Delays in Debridement of Open Femoral and Tibial Fractures Increase Risk of Infection

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Background: Infection remains a costly, devastating complication following the treatment of open fractures. The appropriate timing of debridement is controversial, and available evidence has been conflicting.

Methods: This study is a retrospective analysis of the SIGN (Surgical Implant Generation Network) Surgical Database (SSDB), a prospective registry of fracture cases in predominantly low-resource settings. Skeletally mature patients (≥16 years of age) who returned for follow-up at any time point after intramedullary nailing of an open femoral or tibial fracture were included. Patients were excluded if they had delays in debridement exceeding 7 days after the injury. Utilizing a model adjusting for potential confounders, including patient demographic characteristics, injury characteristics, country income level, and hospital type and resources, local logistic regression analysis was performed to evaluate the probability of infection with increasing time to debridement in 6-hour increments.

Results: In this study, 27.3% of patients met the eligibility criteria and returned for follow-up, with a total of 10,651 fractures from 61 countries included. Overall, the probability of infection increased by 0.17% for every 6-hour delay in debridement. On subgroup analysis, the probability of infection increased by 0.23% every 6 hours for Gustilo-Anderson type-III injuries compared with 0.13% for Gustilo-Anderson type-I or II injuries. The infection risk increased every 6 hours by 0.18% for tibial fractures compared with 0.13% for femoral fractures.

Conclusions: There was a linear and cumulative increased risk of infection with delays in debridement for open femoral and tibial fractures. Such injuries should be debrided promptly and expeditiously. The size and international nature of this cohort make these findings uniquely generalizable to nearly all environments where such injuries are treated.

Level of Evidence: Therapeutic Level III. See Instructions for Authors for a complete description of levels of evidence.

The importance of timely debridement in preventing infection after open fracture is still poorly understood, but it may have a substantial impact on minimizing patient morbidity and optimizing perioperative care. Studying the relationship between debridement time and infection without introducing bias has been challenging, especially because the randomization of time to treatment in a clinical trial format would be unethical. In observational studies on this topic, there is a tendency for more severe injuries to be treated more emergently[1]. As a result, cases receiving early treatment may be associated with a higher rate of infection due to confounding by injury severity[2-4].

Studies aiming to define the relationship between timely debridement and infection have primarily been conducted in high-income countries (HICs) and have been limited by their retrospective designs, small sample sizes, and short-term follow-up[1,5-7]. Nevertheless, traditional clinical guidelines based on limited evidence have recommended a 6-hour window to reduce the risk of infection[5,7,8]. This historical window has been challenged by more recent studies suggesting no increased risk with delayed debridement at >6 hours[1,5,7,9-12]. The 12-hour and 24-hour windows for debridement have also been studied, but these thresholds remain controversial[1,13,14].

Through the provision of free intramedullary nailing implants, SIGN (Surgical Implant Generation Network) Fracture Care International enables surgeons in low and middle-income countries (LMICs) to stabilize long bone fractures without the need for fluoroscopy[15-17]. In an effort to monitor usage of these implants, the SIGN Surgical Database (SSDB) was started in 2003 and is a prospectively populated database

Disclosure: The **Disclosure of Potential Conflicts of Interest** forms are provided with the online version of the article (http://links.lww.com/JBJS/H654).

with deidentified data of nearly all patients treated with a SIGN intramedullary nail[15,18]. With >180,000 unique fracture entries, the SSDB is the largest database of long bone fractures in LMICs. This study aimed to retrospectively analyze the SSDB to evaluate the relationship between time to debridement and infection after the treatment of open long bone fractures of the lower extremity with intramedullary nail fixation. We hypothesized that delays in debridement incrementally increase the risk of infection in a time-dependent manner.

Materials and Methods

Data Source

This investigation utilized the SSDB, a secure web-based registry of all fracture cases treated with a SIGN intramedullary nail since 2003[18]. Surgeons are provided SIGN nails at no cost, contingent on their uploading surgical details, fracture characteristics, and patient demographic characteristics to the SSDB upon completion of each individual case. The minimum follow-up is 1 month after the surgical procedures. Follow-up visits are documented as 1, 3, 6, or 12 months in the database, and data with regard to weight-bearing status as well as complications including infection, implant failure, and reoperation are also recorded. The SSDB contains prospectively collected data of >180,000 unique fracture cases at 633 hospitals from 262 countries.

Prior to study commencement, institutional review board approval was obtained from the University of California, San Francisco (#20-31140). A data export was performed using Metabase software. The deidentified data set was then imported into Stata 16.0 (StataCorp), through which all statistical analyses were performed.

Data Collection

The study population sampled from the database included skeletally mature patients (≥16 years of age) who were treated for an open femoral or tibial fracture with a SIGN intramedullary nail. Patients were excluded if they had no recorded postoperative follow-up or delays in debridement exceeding 7 days after the injury, as such extensive delays could result in infection developing prior to presentation and definitive treatment. Patients were also excluded if they sustained femoral neck or intertrochanteric femoral fractures.

Demographic and injury characteristics including age, sex, mechanism of injury, injury severity according to the Gustilo-Anderson classification, fracture location (proximal, middle, distal, subtrochanteric, segmental), hospital and country name, and country income level based on the World Bank Classification were collected for all patients. The primary operative detail that was collected was the time from the injury (a patient-reported estimate given at presentation) to the initial debridement (measured in hours), and the primary outcome variable was infection after treatment at any follow-up time point. Infection was measured as a binary variable self-reported by the treating surgeon, not using any standardized definition or differentiated by the depth of the infection.

To better account for variation in hospital resources within the database, additional hospital-level data were also gathered for every hospital within the SSDB. Two study investigators (A.C. and M.U.) performed a comprehensive web search on all included hospitals, and collected data including bed capacity, hospital type (defined a priori as a government or public hospital or a private, mission, nonprofit, or mixed hospital), specialty hospital status (defined as an orthopaedic specialty hospital or a general hospital), hospital academic status (defined as a teaching hospital or a non-academic hospital), and World Health Organization (WHO) classification of the level of hospital care (as previously described by Mulligan et al.[19]). These data were merged with the previously exported data set, such that nearly all fracture cases also included hospital resource data.

Statistical Analysis

Descriptive statistics were used to characterize demographic, clinical, and hospital characteristics. After we had performed an exploratory analysis of time to debridement as a continuous variable, we evaluated the probability of infection with increasing time to debridement in 6-hour increments using locally weighted scatterplot smoothing analysis (LOWESS). To adjust for any potential confounding, the final logistic regression model included baseline covariates that were determined a priori to be potential confounders in a causal relationship between debridement timing and infection. These included sex, age, mechanism of injury, injury severity (according to the Gustilo-Anderson classification), bone (femur or tibia), fracture location (proximal, midshaft, or distal), country income level (according to the World Bank Classification), and each of the previously defined hospital-level variables (bed capacity, specialty compared with general hospital, WHO hospital level, public compared with mixed or private, and academic compared with non-academic). Appendix Supplementary Figure 1 illustrates the proposed causal relationship between debridement timing and infection, as well as all covariates potentially influencing treatment and/or outcome that were considered as potential confounders in the model.

Source of Funding

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Results

The SSDB was queried and 44,977 unique open femoral and tibial fractures in patients ≥16 years of age were assessed for eligibility (Fig. 1). After application of the exclusion criteria to this sample and after further excluding those with missing infection data or those lost to follow-up, 10,651 open lower-extremity fractures (3,210 femoral and 7,441 tibial fractures) from 61 countries were available for data analysis. The overall follow-up rate of the sample was 27.3%. Appendix Supplementary Figure 2 demonstrates the distribution of patients by the number of days from the injury to surgical debridement and nailing.

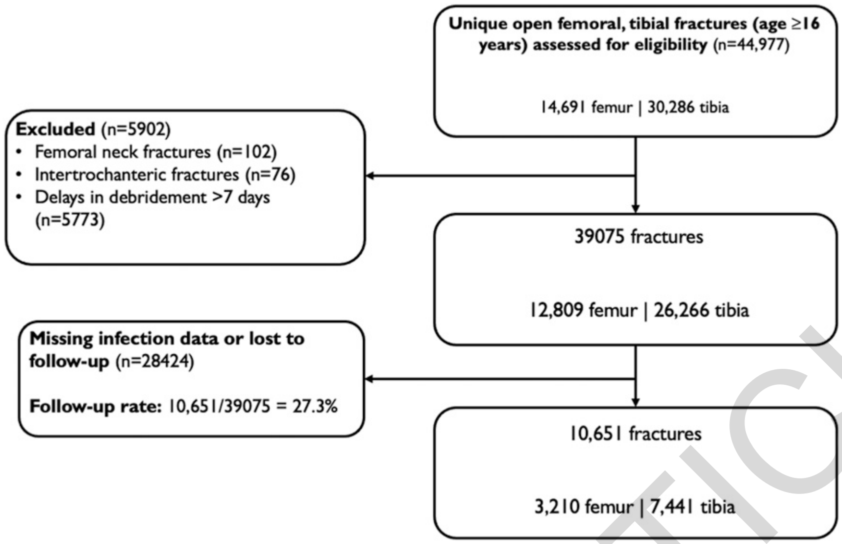

Fig. 1

Flowchart demonstrating the total number of unique open femoral and tibial fractures from the SSDB eligible for inclusion. Values are shown before and after the application of exclusion criteria. Note that multiple fractures were excluded for more than 1 reason.

Analysis of the 10,651 unique fracture entries in the cohort indicated that the average patient treated with a SIGN intramedullary nail was a male around 33 years of age who sustained a mild to moderate open tibial or femoral fracture from a road traffic accident in an LMIC (Table I). Infection developed in 719 of the 10,651 fractured limbs, for an overall rate of 6.75%. These fractures were typically treated in government-funded tertiary referral hospitals and academic centers (Table I). The mean time (and standard deviation) to operative debridement was 23.8 ± 32.4 hours for patients with infection compared with 18.8 ± 27.4 hours for patients without infection ($p < 0.001$).

Patients lost to follow-up significantly differed from the study group with respect to sex, injury severity, mechanism of injury, location of the fracture on the bone, country income level as defined by the World Bank Classification, hospital bed capacity, hospital funding type, WHO hospital classification, and mean time to operative debridement (Table II). The differences were significant due to the large sample size, but were not clinically meaningful with the possible exception of hospital funding type.

Local Regression Analysis of Time to Debridement

Risk of infection was plotted as a function of increasing time to debridement, using 6-hour intervals over the first 72 hours after the injury. Figure 2 demonstrates the unadjusted LOWESS plots of the probability of infection, not assuming linearity, whereas Figure 3 demonstrates the adjusted mean probability of infection with increasing time to debridement in 6-hour increments using a marginal-effects plot of the fitted logistic regression model, assuming linearity. For the overall cohort, the probability of infection increased by 0.17% for every 6-hour delay in debridement ($p < 0.001$). At all time points, the risk of developing infection was higher in high-grade open fractures compared with low-grade open fractures, and the risk of infection increased at a higher rate. The probability of infection increased by 0.23% every 6 hours for Gustilo-Anderson type-III injuries compared with 0.13% for Gustilo-Anderson type-I or II injuries. Tibial fractures were associated with a higher risk of infection compared with femoral fractures at all time points, but the risk of infection increased at similar rates with increasing delay. The infection risk increased every 6 hours by 0.18% for tibial fractures and by 0.13% for femoral fractures.

Discussion

The purpose of this study was to utilize a large musculoskeletal trauma database of patients treated with a SIGN intramedullary nail for an open femoral or tibial fracture in order to investigate the effect of timeliness of debridement on the risk of infection. With a large sample size of >10,000 unique fractures, we employed a local regression model adjusting for potential confounding to evaluate the relationship between increasing time to surgical debridement and infection. We found a linear and cumulative increase in the risk of infection with ongoing delays in debridement for open femoral and tibial fractures. On further subgroup analysis, higher-grade open injuries had a higher overall risk of infection development compared with lower-grade injuries, and tibial fractures had a higher overall risk of infection development compared with femoral fractures.

Given the inherent challenges of using an observational approach to study infection based on the time to debridement, our study's objective was to reduce confounding within our large sample to better understand and characterize the effect of timely debridement on the risk of infection in open fractures. Furthermore, our study is unique in its ability to analyze time to debridement on a continuous scale, in contrast to previous

TABLE I Characteristics of Study Participants*†

Characteristic	Total (N = 10,651)	Patients without Infection (N = 9,932)	Patients with Infection (N = 719)	P Value
Age‡ *(yr)*	33.58 ± 12.91	33.59 ± 12.93	33.49 ± 12.59	0.84
Sex§				0.16
Female	1,941 (18.2%)	1,824 (18.4%)	117 (16.3%)	
Male	8,710 (81.8%)	8,108 (81.6%)	602 (83.7%)	
Injury severity§,#				<0.001
Type I	3,330 (31.3%)	3,203 (32.3%)	127 (17.7%)	
Type II	3,644 (34.3%)	3,396 (34.3%)	248 (34.5%)	
Type IIIA	2,616 (24.6%)	2,410 (24.3%)	206 (28.7%)	
Type IIIB	964 (9.1%)	838 (8.5%)	126 (17.5%)	
Type IIIC	73 (0.7%)	61 (0.6%)	12 (1.7%)	
Bone§				<0.001
Femur	3,210 (30.1%)	3,047 (30.7%)	163 (22.7%)	
Tibia	7,441 (69.9%)	6,885 (69.3%)	556 (77.3%)	
Mechanism of injury§				0.14
Road traffic accident	4,649 (80.6%)	4,372 (80.7%)	277 (79.1%)	
Fall	240 (4.2%)	231 (4.3%)	9 (2.6%)	
Explosive blast	70 (1.2%)	62 (1.1%)	8 (2.3%)	
Gunshot	479 (8.3%)	445 (8.2%)	34 (9.7%)	
Other	331 (5.7%)	309 (5.7%)	22 (6.3%)	
Location of fracture on bone§				0.061
Distal	3,394 (33.0%)	3,161 (32.9%)	233 (34.7%)	
Middle	5,150 (50.1%)	4,843 (50.4%)	307 (45.7%)	
Proximal	1,170 (11.4%)	1,088 (11.3%)	82 (12.2%)	
Segmental	504 (4.9%)	459 (4.8%)	45 (6.7%)	
Subtrochanteric	57 (0.6%)	52 (0.5%)	5 (0.7%)	
World Bank Classification§				0.12
LIC	3,423 (32.1%)	3,167 (31.9%)	256 (35.6%)	
LMIC	6,857 (64.4%)	6,418 (64.6%)	439 (61.1%)	
UMIC	371 (3.5%)	347 (3.5%)	24 (3.3%)	
Hospital bed capacity‡	485.08 ± 477.07	484.79 ± 469.57	489.13 ± 573.28	0.82
Orthopaedic specialty hospital§				<0.001
No	6,668 (67.1%)	6,179 (66.6%)	489 (73.6%)	
Yes	3,268 (32.9%)	3,093 (33.4%)	175 (26.4%)	
Academic hospital§				<0.001
No	3,868 (38.9%)	3,570 (38.4%)	298 (44.9%)	
Yes	6,084 (61.1%)	5,719 (61.6%)	365 (55.1%)	
Hospital type§				<0.001
Nongovernmental	4,263 (42.1%)	3,924 (41.6%)	339 (49.4%)	
Governmental	5,854 (57.9%)	5,507 (58.4%)	347 (50.6%)	
WHO hospital classification§				<0.01
Level 1	2,491 (26.2%)	2,250 (25.4%)	241 (37.4%)	
Level 2	1,836 (19.3%)	1,750 (19.7%)	86 (13.4%)	
Level 3	5,181 (54.5%)	4,864 (54.9%)	317 (49.2%)	

*LIC = low-income country, and UMIC = upper-middle-income country. †Data were not available for all characteristics. ‡The values are given as the mean and the standard deviation. §The values are given as the number of patients, with the percentage in parentheses. #Defined by the Gustilo-Anderson classification system.

TABLE II Characteristics of Participants with or without Follow-up*†

Characteristic	Lost to Follow-up (N = 13,312)	Follow-up (N = 10,651)	P Value
Age‡ *(yr)*	33.92 ± 13.53	33.60 ± 12.91	0.060
Sex§			<0.001
Female	1,877 (14.1%)	1,941 (18.2%)	
Male	11,435 (85.9%)	8,710 (81.8%)	
Injury severity§,#			<0.001
Type I	4,354 (32.8%)	3,330 (31.3%)	
Type II	4,828 (36.4%)	3,644 (34.2%)	
Type IIIA	3,037 (22.9%)	2,616 (24.6%)	
Type IIIB	929 (7.0%)	964 (9.1%)	
Type IIIC	127 (1.0%)	73 (0.7%)	
Bone§			0.19
Femur	4,484 (33.7%)	3,210 (30.1%)	
Tibia	8,828 (66.3%)	7,441 (69.9%)	
Mechanism of injury§			<0.001
Road traffic accident	3,541 (73.8%)	4,693 (80.5%)	
Fall	225 (4.7%)	245 (4.2%)	
Explosive blast	111 (2.3%)	74 (1.3%)	
Gunshot	684 (14.2%)	485 (8.3%)	
Other	240 (5%)	332 (5.7%)	
Location of fracture on bone§			0.002
Distal	3,238 (31.9%)	3,395 (33.0%)	
Middle	5,006 (49.4%)	5,152 (50.1%)	
Proximal	1,301 (12.8%)	1,173 (11.4%)	
Segmental	508 (5.0%)	505 (4.9%)	
Subtrochanteric	85 (0.8%)	57 (0.6%)	
World Bank Classification§			<0.001
LIC	3,420 (26.3%)	3,423 (32.1%)	
LMIC	8,725 (67.2%)	6,857 (64.4%)	
UMIC	847 (6.5%)	371 (3.5%)	
Hospital bed capacity‡	533.36 ± 527.94	485.71 ± 477.66	<0.001
Orthopaedic-specific hospital§			0.099
No	7,756 (68.1%)	6,747 (67.1%)	
Yes	3,626 (31.9%)	3,310 (32.9%)	
Academic hospital§			0.47
No	4,367 (38.5%)	3,929 (39.0%)	
Yes	6,972 (61.5%)	6,147 (61.0%)	
Hospital type§			<0.001
Nongovernmental (private, mission, nonprofit, mixed)	3,856 (33.2%)	4,319 (42.2%)	
Governmental	7,769 (66.8%)	5,922 (57.8%)	
WHO hospital classification§			<0.001
Level 1	2,655 (24.0%)	2,526 (26.3%)	
Level 2	2,583 (23.3%)	1,851 (19.2%)	
Level 3	5,843 (52.7%)	5,244 (54.5%)	
Time from injury to debridement‡ *(hr)*	17.68 ± 27.54	19.14 ± 27.81	<0.001

*LIC = low-income country, and UMIC = upper-middle-income country. †Data were not available for all characteristics. ‡The values are given as the mean and the standard deviation. §The values are given as the number of patients, with the percentage in parentheses. #Defined by the Gustilo-Anderson classification system.

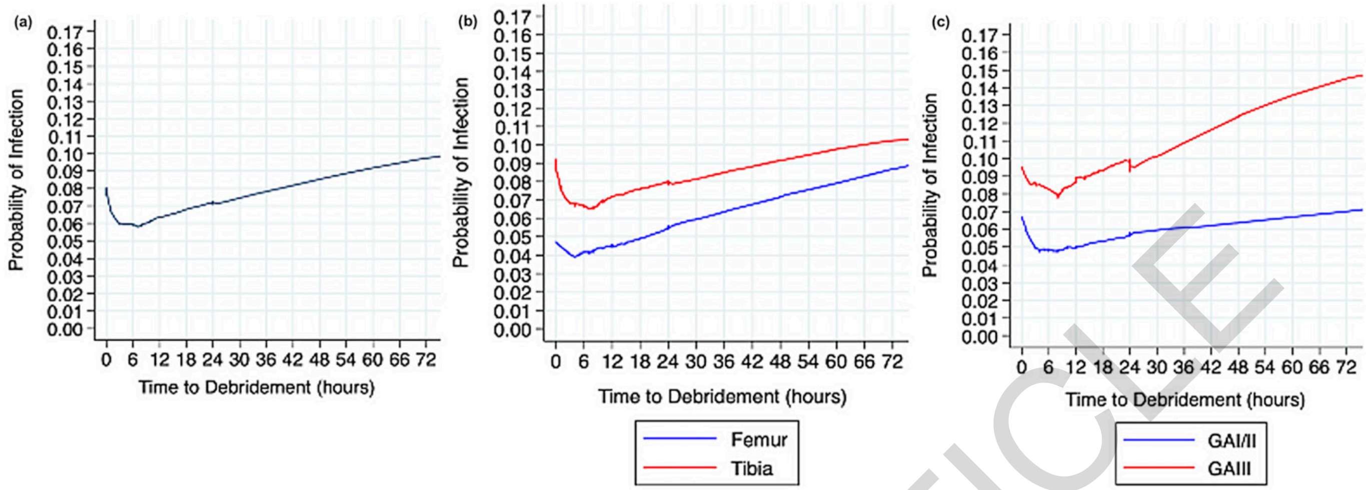

Fig. 2
LOWESS plot of the probability of infection with increasing time to debridement in 6-hour increments (Fig. 2-A), with subgrouping by bone (Fig. 2-B) and injury severity (Fig. 2-C). GA = Gustilo-Anderson.

methods in the literature that evaluated this relationship based on binary, early versus late, debridement time thresholds. The results of our study are largely consistent with these previous studies; earlier debridement was associated with a reduced likelihood of infection. With a similar intent to minimize confounding with a large sample size, the Global Open Fracture Collaborative to Investigate Available Evidence in The Literature (GOLIATH Collaborative) conducted a meta-analysis of late versus early debridement in 84 studies with various time thresholds[1]. Those authors found that progressive delays to debridement had a significant overall impact on infection risk (odds ratio [OR], 1.29 [95% confidence interval (CI), 1.11 to 1.49]; $p < 0.001$; n = 18,239). When evaluating the debridement of high-grade fractures alone at multiple debridement time thresholds, the authors detected an increase in the odds of infection with progressive delays in treatment. There was moderate-quality evidence to suggest that Gustilo-Anderson type-III open fractures, the majority of which were in the lower extremity, are at a twofold greater risk for infection after receiving treatment >24 hours after injury (OR, 2.17 [95% CI, 1.73 to 2.72]; $p < 0.001$; 29 studies [n = 5,214]). A separate analysis revealed an estimated increased odds of infection with a delay of >12 hours for tibial fractures (OR, 1.37 [95% CI, 1.00 to 1.87]; $p = 0.05$; 12 studies [n = 2,065]) and an even greater increase for Gustilo-Anderson type-IIIB fractures (OR, 1.46 [95% CI, 1.13 to 1.89]; $p = 0.004$; 12 studies [n = 1,255])[1]. Based on their adjusted analyses, the authors recommended that their findings only be applied to high-grade fractures. Our findings from the SIGN database are in line with the GOLIATH meta-analysis and support the expeditious debridement of

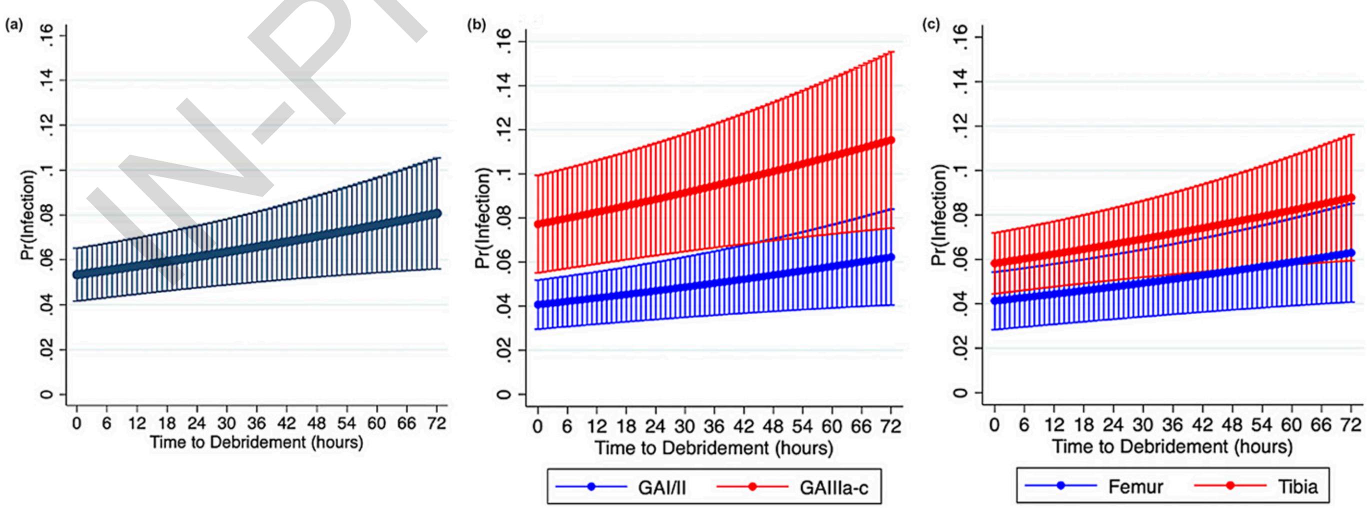

Fig. 3
Mean probability of infection with increasing time to debridement in 6-hour increments using a marginal-effects plot of the fitted logistic regression model (Fig. 3-A), with subgrouping by injury severity (Fig. 3-B) and bone (Fig. 3-C). The shaded areas indicate the 95% CIs. GA = Gustilo-Anderson.

open lower-extremity fractures. We demonstrated a higher probability of infection at all times points for higher-grade fractures compared with lower-grade fractures and for open tibial fractures compared with femoral fractures. Although our study had a sample size comparable with that of the GOLIATH study, we had the advantage of being able to make multivariable adjustments to our primary data to minimize confounding across the entire cohort.

Although the size and international nature of the SSDB cohort make the findings from this study uniquely generalizable, there were a number of limitations that are worth noting. First, the observational nature of this study may have led to potential confounding. Although we attempted to address this issue by including multiple demographic, injury, and hospital variables in our logistic regression model and subgroup analyses, we could not adjust for any unmeasured confounding within the database. Second, data on the time from the injury to treatment were subject to patient recall with regard to the time of the injury, which was likely a source of error. Third, outcome assessment was limited to self-reporting of infection within the database. Criteria used to define infection were unknown and were used at the discretion of the treating surgeon, including both superficial and deep infections. We grouped all infections together on the assumption that an infectious complication would be clinically severe enough to compel a patient to present for follow-up and also compel the treating surgeon to record it in the SSDB. Third, data on perioperative antibiotic administration were not included in our analysis. We acknowledge the well-demonstrated impact of antibiotic use on reducing infection in the setting of open fractures. Although there have been some data available about antibiotic usage in the SSDB, reporting was inconsistent over the time frame of the study; therefore, we were not able to make adjustments for this factor. Furthermore, we lacked information with regard to patient comorbidities, time to hospital presentation, and definitive fixation compared with staged fixation for higher-grade open injuries that may have required wound coverage. These factors may also have had an effect on the probability of infection, which may limit the generalizability of our findings only to low-income and middle-income practice settings. Lastly, the overall follow-up rate of our patient cohort was only around 27.3%. This reflects an improvement compared with previous studies using the SSDB[18,20,21], likely due to a greater emphasis on follow-up reporting and data quality by SIGN Fracture Care International. Nonetheless, loss to follow-up may have led to a selection bias, particularly if patients were not lost at random.

In conclusion, our study aimed to assess the relationship between time to debridement and infection in open tibial and femoral fractures. Incremental delays in debridement increased the risk of infection in open femoral and tibial fractures, and the probability of infection was higher at baseline for higher-grade injuries and tibial fractures. Based on the results of our study, there does not appear to be a discrete time threshold within which open fractures should be managed to minimize the risk of infection development. Rather, open lower-extremity injuries should undergo debridement as quickly and as practically as possible.

Appendix

eA Supporting material provided by the authors is posted with the online version of this article as a data supplement at jbjs.org (http://links.lww.com/JBJS/H655). ■

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