization compared to surgical fixation. It was also found that the rate of infection in the patients who had external fixators was higher than those with intramedullary nails at 18.4% and 7.4% respectively, higher than what was found in other studies (16,18).

The study involved assessing ten predictors of infection as suggested in previous studies, out of which history of smoking and perioperative antibiotic prophylaxis were identified as predictors in univariate analysis. Only a history of smoking remained as an important factor within multivariable logistic regression analysis although no statistical association was found in contrast to other studies by Metsemakers *et al*. (15) which identified previous need for external fixators, Gustillo-Anderson Grade and time to surgical intervention as significant risks for developing infection postoperatively (17). Another study by Kortran *et al*. (10) identified male gender, diabetes mellitus, smoking, and Gustillo-Anderson Grade 3 open fracture as significant risk factors. The Pakistan study by Tahir *et al*. (16) also identified smokers being at risk of developing fracture-related infection.

About two thirds of patients (65.3%) with fracture-related infection were classified as late presentation with as purulent discharge in 79.6%, wound breakdown in 61.2%, pain without weight bearing noted in 63.3%, and persistent serous discharge in more than a quarter of patients with infection (26.5%). This is in contrast to the study by Abraham *et al* (13), where less than a third of patients had clinically overt signs of infection implying a late presentation in the index study population. There were more overt signs of infection in the recent study as compared to 53.8% purulent discharge and wound healing disturbance 38.4% and local pain 46.2% identified in a study involving open tibial shaft fractures (17).

Complications associated with infection in this study were delayed union in more than two-thirds of patients (70.3%) who were evaluated 12 weeks post operatively similar to the findings in a study by Doshi *et al*. (17) and Henkelman *et al*. (11) studies that indicated delayed unions in infected fractures. It's striking to point out the reoperation rate in patients who were managed with a solid intramedullary nail was one and half times (5.5%) the rate reported by Haonga *et al*. (18) (3.8%) while the rate of reoperation in patients with external fixators (11.8%) was one third the rate reported (37.5%) in the similar study. This finding could imply lower operation rates during the study period. No patient underwent amputation as a result of open tibial fracture-related infection in this study contrary to the 2% amputation rate reported by Cent (7) and 5.4% rate in the systematic review by Henkelman *et al*. (11).

Microbiological isolation of the offending bacteria is crucial in the management of fracture-related infection and in this study intraoperative tissue or bone sampling had high culture yield of 96.5% identifying 73 bacterial isolates. This is consistent with other studies and current recommendations on microbiological diagnosis of fracture-related infection (19). In a different study by Hariharan *et al*. (20) only 51.2% of the samples were cultured. Polymicrobial isolates were 57.9% and mostly contained Gram-negative bacteria at 76.7%. High cultural yields were also noted in other studies (4,13,21), although the proportions in the present study are slightly higher implying more infection with Gram negative bacterial emulating the late presentation of infection in this study population. The finding of polymicrobial isolates which make a larger proportion is also a different finding from a study by Manyahi *et al*. (22) which evaluated surgical infections using swabs in which 52.2% were mono-isolates. This may imply the advantage of tissue sampling over swabs in accurate diagnosis of surgical infections. *Staphyloccocus aureus* and *Coagulase Negative Staphylococci* were the only Gram- positive bacteria isolated making 23.3% of all isolates, which is higher than what was found in a study by Abraham *et al*. (13) in Ethiopia.

Strength and limitations

This appears to be the first study on musculoskeletal infection involving tissue or bone samples to be conducted at the Muhimbili Orthopaedic Institute. The study is however limited by the small sample size owing to the short study period and hence generalization to the population should be taken cautiously although it forms a benchmark for future studies. Sonication of extracted implants was not carried out due to lack of appropriate containers and transport media, which could increase the

bacterial isolates. Anaerobic culture and molecular characterization of the microbes were not carried out due to lack of facilities in the laboratory used and other laboratories in the study setting.

CONCLUSION

The present study found one in every four patients with open tibial shaft fractures has FRI and the risk is higher among smokers. Strikingly all patients (100%) were managed with an external fixator or an intramedullary nail. Delayed union was found in about two thirds of patients with FRI. Tissue or bone sampling should be the modality towards reaching a microbiological diagnosis of infection and clinicians should be aware of increasing trend of Gram-negative bacteria in delayed and late FRI in order to select appropriate antibiotics for empirical treatment.

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