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Risk factors for infection in severe open tibial shaft fractures

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ABSTRACT

Objective: To evaluate risk factors for infection in severe open tibial shaft fractures.

Methods: A secondary analysis of a multicenter prospective study investigated internal versus external fixation of severe open tibia fractures at 20 US Level I trauma centers. Adult patients, aged <65 years, with a Gustilo-Anderson Type IIIB or severe IIIA metaphyseal or diaphyseal tibia fracture were included. All fractures underwent definitive fixation with either a modern ring external fixator, intramedullary device, and/or plate. Fourteen variables previously identified as risk factors for infection were included in the analysis. Deep surgical site infection was defined as an infection treated with surgical debridement within 1 year of index surgery.

Results: The study cohort included 430 patients. Deep surgical site infection requiring reoperation occurred in 108 (25 %) patients. The final model identified four risk factors for infection: age >40 years (OR, 2.00; 95 % CI, 1.3–3.1), Gustilo-Anderson Type IIIB (OR, 1.80; 95 % CI, 1.1–3.0), embedded wound contamination (OR, 1.69; 95 % CI, 1.1–2.7), and wound length (OR, 1.02/cm; 95 % CI, 1.0–1.05). The model performed poorly at distinguishing infected from uninfected patients (Area Under the Curve=0.57; 95 % CI, 0.51–0.63).

Conclusions: Surgeons can now counsel patients with these risk factors that they are at a markedly higher risk of infection. The identification of these risk factors may direct future research aimed at mitigating the risk of deep surgical site infection in this patient population.

Introduction

Infection after operative treatment of Gustilo-Anderson Type III open tibial shaft fractures is common, with reports ranging between 9 % to 33 % in the literature [1–4]. Infections lead to more total surgical procedures, an increased rate of amputation, higher healthcare costs, and lower quality of life [5,6]. Open tibial shaft fractures are associated with particularly high rates of infection [7–10].

Continued difficulty in preventing infections has led some prior investigators to attempt to identify risk factors for infection in open tibial shaft fractures. To date, little work exists examining the most severe injuries that have been shown to have the highest risk of infection. Furthermore, little work exists in prospective datasets that have both higher quality data as well as information that is not typically available in retrospective data.

The deep infection rate of the Lower Extremity Assessment Project (LEAP) salvage group was 23.2 % which is similar to the 28 % deep infection rate reported in FIXIT and published 22 years later [4,9,11]. However, the LEAP study included a variety of fracture locations, penetrating trauma and dysvascular limbs. Very little progress has been made in diminishing infection in these severe limb threatening open tibial shaft fractures over the past quarter of a century. An important

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consideration to decreasing infection is to identify the factors that place patients at higher risk for infection. The goal of this study was to use high-quality prospective data to identify risk factors for infection in severe Type IIIA and IIIB open tibia fractures. The hypothesis was that risk factors can be identified which independently predict infection in severe open tibia shaft fractures [9,12,13].

Methods

Data source and study population

A secondary analysis was conducted of the data from the FIXIT trial, a multicenter, randomized controlled trial (NCT01494519) coordinated by the Major Extremity Trauma Research Consortium [4]. FIXIT investigated the use of modern external ring fixation versus internal fixation (including intramedullary nailing and/or plate fixation) for the treatment of severe open tibial shaft fractures [4]. The previously published protocol was approved by the appropriate institutional review boards and completed at 20 Level I US trauma centers from 2011 to 2017. The planned secondary analyses were approved at the time of the initial trial. As discussed in this protocol, the timing and choice of antibiotic prophylaxis, the use of intrawound antibiotics and timing between definitive fixation and flap coverage was left at the discretion of the treating institution. Two hundred sixty patients underwent randomization to the external fixation group versus the internal fixation group. The investigators also collected data on an observational cohort of patients who declined randomization. This included an additional 170 patients, resulting in a total cohort of 430 patients for this secondary analysis [14].

Study exposure and outcome

The primary outcome of this secondary study was deep surgical site infection, defined as an infection treated by surgical debridement within 1 year of the index surgery. This outcome was evaluated by an independent adjudication committee, as described in the original FIXIT paper.

Fourteen variables were investigated based on previous literature demonstrating a potential effect on orthopaedic trauma-related infection [7,8,10,15–19]. Demographic variables included age, sex, and race. Age was dichotomized at age 40 based on previous risk factor studies [20]. Patient comorbidities included body mass index (BMI), drug abuse, alcohol abuse, and diabetes. Injury characteristics investigated were Gustilo Anderson classification (Type IIIA or IIIB), and the components of the OTA/AO fracture classification system that includes: muscle damage (no appreciable muscle necrosis, some loss of muscle, dead muscle), skin damage (laceration with edges that approximate, laceration with edges that do not approximate, and laceration with extensive degloving), arterial injury, wound contamination (no or minimal contamination, surface contamination, embedded contamination), any bone gap, and pre-debridement wound length. All variables were recorded prospectively as part of the FIXIT study.

Statistical analysis

Continuous variables were reported as median and interquartile range (IQR) and compared using the Wilcoxon rank sum test. Categorical variables were reported as counts and percentages and compared with chi-square tests. A Yates' continuity correction was performed for all 2 × 2 tables. Three patients were missing pre-debridement wound length data, which were imputed in five datasets in preprocessing using predictive mean matching and pooled as a single mean data set for the modeling. For the multivariate model, the factors were selected from an initial multivariable logistic regression model using forward stepwise elimination to optimize model fit based on the Akaike Information Criterion. A repeated 10-fold cross validation was used to internally validate the model and optimism-correct the point estimates and standard errors. The linearity of the relationship between wound length and surgical site infection was assessed visually. We assessed the prognostic performance of the model using the area under the receiver operating characteristics curve (AUC), where 0.5 indicates the model performs no better than a random guess, and 1.0 indicates a model that can perfectly distinguish between patients who will develop a deep surgical site infection and those who will not. The data were analyzed using R version 4.0.3 (R Foundation for Statistical Computing) [21].

Results

In the cohort of 430 patients, 187 (43 %) patients were aged >40 years, and 358 (83 %) were male. The 6-month follow-up rate was 96 %, and the 1-year follow-up rate was 78 % of patients. One-third-of patients (n = 141, 33 %) had a BMI greater than 30 and nearly two-thirds of fractures (n = 269, 63 %) were Gustilo-Anderson Type IIIB, while 26 (6 %) patients reported pre-injury illicit drug use. Surgeons reported that 92 (21 %) patients had dead muscle at the time of injury. One-third-of wounds (n = 144, 33 %) were described as having embedded contamination (Table 1).

Deep infection requiring reoperation occurred in 108 (25 %) patients. Bivariate analysis demonstrated several potential risk factors for infection. Infected patients were older (age >40 years) than uninfected patients (56 % versus 39 %; $p < 0.01$). Type IIIB fractures had a higher infection rate than Type IIIA (30 % versus 16 %; $p < 0.01$). Injuries that ultimately developed infection were more likely to have dead muscle (31 % versus 18 %) and embedded contamination (45 % versus 30 %; $p = 0.01$). Deep infections had a longer initial median wound length (12 cm; IQR [8,20]) than uninfected patients (10 cm; IQR [6,16]) (Table 1).

Patients with a postoperative infection had a median number of surgeries of 6 (IQR [5,9]) compared to 3 (IQR [3,5]; $p < 0.0001$) in those patients without an infection. Patients who developed a deep infection had a similar median length of stay during the index hospitalization (17 days; IQR [10,29]) versus those patients who did not develop a deep infection (17 days; IQR [12,25]; $p = 0.96$). In addition, patients whose course was complicated by deep infection had only a slightly longer median length to radiographic and clinical healing (386 days; IQR [348, 543]) compared to uninfected patients (352 days; IQR [183.5, 381.8]; $p = 0.02$).

The final multivariable model identified four risk factors for infection in this population. Age >40 years was the strongest predictor of developing a deep surgical site infection (OR, 2.00; 95 % CI, 1.27–3.13). Gustilo-Anderson Type IIIB (OR, 1.80; 95 % CI, 1.09–2.96), embedded wound contamination (OR, 1.69; 95 % CI, 1.05–2.72), and wound length (OR, 1.02 per cm; 95 % CI 1.00–1.05) were also identified as predisposing patients to a higher risk of infection (Table 2). No other factor was predictive of infection in the final model. Overall, the model performed poorly at distinguishing infected from uninfected patients (AUC = 0.57; 95 % CI, 0.51–0.63).

Discussion

This secondary study identified age >40 years, embedded wound contamination, Gustilo-Anderson Type IIIB open fracture pattern, and wound length as significant risk factors for infection after severe open tibia shaft fractures. These findings add to the existing body of literature on risk factors for infection by focusing on the most severe injuries and utilizing high-quality prospective data. The risks associated with these common variables may influence salvage and prognosis discussion.

Previous studies have identified Type III open fractures to be associated with an increased risk of infection, but few studies have the power to compare Type IIIA to Type IIIB fractures. Wise et al. [16] investigated deep surgical site infection in a heterogenous group of fracture patterns including extremity, pelvis, and acetabulum. Among the 27 factors studied, 8 factors were independently associated with infection: male

Table 1
Patient characteristics stratified by outcome of deep surgical site infection (SSI).

Characteristic	Overall, $N = 430$	SSI, $N = 108$	No SSI, $N = 322$	P-value
Age >40 years	187 (43 %)	61 (56 %)	126 (39 %)	<0.01
Sex, male	358 (83 %)	91 (84 %)	267 (83 %)	0.86
Race/ethnicity				0.36
Non-hispanic white	230 (53 %)	57 (53 %)	173 (54 %)	
Non-hispanic black	91 (21 %)	26 (24 %)	65 (20 %)	
Hispanic	73 (17 %)	20 (19 %)	53 (16 %)	
Other	36 (8 %)	5 (5 %)	31 (10 %)	
Body mass index, kg/m^2				0.21
<25	138 (32 %)	26 (24 %)	112 (35 %)	
25–29.9	151 (35 %)	43 (40 %)	108 (34 %)	
30–35	86 (20 %)	25 (23 %)	61 (19 %)	
>35	55 (13 %)	14 (13 %)	41 (13 %)	
Drug abuse	26 (6 %)	6 (6 %)	20 (6 %)	0.99
Alcohol abuse	20 (5 %)	6 (6 %)	14 (4 %)	0.80
Diabetes	26 (6 %)	10 (9 %)	16 (5 %)	0.17
Gustilo-Anderson classification				<0.01
IIIA	161 (37 %)	28 (26 %)	133 (41 %)	
IIIB	269 (63 %)	80 (74 %)	189 (59 %)	
Muscle damage				0.02
No appreciable muscle necrosis	71 (17 %)	13 (12 %)	58 (18 %)	
Some loss of muscle	267 (62 %)	62 (57 %)	205 (64 %)	
Dead muscle	92 (21 %)	33 (31 %)	59 (18 %)	
Skin damage				0.36
Laceration with edges that approximate	214 (50 %)	55 (51 %)	159 (49 %)	
Laceration with edges that do not approximate	116 (27 %)	24 (22 %)	92 (29 %)	
Laceration with extensive degloving	100 (23 %)	29 (27 %)	71 (22 %)	
Arterial injury				0.21
No major vessel disruption	339 (79 %)	80 (74 %)	259 (80 %)	
Vessel injury	91 (21 %)	28 (26 %)	63 (20 %)	
Wound contamination				0.01
No or minimal contamination	84 (20 %)	17 (16 %)	67 (21 %)	
Surface contamination	202 (47 %)	42 (39 %)	160 (50 %)	
Embedded contamination	144 (33 %)	49 (45 %)	95 (30 %)	
Any bone gap	175 (41 %)	46 (43 %)	129 (40 %)	0.73
Wound length (cm)[†]	11 (6, 18)	12 (8, 20)	10 (6, 16)	0.01

[†] The wound length data were missing for one patient with a surgical site infection and two patients without a surgical site infection.

Table 2
Factors associated with deep surgical site infection.

Factor	Odds ratio	95 % CI	P-value
Age > 40 years vs. ≤ 40 years	2.00	1.27 to 3.13	<0.01
Gustilo-Anderson type IIIB vs. IIIA	1.80	1.09 to 2.96	0.02
Embedded wound contamination vs. no or minimal contamination / surface contamination	1.69	1.05 to 2.72	0.03
Wound length, per 1 cm	1.02	1.00 to 1.05	0.09

sex, obesity, diabetes, alcohol abuse, fracture region, Gustilo-Anderson Type III, MRSA positivity on a nasal swab, and American Society of Anesthesiology (ASA) score. Paryavi et al. [17] investigated patients with higher-risk fractures, including tibial plafond, tibial plateau, and calcaneus. The authors developed the "Risk of Infection in Orthopaedic Trauma Surgery," which included male sex, ASA class of 3 or higher, BMI of <30, and insulin use as risk factors for orthopaedic infection. In these retrospective studies, it is difficult to study injury factors such as contamination, wound length, and skin injury because one is limited by the details of the operative report. In addition, these aforementioned studies had 16 % and 34 % of open fractures, respectively; in these studies primarily consisting of closed fractures, patient characteristics played a greater role in development of infection. In contrast, all patients in the current study had severe, high-energy open fractures, and thus, injury characteristics (wound length and contamination) are more associated with development of infection. The authors theorize that this homogeneity of the patient population (young patients with high energy trauma) contributed to the poor performance of the model. The patients in the deep infection cohort had a larger median wound length than the uninfected patients (12 cm versus 10 cm). Although the net difference in wound length is small, the larger wound suggests a higher energy mechanism with greater soft tissue damage which can lead to greater infection risk.

Presumably, in these most severe open fractures, the economic impact is even larger than typical infections. The economic burden of postoperative infections is significant in general. Surgical site infections nearly double the cost of care for orthopaedic trauma patients from $57,418 to $108,782 [22]. In addition to the financial impact to the healthcare system, there is substantial deleterious financial effect on the patient with a $6080 annual decrease in income and a 45 % increase in the odds of receiving social security benefits [23]. In our cohort, patients with a postoperative infection had a greater median number of surgeries compared to those without an infection which could help explain this economic impact.

In 1976, a case series published by Gustilo et al. [1] demonstrated a striking decrease in the open fracture infection rate after surgical debridement and provision of intravenous antibiotics. Patzakis et al. [24] also provided groundbreaking evidence that antibiotic choice is important in reducing infections. It could be argued that since these advances, little progress has been made to decrease infection rates in these most severe open fractures. The inclusion criteria for the FIXIT study were modelled after the Lower Extremity Assessment Project (LEAP) study which followed patients treated in the 1990s [5]. The deep infection rate in the LEAP salvage group was 23.2 %, which is very similar to the infection rate of 25.1 % reported in this study [9]. Earlier debridement and different antibiotic protocols did not significantly change infection rates [25–27]. Recently, intrawound vancomycin demonstrated efficacy in preventing gram-positive infections in tibial plateau and plafond fractures but it is unknown if this benefit will transfer to open tibia shaft fractures [28].

This study has a number of strengths. First and foremost, data were collected prospectively with strong follow-up (93 % expected person-time of follow-up). In addition, this is a relatively large sample size for this specific injury and the fact that 20 centers participated increases the generalizability. In addition, no studies to our knowledge have looked at exclusively Type III open fractures in a prospective fashion. For the 59 % of our patients who were in the randomized arm, all infections were independently adjudicated by 3 experienced orthopaedic trauma surgeons.

This study has several limitations. The investigators did not collect culture data on the organisms causing deep infections, so no microbiologic information could be included to potentially determine if risk factors for different pathogens exist. The investigators were limited by the variables available from the FIXIT trial so not all comorbidities linked to infection could be included in the study such as nutritional status. The study uses a strict definition of deep infection requiring reoperation; therefore, superficial infections were not assessed with this model. The investigators selected this definition to decrease the subjectivity of determining if a patient was truly infected. This study did not control for surgeon modifiable factors such as the length and duration of preoperative antibiotics, the number of surgical debridements before definitive fixation, the time from definitive fixation to coverage, and the use of intrawound antibiotics, which may all affect the incidence of infection.

These findings suggest that age >40 years, Gustilo Type IIIB open fractures, embedded wound contamination, and longer wound length each independently increase the risk of infection after severe open tibial shaft fractures. These results may be helpful to future researchers to continue work in this area including studies directed at surgeon modifiable factors such as the interval between definitive fixation and flap coverage, number of surgical debridements, timing of debridement, and experience of surgeon performing debridement. Clinicians will also benefit from improved information with which to counsel patients and to take measures to reduce infection in patients at the highest risk.

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CRediT authorship contribution statement

Daniel J. Johnson: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Nathan N. O'Hara:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Lisa Reider:** Writing – review & editing, Methodology, Investigation, Data curation, Conceptualization. **Joshua L. Gary:** Writing – review & editing, Data curation, Conceptualization. **William Obremskey:** Writing – review & editing, Data curation, Conceptualization. **Stephen M. Quinnan:** Writing – review & editing, Data curation, Conceptualization. **Paul Tornetta III:** Writing – review & editing, Data curation, Conceptualization. **Heather A. Vallier:** Writing – review & editing, Data curation, Conceptualization. **Eben A. Carroll:** Writing – review & editing, Data curation, Conceptualization. **Robert V. O'Toole:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

Byline author Paul Tornetta discloses intellectual property with Smith & Nephew and publishing royalties from Wolters Kluwer. The remaining byline authors have no actual or potential conflicts of interest to disclose. Corporate author Joseph Hsu discloses consulting, speaking, and monetary payment from Smith & Nephew, and consulting, speaking and monetary payment from Stryker. The remaining corporate authors have no actual or potential conflicts of interest to disclose.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.injury.2024.111822.

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