OTA HIGHLIGHT PAPER

Time to Initial Operative Treatment Following Open Fracture Does Not Impact Development of Deep Infection: A Prospective Cohort Study of 736 Subjects

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Objectives: To evaluate the association between time to surgery, antibiotic administration, Gustilo grade, fracture location, and development of deep infection in open fractures.

Design: Prospective cohort between 2001 and 2009.

Setting: Three Level 1 Canadian trauma centers.

Participants: A total of 736 (791 fractures) subjects were enrolled and 686 subjects (93%; 737 fractures) provided adequate follow-up data (1-year interview and/or clinical follow-up >90 days).

Intervention: Demographics, injury information, time to surgery, and antibiotics were recorded. Subjects were evaluated using standardized data forms until the fracture(s) healed. Phone interviews were undertaken 1 year after the fracture.

Main Outcome Measures: Infection requiring unplanned surgical debridement and/or sustained antibiotic therapy.

Results: Tibia/fibula fractures were most common (n = 413, 52%), followed by upper extremity (UE) (n = 285, 36%), and femoral (n = 93, 12%) fractures. Infection developed in 46 fractures (6%). The median time to surgery was 9 hours 4 minutes (interquartile range, 6 hours 39 minutes to 12 hours 33 minutes) and 7 hours 39 minutes (interquartile range, 6 hours 10 minutes to 9 hours 54 minutes) for those without and with infection, respectively ($P = 0.04$). Gustilo grade 3B/3C fractures accounted for 17 of 46 infections (37%) ($P < 0.001$). Four UE (1.5%), 7 femoral (8%), and 35 tibia/fibula (9%) fractures developed infections ($P = 0.001$). Multivariate regression found no association between infection and time to surgery [odds ratio (OR), 0.97; 95% confidence interval (95% CI), 0.90–1.06] or antibiotics (OR, 1.0; 95% CI, 0.90–1.05). Grades 3A (OR, 6.37; 95% CI, 1.37–29.56) and 3B/3C (OR, 12.87; 95% CI, 2.72–60.95) relative to grade 1 injuries and tibia/fibula (OR, 3.91; 95% CI, 1.33–11.53) relative to UE fractures were significantly associated with infection.

Conclusion: Infection after open fracture was associated with increasing Gustilo grade or tibia/fibula fractures but not time to surgery or antibiotics.

Key Words: open fracture, deep infection, surgical timing

Level of Evidence: Prognostic Level I. See Instructions for Authors for a complete description of levels of evidence.

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INTRODUCTION

Contemporary guidelines for managing open fractures dictates urgent surgical debridement (within 6 hours), lavage, administration of antibiotics, and fracture stabilization. Numerous studies[1–9] have questioned the association between delayed surgical treatment and the development of deep infection in open long bone fractures. Schenker et al,[10] in a recent meta-analyses of 3539 open fractures, reported similar findings. A delay beyond the "6-hour" time frame for treatment of open fractures was not associated with increased rates of deep infection.

Multiply injured patients requiring resuscitation, protracted transport times, and urgent availability of operative theaters are the main reasons for delays to surgery. Development of deep infection has drastic consequences for patients as well as resource demands for the health care system.[11] Delays to surgery may be unavoidable and in some cases advisable, given the patient and resource factors. It is imperative to understand factors that impact the ultimate outcome of patients with open long bone fractures.

The primary study objective was to evaluate the relationship between time to initial orthopaedic surgical management and development of deep infection in open long bone fractures. Second, we examined the association of timing of antibiotics, Gustilo grade,[12] fracture location, and transfusions with development of deep infection. We hypothesized that time to initial surgical management or antibiotic administration would not be significantly associated with the

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development of deep infection, but that higher Gustilo grades, tibia/fibula fractures, and transfusions would be associated with developing deep infection.

PATIENTS AND METHODS

Design and Setting

Between 2001 and 2009, 939 subjects were screened for enrollment in a prospective cohort study at 3 Level 1 trauma centers in Canada; 736 subjects with 791 open fractures were enrolled and followed for at least 1 year postoperatively. One center was the primary enrollment center and enrolled 523 subjects (71%) with 561 fractures (71%), whereas the other 2 sites enrolled 104 subjects (14%) with 112 fractures (14%) and 109 subjects (15%) with 118 fractures (15%), respectively (Fig. 1).

The primary enrollment center serves a vast geography with prolonged extraction times to the surgical hospital resulting in a broad dispersion of time to initial surgical management. This allowed comparison of variable times to surgery and antibiotic administration across all grades and fracture locations. The other 2 centers serve smaller geographical regions, but still had substantial numbers of patients requiring transfer from regional nonsurgical hospitals, allowing for a similar comparison of time to initial surgery across a broad array of fracture locations and grades. All participating surgeons were trauma fellowship-trained surgeons with a minimum of 2 years of experience. Most surgeons (>95%) had more than 5 years of experience and all centers are high volume trauma centers.

All subjects or available proxy respondents provided signed informed consent at index hospitalization. The regional health ethics board approved this study.

Selection Criteria

To be eligible for study enrollment, subjects met the following criteria: skeletal maturity (as seen on radiographs),

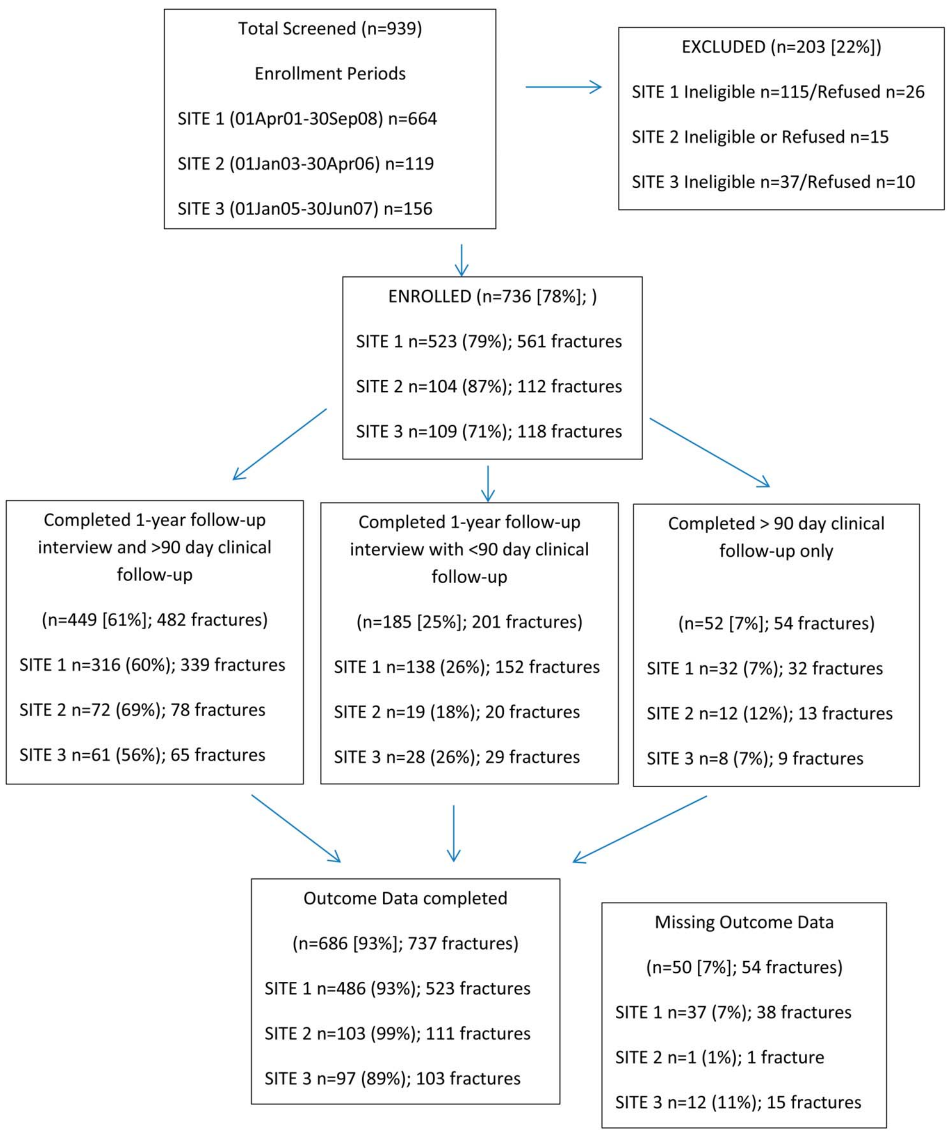

FIGURE 1. Flowchart of patient screening, enrollment, and follow-up. **Editor's note:** A color image accompanies the online version of this article.

long bone open fractures (humerus, radius/ulna, femur, tibia/fibula), presenting for initial surgical debridement, and patient or proxy respondent able to provide consent. The following criteria were reasons for exclusion: pathologic fractures, fractures resulting from penetrating trauma (eg, gunshot wounds, stabbings), patients with unsalvageable limb injuries (ie, requiring immediate amputation), or other medical conditions precluding surgical management.

Intervention

Longstanding principles of open fracture management were incorporated including initial surgical debridement and fracture fixation with copious irrigation (3 L or more) and debridement of soft tissues and contaminated bone. Surgical fixation was at the surgeons' discretion. This was repeated as necessary at intervals of 48 hours until the tissues were clean, all nonviable tissue had been removed, and delayed wound closure could occur. Tetanus prophylaxis was provided when immunization status was either unclear or not up to date and a standardized antibiotic regimen was followed for all patients (see **Appendix**, **Supplemental Digital Content 1**, http://links.lww.com/BOT/A176). Initial medical care provided at nonsurgical centers included medical stabilization, initiation of antibiotics, and external stabilization of the fracture(s) while the patient waited for medical transport.

Data Collection

Demographics, injury information (Gustilo grade, fracture site; timing of antibiotic administration, transfusion requirement), and time from injury to initial surgical management were recorded. Research associates asked participants about smoking status and preexisting medical conditions using the standardized Canadian National Population Health Survey listing. Surgeons completed wound classification forms[13] following the first surgery. Fractures were classified as humeral, radioulnar, femoral, or tibia/fibula, in location. The humeral and radioulnar fractures were subsequently collapsed into an upper extremity (UE) category for analysis.

Subjects were evaluated at outpatient clinics by attending surgeons using standardized data forms until the fracture (s) healed. Phone interviews were undertaken by research associates at least 1 year after the fracture to confirm outcomes, including reoperation, infection, and nonunion. Regional chart reviews were undertaken to capture reoperations that occurred within the health region as participating surgeons operated out of multiple hospitals. For adequate follow-up, subjects needed to complete the 1-year telephone interview or have clinical follow-up of at least 90 days after surgery with a definitive clinical outcome recorded.

Main Outcome Measures

The primary outcome, deep infection, was defined as infection requiring unplanned surgical debridement and/or sustained antibiotic therapy following definitive wound closure. Cellulitis and pin tract infections alone were not considered indicative of deep wound infection, but these were treated with the appropriate antibiotics at the surgeons' discretion and outcomes recorded.

To classify outcomes, outpatient clinic data collection forms, telephone interviews at 1-year, and regional chart reviews were used. The outpatient clinic data collection forms were the primary source of information with infection status recorded by attending surgeons. One-year interview information and regional chart reviews were used to confirm outcomes. Where discrepancies were found, the most recent source of either a reoperation report or surgeon record of outcome on the data forms were used as the definitive sources of outcome. All infections were confirmed through the clinical record. Overall, of those with 1-year patient-reported outcomes and adequate clinical follow-up (n = 481 fractures in 449 patients), 412 patient-reported outcomes (86%) agreed with surgeons' recorded outcomes. Subjects were more likely to report that they had an infection when they did not (n = 51, 11%) although a small number of patients did not report superficial infections (n = 18, 4%). Over two-thirds of reported discordances (47/69, 68%) occurred when subjects had higher grade injuries (Gustilo grade 3 injuries) or delayed healing/nonunion.

Sample Size

The study was powered to detect a 10% difference (which we defined as a clinically important difference) in infection between subjects who underwent initial surgical debridement within 8 hours and those who underwent surgical debridement after 8 hours. Based on our previous retrospective study,[3] we expected that the cohort would disperse similarly between these 2 time periods. Using power of 0.80, a level of significance of 0.05 and 15% attrition, 389 fractures were required in each group for a total of 778 fractures.

Analysis

Descriptive analyses were initially undertaken with comparisons across the enrollment sites. Sites were similar in terms of subjects and fracture characteristics; thus, the groups were treated as a single cohort. Unadjusted logistic regression was performed on time from injury to initial surgical management and antibiotic administration (calculated in hours), Gustilo grade, fracture location (UE, femur, tibia/fibula), and transfusion status to determine their impact on the development of deep infection. Multivariate logistic regression analyses, in which all these variables were entered into a single model, was then used to determine the risk-adjusted association between each variable and the development of deep infection. Gustilo grade 3B/3C fractures were collapsed into a single category for the multivariate analysis. Timing of surgical debridement and antibiotic administration were retained in the final model despite nonsignificance due to their clinical importance.

Time from injury to initial surgery was also calculated categorically examining those who went to surgery within (1) 6 hours, (2) 6–12 hours, and (3) >12 hours relative to development of deep infection. The median time to initial surgery and antibiotic administration was compared between those who developed a deep infection and those who did not using a Mann–Whitney *U* test. We also undertook this time comparison within each Gustilo grade.

All analyses were performed using the Statistical Package for the Social Sciences, version 19.0 (SPSS Inc, Chicago, IL) using 2-tailed tests and a significance level of $\alpha = 0.05$.

RESULTS

Demographics

Most subjects were men (n = 530, 72%) and the median age was 39.6 years (minimum 17, maximum 93) (Table 1). Almost half (n = 359, 49%) of injuries occurred in motor vehicle accidents; falls (n = 230, 31%), crush injuries (n = 131, 18%), and assaults (n = 16, 2%) were other mechanisms of injury. Fifty-five subjects (7%) sustained multiple open fractures and 382 subjects (52%) sustained other injuries. For the primary enrollment site, 278 subjects (53%) received initial medical care at a nonsurgical center, whereas for the other 2 sites, 59 subjects (28%) received initial medical care at a nonsurgical center ($P < 0.001$).

Fracture Characteristics

Tibia/fibula fractures were most common (n = 413, 52%), followed by UE (n = 285, 36%) and femoral (n = 93, 12%) fractures. A total of 292 fractures (37%) were classified as Gustilo grade 2 fractures, whereas 226 (29%) were Gustilo grade 1 fractures. For Gustilo grade 3 fractures, 162 (21%) were grade 3A, 96 (12%) were grade 3B, and 7 (1%) were grade 3C fractures. Grade 3 fractures occurred most often in femoral (n = 39, 43%) and tibia/fibula fractures (n = 160, 40%) compared with UE fractures (n = 66, 24%) ($P < 0.001$). Nine fractures did not have grades assigned.

The OTA fracture classification was also completed for 598 fractures (75%). Of these, 38 UE (13%), 4 femoral (4%), and 32 tibia/fibula (8%) fractures were proximal, whereas 109 UE(38%), 28 femoral (30%), and 90 tibia/fibula (22%) fractures were distal. Diaphyseal fractures accounted for 74 UE (26%), 40 femoral (43%), and 140 tibia/fibula (34%) fractures. Malleolar fractures occurred in 43 tibia/fibula fractures (10%).

For fracture fixation, 403 subjects (51%) received open reduction and internal fixation, 204 subjects (26%) received an intramedullary nail (reamed or unreamed), 82 subjects (10%) received external fixation, and 97 subjects (12%) received percutaneous pinning (n = 10), casting (n = 33), or combined fixation (n = 54). Of 791 fractures, 104 (13%) required split thickness skin grafts (STSG) or flaps (free or local) for wound closure. Of these, 79 fractures required a single soft tissue procedure (64 STSG, 11 local, and 4 free flaps), whereas 25 required multiple soft tissue procedures (11 STSG with free flaps, 11 STSG with local flaps, and 3 with STSG, local and free flaps). Most subjects underwent 1 (n = 302, 38%) or 2 (n = 327, 42%) surgical debridements before definitive wound closure. The remaining subjects had 3 (n = 93, 12%), 4 (n = 42, 5%), or 5–6 (n = 20, 3%) debridements before definitive wound closure.

Follow-up

Overall, 634 subjects (86%) (682 fractures) completed the 1-year interview at a median of 412 days [interquartile range (IQR), 375–546 days] postoperatively and 501 subjects (67%) (536 fractures) completed clinic follow-up of more than 90 days (median follow-up = 188 days; IQR, 122–286 days). Only 50 subjects (7%) provided inadequate follow-up data (no telephone interview and clinical follow-up <90 days) (Fig. 1). These 50 subjects were similar to those who provided outcome data in time to initial surgery and antibiotic

TABLE 1. Characteristics of 736 Subjects With Compound Fractures of Long Bones

	Site 1 (n = 523)	Site 2 (n = 104)	Site 3 (n = 109)	Total (n = 736)	P
Subject characteristics					
Median age (IQR)	40.0 (25.9–54.1)	39.8 (29.5–51.3)	36.7 (26.0–50.0)	39.6 (26.5–52.8)	0.52*
Gender, male, n (%)	378 (72)	68 (65)	84 (77)	530 (72)	0.16†
Comorbidities, n (%)					
None	128 (24)	23 (22)	29 (27)	180 (24)	0.83†
1–2 conditions	330 (64)	71 (68)	67 (61)	468 (64)	
3 or more conditions	65 (12)	10 (10)	13 (12)	88 (12)	
Smoking, n (%)					
Never	243 (47)	58 (56)	49 (45)	350 (48)	0.07†
Current	206 (39)	32 (31)	52 (48)	290 (39)	
Quit	74 (14)	14 (14)	8 (7)	96 (13)	
Injury characteristics					
Median time to antibiotic administration (IQR)	3 h 35 min (1 h 50 min to 10 h 22 min)	1 h 49 min (1 h 8 min to 3 h 9 min)	3 h 43 min (1 h 51 min to 7 h 19 min)	3 h 8 min (1 h 40 min to 8 h 0 min)	<0.001*
Median time to initial surgical debridement (IQR)	9 h 30 min (6 h 45 min to 12 h 45 min)	7 h 43 (6 h 2 min to 11 h 31 min)	8 h 48 min (6 h 49 min to 12 h 57 min)	9 h 15 min (6 h 36 min to 12 h 35 min)	0.04*
Associated injuries, n (%)	252 (48)	63 (61)	67 (62)	382 (52)	0.007†
Blood transfusions, n (%)	134 (25)	39 (38)	25 (24)	198 (27)	0.02†

*As analyzed by Mann–Whitney *U* test.
†As analyzed by χ^2 test.

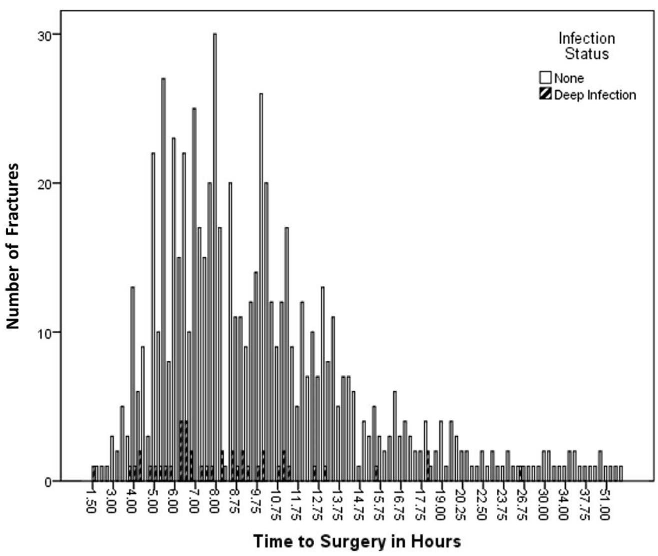

FIGURE 2. Frequency of infection status by time to surgery in hours.

administration, fracture location, Gustilo grade, age, and comorbidities ($P > 0.24$), but more men than women were lost to follow-up ($P = 0.01$).

Unadjusted Outcomes

Of 737 fractures with defined outcomes, 46 (6%) developed deep infections. An additional 56 (7%) developed pin tract infections or cellulitis that resolved with antibiotics. The median time to initial surgery was 9 hours 04 minutes (IQR, 6 hours 39 minutes to 12 hours 33 minutes) for those without and 7 hours 39 minutes (IQR, 6 hours 10 minutes to 9 hours 54 minutes) for those with deep infection ($P = 0.04$). Of those with infection, 9 (21%) underwent surgery within 6 hours, 28 (65%) between 6 and 12 hours, and 6 (14%) after 12 hours of injury (Fig. 2). Within Gustilo grades, there were no differences in time to surgery for those who did or did not develop infections ($P \geq 0.10$) (Table 2).

The proportion of infections among Gustilo grades was significantly different ($P < 0.001$), ranging from 1% in grade 1 (4% in grade 2, 9% in grade 3A) to 16% in grade 3B (Table 3). Four UE (1.5%), 7 femoral (8%), and 35 tibial/fibular (9%) fractures developed deep infections ($P = 0.001$). Of 732 fractures with transfusion information, 22 of 230 (10%) who received transfusions developed deep infections compared with 23 of 502 (5%) who did not receive transfusions ($P = 0.02$).

The median time to antibiotic administration was 3 hours 05 minutes (IQR, 1 hours 40 minutes to 7 hours 30 minutes) for those without and 2 hours 37 minutes (IQR, 1 hours 30 minutes to 7 hours 00 minutes) for those who developed deep infection ($P = 0.67$). For 103 subjects, antibiotics were administered before surgical hospital admission, but the administration time was not provided on the transfer information.

Risk-Adjusted Analyses

Multivariate logistic regression showed no significant association between developing deep infection and time to initial operative management ($P = 0.49$) or antibiotic administration ($P = 0.90$). Although transfusion was significant in the univariate analysis, this finding was not significant in the multivariate model ($P = 0.51$). Grades 3A and 3B/3C relative to grade 1 injuries ($P < 0.001$) and tibia/fibula relative to UE fractures ($P = 0.047$) were associated with developing deep infection (Table 4).

DISCUSSION

In our study of almost 800 open long bone fractures, development of deep infection was not associated with time to initial surgery; instead increasing Gustilo grade or tibia/fibula fractures were associated with developing a deep infection. To our knowledge, this study represents the largest prospective cohort study performed to date to evaluate the association of time to initial surgery and development of deep infection following open fracture of a long bone.

Similar to our study, Schenker et al[10] found that infection rates were associated with increasing grade of injury and lower extremity fractures. In our study and the meta-analyses, those with high grades of injury (3B/3C) were more likely to be taken to surgery expeditiously than those with lower grade injuries, representing clinical decision making to address more serious fractures and tissue damage soon after surgical hospital admission.

There was no difference in the median timing of the initial antibiotic administration between those who developed deep infections and those who did not. However, this finding may not be surprising when the majority of patients received antibiotics within 3–4 hours of injury.

TABLE 2. Comparison of Gustilo Grade and Median Time to Surgery by Infection Status*

Gustilo Grade	Median Time to Surgery for Infected Fractures (IQR)	Median Time to Surgery for Noninfected Fractures (IQR)	P*
Grade 1	8 h 34 min (6 h 21 min to 10 h 09 min)	9 h 45 min (6 h 51 min to 13 h 00 min)	0.18†
Grade 2			
Grade 3A	8 h 47 min (6 h 05 min to 11 h 24 min)	8 h 15 min (6 h 35 min to 11 h 00 min)	0.84
Grade 3B	6 h 29 min (5 h 18 min to 8 h 21 min)	7 h 55 min (5 h 51 min to 10 h 31 min)	0.10†
Grade 3C			

*As analyzed using Mann–Whitney *U* test.
†Collapsed for time analysis because of the small numbers in cells.

TABLE 3. Fracture Location by Gustilo Grade of Fracture and Infection Status

Gustilo Grade	UE (N = 285), n (%)	Femur (N = 93), n (%)	Tibia/ Fibula (N = 413), n (%)	Total (N = 791), n (%)*
Grade 1 noninfected	118 (91)	16 (94)	72 (90)	206 (91)
Grade 1 infected	1 (1)	0 (0)	1 (1)	2 (1)
Grade 1 outcome unknown	10 (8)	1 (6)	7 (9)	18 (8)
Grade 2 noninfected	75 (86)	31 (91)	150 (88)	256 (88)
Grade 2 infected	2 (3)	0 (0)	10 (6)	12 (4)
Grade 2 outcome unknown	10 (11)	3 (9)	10 (6)	23 (8)
Grade 3A noninfected	37 (97)	23 (85)	82 (85)	142 (88)
Grade 3A infected	1 (3)	2 (7.5)	12 (13)	15 (9)
Grade 3A outcome unknown	0 (0)	2 (7.5)	2 (2)	4 (3)
Grade 3B noninfected	21 (91)	6 (50)	48 (77)	75 (77)
Grade 3B infected	0 (0)	5 (42)	11 (18)	16 (16)
Grade 3B outcome unknown	2 (9)	1 (8)	3 (5)	6 (6)
Grade 3C noninfected	4 (80)	0 (0)	1 (50)	5 (72)
Grade 3C infected	0 (0)	0 (0)	1 (50)	1 (14)
Grade 3C outcome unknown	1 (20)	0 (0)	0 (0)	1 (14)
Grade unknown noninfected	2 (67)	3 (100)	2 (67)	7 (78)
Grade unknown infected	0 (0)	0 (0)	0 (0)	0 (0)
Grade and outcome unknown	1 (33)	0 (0)	1 (33)	2 (22)

*$P < 0.001$ for overall comparison of infection by Gustilo grade of fracture.

Elective delay to surgical treatment is not recommended, but with the low number of infections noted in the Gustilo grade 1 and 2 fractures, as well as all open UE fractures, daily trauma theaters may be the most efficacious way to deal with these injuries.[14,15] In fact, a number of trauma centers have already moved toward this mode of practice (R. Leighton, MD, FRCS (C) personal communication, Canadian Orthopaedic Trauma Society March 2014). Although delayed debridement does not seem to increase morbidity due to infection, it is imperative that open fractures receive early antibiotics and splinting. Resources should be in place to allow for meticulous surgical debridement and lavage as well as appropriate surgical stabilization as judged by the treating surgeon.

This study has a number of strengths. As a prospective cohort study, we screened all patients admitted with open long bone fractures during the specified enrollment periods. A standardized antibiotic regimen was used and surgeons classified fractures at the index surgery using a standardized form. Standardized forms were also used at follow-up evaluations with a priori definitions of infection. In addition, we achieved more than 85% patient follow-up at 1 year postoperatively and only 7% of subjects provided no follow-up data in the form of either clinic visits beyond 90 postoperatively or completion of the 1-year interview.

TABLE 4. Multivariate Logistic Regression of Factors Associated With Development of Deep Infection Following an Open Fracture

	Unadjusted Analysis		Adjusted Analysis	
Variables	OR	95% CI	OR	95% CI
Transfused	**2.20**	**1.20–4.03**	1.27	0.63–2.54
Time to surgery (h)	0.93	0.86–0.99	0.97	0.90–1.06
Time to antibiotic administration (h)	0.98	0.93–1.03	1.0	0.95–1.05
Fracture location				
UE	1.0	Reference	1.0	Reference
Femur	**5.67**	**1.62–19.88**	3.29	0.65–14.24
Tibia/fibula	**6.29**	**2.21–17.92**	**3.91**	**1.33–11.53**
Gustilo grade				
1	1.0	Reference	1.0	Reference
2	**4.81**	**1.06–21.71**	3.01	0.66–14.24
3A	**10.75**	**2.4–47.74**	**6.37**	**1.37–29.56**
3B/3C	**21.78**	**4.92–96.43**	**12.87**	**2.72–60.95**

Statistically significant values ($P < 0.05$) shown in bold.

Because the involved sites serve a large geographic region, we had a broad dispersion of time to surgery among all fracture grades and locations. We were able examine the impact of delayed time to surgery even for significant injury grades including more than 100 Gustilo grade 3B/3C fractures.

However, there are some notable limitations. Despite our broad range of time to surgery, we still identified a clinical bias in taking Gustilo grade 3B/3C open fractures to the operating room quicker than lower fracture grades, a factor that could not be controlled with a nonrandomized study design. Thus, time to initial operative treatment was partially at the surgeons' discretion.

In addition, although our infection rate aligns with that previously reported in the literature,[10] the number of infections was lower than anticipated, which may suggest that even our large study is underpowered. However, there is no suggestion in our current data that reducing time to the initial surgical debridement will reduce the number of infections; in fact, our unadjusted time analysis found that those who subsequently developed deep infections underwent initial surgical debridement earlier than those who did not develop deep infections ($P = 0.04$).

The small number of infections also restricted the number of variables that could be examined in our multivariate model to determine clinical factors associated with the development of deep infection. Based on this limitation, we focused primarily on factors that have previously been reported as being associated with development of deep infections—Gustilo grade and location of fracture. We also did not record the injury severity score. We did, however, examine the role of transfusions and did not find a significant relationship between transfusion and infection outcome in the multivariate analysis. Finally, surgeons were in practice in level 1 trauma centers and were free to carry out the stabilization they deemed appropriate and used their discretion as to the number of surgical debridements performed before definitive wound closure.

Schenker et al[10] concluded that a well-designed prospective trial could answer the question of timing in relation to infection rates with open fractures. Although our study is nonrandomized, it comprises the largest prospective study to address this question to date. Our data clearly support that of smaller studies—there does not appear to be an association with time to surgery and development of deep infection following open fracture. Our findings suggest that with the low number of infections seen in Gustilo grade 1 and 2 fractures and UE open fractures, there may be clinical implications for determining if an open fracture requires surgery in the middle of the night, especially if a trauma room is available in the morning.

REFERENCES

1. Ashford RU, Mehta JA, Cripps R. Delayed presentation is no barrier to satisfactory outcome in the management of open tibial fractures. *Injury.* 2004;35:411–416.
2. Charalambous CP, Siddique I, Zenios M, et al. Early versus delayed surgical treatment of open tibial fractures: effect on the rates of infection and need of secondary surgical procedures to promote bone union. *Injury.* 2005;36:656–661.
3. Harley BJ, Beaupre LA, Jones CA, et al. The effect of time to definitive treatment on the rate of nonunion and infection in open fractures. *J Orthop Trauma.* 2002;16:484–490.
4. Kindsfater K, Jonassen EA. Osteomyelitis in grade II and III open tibia fractures with late debridement. *J Orthop Trauma.* 1995;9:121–127.
5. Noumi T, Yokoyama K, Ohtsuka H, et al. Intramedullary nailing for open fractures of the femoral shaft: evaluation of contributing factors on deep infection and nonunion using multivariate analysis. *Injury.* 2005;36:1085–1093.
6. Pollak AN, Jones AL, Castillo RC, et al. The relationship between time to surgical debridement and incidence of infection after open high-energy lower extremity trauma. *J Bone Joint Surg Am.* 2010;92A:7–15.
7. Reuss BL, Cole JD. Effect of delayed treatment on open tibial shaft fractures. *Am J Orthop.* 2007;36:215–220.
8. Spencer J, Smith A, Woods D. The effect of time delay on infection in open long-bone fractures: a 5-year prospective audit from a district general hospital. *Ann R Coll Surg Engl.* 2004;86:108–112.
9. Tripuraneni K, Ganga S, Quinn R, et al. The effect of time delay to surgical debridement of open tibia shaft fractures on infection rate. *Orthopedics*. 2008;31:1195.
10. Schenker ML, Yannascoli S, Baldwin KD, et al. Does timing to operative debridement affect infectious complications in open long-bone fractures? A systematic review. *J Bone Joint Surg Am.* 2012;94A:1057–1064.
11. Hung KC, Saddawi-konefka D, Haase SC, et al. A cost-utility analysis of amputation versus salvage for Gustilo type IIIB and IIIC open tibial fractures. *Plast Reconstr Surg.* 2009;124:1965–1973.
12. Gustilo RB, Anderson JT. Prevention of infection in the treatment of one thousand and twenty-five open fractures of long bones: retrospective and prospective analyses. *J Bone Joint SurgAm.* 1976;58A:453–458.
13. Marsh JL, Slongo TF, Agel J, et al. Fracture and dislocation classification compendium—2007: Orthopaedic Trauma Association classification, database and outcomes committee. *J Orthop Trauma.* 2007;21(suppl 10):1–163.
14. Henriques JP, Haasdijk AP, Zijlstra F, et al; Myocardial Infarction Study Group. Outcome of primary angioplasty for acute myocardial infarction during routine duty hours versus during off-hours. *J Am Coll Cardiol.* 2003;41:2138–2142.
15. Ricci WM, Gallagher B, Brandt A, et al. Is after-hours orthopaedic surgery associated with adverse outcomes? A prospective comparative study. *J Bone Joint Surg Am.* 2009;91A:2067–2072.