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Scientific Articles
Observational Studies

Infection and Nonunion Rates in Open Fractures

Description of 6,042 Fractures from the FLOW and PREP-IT Trials

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Background: Infection and nonunion are common sequelae of open fractures. Studies have shown infection and nonunion rates ranging from 2% to 52% and 12% to 17%, respectively. The present article describes the rates of surgical site infection (SSI) and delayed union/nonunion following open fractures in a large contemporary series of patients from prospective clinical trials with adjudicated outcomes.

Methods: A descriptive analysis was performed with use of patient data from the FLOW, Aqueous-PREP, and PREPARE-Open studies. These studies, published within the past 10 years, included multiple international trauma centers and shared definitions for SSI and delayed union/nonunion. SSI and delayed union/nonunion rates were stratified by the OTA/AO fracture and Gustilo-Anderson open fracture classification systems. Kaplan-Meier estimators were utilized to obtain point estimates, and the log-log transformation approach was utilized to calculate 95% confidence intervals (CIs) for outcome rates.

Results: A total of 6,042 open fractures were included. The cumulative SSI rates at 12 months for Gustilo-Anderson Types 1, 2, 3A, 3B, and 3C were 5.1%, 9.7%, 13.8%, 28.9%, and 26.2%, respectively. The cumulative rates of delayed union/nonunion at 12 months for Gustilo-Anderson Types 1, 2, 3A, 3B, and 3C were 3.0%, 5.2%, 8.0%, 14.0%, and 17.0%, respectively. Utilizing the OTA/AO fracture classification to increase the point estimate granularity, the estimated 12-month SSI and delayed union/nonunion rates in 156 Gustilo-Anderson type 3B open tibial shaft fractures (OTA/AO 42) were 34.7% (95% CI, 26.7% to 41.9%) and 18.4% (95% CI, 12.0% to 24.4%), respectively. A companion website with SSI and delayed union/nonunion rates was developed to supplement this article.
continued

*Members of the Flow Investigators and of the PREP-IT Investigators are included in a note at the end of the article.

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Conclusions: Open fractures are a substantial problem with complications that include infection and nonunion. The present data are useful for prognosis, research study design, and informing public awareness and policy. These results show that, despite current treatment approaches, the rates of SSI and delayed union/nonunion following treatment of open fractures remain high at 1 year and are not substantially improved from historical rates spanning several decades. Although open fracture sequelae remain a burden for patients, orthopaedic surgeons, and health-care systems, there may be opportunities for improvement in outcomes.

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

Open fractures have greater risk of infection and nonunion than closed fractures[1]. Treatment of fracture-related infection is not only costly to health-care systems but results in substantial patient cost burden[2], estimated to exceed $23,000 per infection[3]. Additionally, open fracture[4-6] and infection[4,7,8] are major risk factors for nonunion. Nonunion has a detrimental effect on patients[9,10] and comes with substantial societal costs from lost opportunity and work-related limitations[11]. Because of their profound impact on health, open fractures were recognized by the Lancet Commission on Global Surgery in 2015 as a top-3 surgical priority[12,13].

Treatment of open fractures involves many elements, including systemic and local antibiotic delivery, timely irrigation and debridement, and, for the most severe open fractures, soft-tissue coverage procedures. In response, treatment of open fractures has evolved to optimize the time to initial debridement[14], timing and type of prophylactic antibiotic delivery[15], local antibiotic usage[16], types of definitive fracture management[17,18], and temporal relationship of definitive fixation to soft-tissue coverage when required[19,20]. In large studies of patients with open fractures since 1976, infection and nonunion rates have ranged from 2% to 52% and 12% to 17%, respectively[8,12,17,18,21].

Despite current treatment approaches, the rates of SSI and delayed union/nonunion following treatment of open fractures remain high at 1 year and are not substantially improved from historical rates spanning several decades.

Three large, randomized trials of open fractures have been published in the last decade[1,22,23]. The purpose of the present article is to describe the rates of surgical site infection (SSI) and delayed union/nonunion based on the fracture location (OTA/AO fracture classification[24]) and severity (Gustilo-Anderson[18] classification system). Secondarily, these data are qualitatively compared with historical controls from large series of open fractures[8,12,17,18,21]. The goal of combining the 3 parent trials with similar patients is to provide accurate point-estimates of open fracture complications with use of prospectively collected data with adjudicated outcomes in a cohort of patients managed with contemporary treatment strategies. In doing so, these data establish the rates of SSI and delayed union/nonunion that may be expected following treatment of an open fracture.

Materials and Methods

Study Design and Population

The present study is a descriptive analysis of patients with open fractures enrolled in the PREP-IT trials (Aqueous-PREP[23] and PREPARE-Open[1]) and FLOW trial[22]. These trials collected similar baseline data; however, the FLOW trial did not record body mass index, Injury Severity Score, or American Society of Anesthesiologists (ASA) Physical Status class. Trial participants had their OTA/AO fracture and Gustilo-Anderson open fracture classifications recorded at the time of initial debridement. A description of the Gustilo-Anderson classification system utilized for this study is provided in the FLOW trial[22] Supplementary Appendix. Both OTA/AO fracture and Gustilo-Anderson open fracture classifications were reported by the treating surgeon. Furthermore, gunshot injuries were included if the surgeon felt that formal open fracture irrigation and debridement were warranted. Participants in all 3 trials were prospectively followed for 1 year after enrollment. The trials shared definitions for reoperations related to SSI and delayed union/nonunion, allowing their outcomes to be pooled for descriptive analyses. Of note, the FLOW trial[22] was published with data for 2,447 patients. Two patients were determined ineligible after publication, and an additional 30 patients did not have OTA/AO fracture and Gustilo-Anderson open fracture classifications. Ethical approval for this secondary analysis was obtained from the Hamilton Integrated Research Ethics Board (HiREB) (#17597).

Study Outcomes

Infection was defined as superficial or deep/organ space, as guided by the 2017 U.S. Centers for Disease Control and Prevention (CDC) National Healthcare Safety Network reporting criteria[25], with an observation window extended to 12 months post-injury. Delayed unions/nonunions were specified by the trials as surgical interventions to promote bone healing[26]. These bone-healing reoperations were recorded at 3, 6, and 12 months post-injury, recognizing that procedures before 6 months likely reflected delayed unions and did not fulfill common definitions of nonunion[27]. Amputations were also recorded. Once an amputation occurred, the fracture no longer contributed to SSI or delayed union/nonunion estimates. It bears mentioning that for a patient to be included in the parent trials, they had to have undergone attempted limb salvage (i.e., acute amputations were not included). All outcomes were verified by independent adjudication committees for the respective studies.

Statistical Analysis

We calculated outcome rates at 3, 6, and 12 months with use of Kaplan-Meier estimators. Trial participants with incomplete follow-up were censored at their latest observation. We utilized the log-log transformation approach to calculate 95% confidence intervals (CIs) for estimated outcome rates. The rates are cumulative, so a patient diagnosed at an earlier time is in the numerator for all timepoints thereafter, even if the event had resolved by 12 months. We also calculated binomial probabilities of observing SSI or delayed union/nonunion within each timeframe, stratified by each combination of OTA/AO fracture and Gustilo-Anderson open fracture classification on record. The corresponding 95% CIs for these probabilities were estimated with use of the Wilson score method[28]. Finally, we qualitatively compared rates of SSI or delayed union/nonunion to historical controls from large series of open fractures spanning several decades.

Results

A total of 5,753 patients with 6,042 open fractures were enrolled in the 3 trials (Table 1; some patients in the PREP-IT studies had >1 included fracture). A total of 41 centers participated in the FLOW trial, 14 in the Aqueous-PREP trial, and 22 in the PREPARE-Open trial, resulting in 69 unique centers. For the PREPARE-Open trial, there was insufficient

Table 1. Baseline Characteristics of the Trial Patients

Characteristic*	Aqueous-PREP (N = 1638)	PREPARE Open (N = 1700)	FLOW (N = 2415†)
Mean age ± SD *(yr)*	44.9 ± 18.1	44.6 ± 18.2	44.7 ± 17.8
Sex *(no. [%])*			
Female	627 (38.3)	621 (36.5)	744 (30.8)
Male	1009 (61.6)	1079 (63.5)	1671 (69.2)
Prefer not to answer	2 (<1.0)	0 (0.0)	0 (0.0)
Race *(no. [%])*			
White	1289 (78.7)	1173 (69.0)	1793 (74.2)
Black	261 (15.9)	441 (25.9)	144 (6.0)
Asian	18 (1.1)	39 (2.3)	339 (14.0)
Prefer not to answer	18 (1.1)	15 (<1.0)	0 (0.0)
Indigenous	16 (1.0)	21 (1.2)	64 (2.7)
Central or South American	30 (1.8)	3 (<1.0)	75 (3.1)
Multiracial	5 (<1.0)	6 (<1.0)	0 (0.0)
Native Hawaiian or Pacific Islander	1 (<1.0)	2 (<1.0)	0 (0.0)
Body mass index category (kg/m^2) *(no. [%])*			
Underweight (<18.5)	19 (1.2)	25 (1.5)	Not collected
Normal weight (18.5-24.9)	443 (27.0)	502 (29.5)	Not collected
Overweight (25-29.9)	518 (31.6)	573 (33.7)	Not collected
Obese (≥30)	658 (40.2)	600 (35.3)	Not collected
Diabetes of any type *(no. [%])*	170 (10.4)	144 (8.5)	178 (7.4)
Current smoker *(no. [%])*	567 (34.6)	571 (33.6)	777 (32.2)‡
Mean Injury Severity Score ± SD	13.1 ± 9.3	13.2 ± 8.3	Not collected
ASA Physical Status *(no. [%])*			
Class I or II	859 (52.4)	903 (53.1)	Not collected
Class III or higher	779 (47.6)	797 (46.9)	Not collected
No. of included fractures per patient *(no. [%])*			
1	1528 (93.3)	1553 (91.4)	2415 (100.0)
2	95 (5.8)	130 (7.6)	0 (0.0)
3	15 (<1.0)	17 (1.0)	0 (0.0)

*SD = standard deviation, ASA = American Society of Anesthesiologists. †Two patients included in the primary analysis were deemed to be ineligible after the primary manuscript was published. Thirty patients in the FLOW trial were excluded from this analysis due to missing OTA/AO fracture and/or Gustilo-Anderson classifications. ‡Based on 2,405 patients.

SSI variation at the treatment-center level to fit a multilevel model with clustering by site. For the Aqueous-PREP trial, we were able to fit a multilevel model, and the intraclass correlation coefficient (ICC) for the treatment center level clustering was 0.10. The interpretation of this value is that only 10% of the SSI variance can be attributed to the treatment center in these data. Finally, the between-cluster variance (i.e., ICC) in the FLOW trial was 0.095, similar to that in the Aqueous-PREP trial.

There were 251 gunshot injuries included in the trials (4.2% of 6,042). There were 514 fractures definitively treated with external fixation (8.5% of 6,042). Furthermore, 84% of upper-extremity fractures were treated with plate-and-screw constructs, and <10% were treated with intramedullary nailing. With respect to lower-extremity shaft fractures, intramedullary nailing was the predominant form of fracture stabilization. For femoral shafts (OTA/AO classification 32), 373 (90.8%) of 411 were treated with intramedullary nailing. For tibial shaft fractures (OTA/AO classification 42), 1,211 (87.5%) of 1,384 were treated with intramedullary nailing.

Many combinations of OTA/AO fracture location and Gustilo-Anderson severity had low numbers. For the tables included in the main article text, we have eliminated any subgroup with <10 fractures; however, tables in the Appendix contain all data. Fractures were grouped according to the following anatomic regions: upper extremity (Table 2), femur and patella (Table 3), tibia (Table 4),

Table 2. Cumulative 12-Month Surgical Site Infection and Delayed Union/Nonunion Rates in Upper-Extremity Fractures*

OTA/AO Fracture Classification	Gustilo Classification	No. of Fractures	Infection Rate *(N [%; 95% CI])*	Delayed Union/Nonunion Rate *(N [%; 95% CI])*
Proximal humerus, 11	1	14	1 (7.1%; 0%-19.7%)	0 (0%; 0%-0%)
	2	12	1 (8.3%; 0%-22.7%)	1 (8.3%; 0%-22.7%)
Humeral shaft, 12	1	60	0 (0%; 0%-0%)	0 (0%; 0%-0%)
	2	49	0 (0%; 0%-0%)	2 (4.1%; 0%-9.5%)
	3A	25	3 (12%; 0%-23.9%)	3 (12%; 0%-23.9%)
Distal humerus, 13	1	76	7 (9.2%; 2.5%-15.5%)	1 (1.3%; 0%-3.8%)
	2	97	3 (3.1%; 0%-6.5%)	3 (3.2%; 0%-6.7%)
	3A	61	3 (4.9%; 0%-10.2%)	1 (1.6%; 0%-4.8%)
Clavicle, 15	1	23	1 (4.3%; 0%-12.3%)	0 (0%; 0%-0%)
Proximal radius, 2R1	1	16	0 (0%; 0%-0%)	0 (0%; 0%-0%)
	2	11	0 (0%; 0%-0%)	1 (9.1%; 0%-24.6%)
Radial shaft, 2R2	1	96	1 (1%; 0%-3.1%)	3 (3.1%; 0%-6.5%)
	2	82	6 (7.4%; 1.5%-12.9%)	7 (8.7%; 2.3%-14.7%)
	3A	50	5 (10%; 1.3%-17.9%)	5 (10%; 1.3%-17.9%)
	3B	15	2 (13.3%; 0%-28.9%)	4 (26.7%; 0.5%-46%)
Distal radius, 2R3	1	189	4 (2.2%; 0%-4.2%)	2 (1.1%; 0%-2.6%)
	2	101	3 (3%; 0%-6.4%)	1 (1%; 0%-3%)
	3A	54	3 (5.8%; 0%-11.9%)	5 (9.8%; 1.3%-17.5%)
Proximal ulna, 2U1	1	99	2 (2.1%; 0%-4.9%)	2 (2.1%; 0%-4.9%)
	2	98	3 (3.1%; 0%-6.4%)	2 (2%; 0%-4.8%)
	3A	28	0 (0%; 0%-0%)	1 (3.8%; 0%-11%)
Ulnar shaft, 2U2	1	123	3 (2.4%; 0%-5.1%)	5 (4.1%; 0.5%-7.5%)
	2	73	2 (2.7%; 0%-6.4%)	2 (2.8%; 0%-6.5%)
	3A	47	3 (6.4%; 0%-13.2%)	2 (4.3%; 0%-9.9%)
	3B	11	2 (18.2%; 0%-38.1%)	1 (9.1%; 0%-24.6%)
Distal ulna, 2U3	1	37	0 (0%; 0%-0%)	0 (0%; 0%-0%)
	2	22	0 (0%; 0%-0%)	1 (4.5%; 0%-12.9%)
	3A	16	0 (0%; 0%-0%)	0 (0%; 0%-0%)
Hand, 7	1	11	0 (0%; 0%-0%)	0 (0%; 0%-0%)
	2	15	1 (6.7%; 0%-18.5%)	0 (0%; 0%-0%)
	3A	12	3 (25%; 0%-45.9%)	3 (25%; 0%-45.9%)

*Totals 1,623 fractures, 62 infections (3.8%), and 58 delayed unions or nonunions (3.6%).

Table 3. Cumulative 12-Month Surgical Site Infection and Delayed Union/Nonunion Rates in Femoral and Patellar Fractures*

OTA/AO Fracture Classification	Gustilo Classification	No. of Fractures	Infection Rate *(N [%; 95% CI])*	Delayed Union/Nonunion Rate *(N [%; 95% CI])*
Proximal femur, 31	3A	11	1 (9.1%; 0%-24.6%)	0 (0%; 0%-0%)
Femoral shaft, 32	1	63	2 (3.2%; 0%-7.4%)	0 (0%; 0%-0%)
	2	93	0 (0%; 0%-0%)	6 (6.5%; 1.3%-11.3%)
	3A	243	12 (5%; 2.2%-7.6%)	21 (8.7%; 5.1%-12.2%)
Distal femur, 33	1	40	2 (5.1%; 0%-11.8%)	5 (12.8%; 1.7%-22.7%)
	2	81	5 (6.2%; 0.8%-11.3%)	4 (4.9%; 0.1%-9.5%)
	3A	186	16 (8.7%; 4.5%-12.7%)	15 (8.3%; 4.2%-12.2%)
	3B	19	4 (21.1%; 0.4%-37.4%)	1 (5.3%; 0%-14.8%)
Patella, 34	1	30	1 (3.3%; 0%-9.5%)	0 (0%; 0%-0%)
	2	79	4 (5.1%; 0.1%-9.9%)	1 (1.3%; 0%-3.7%)
	3A	57	4 (7.1%; 0.1%-13.5%)	2 (3.6%; 0%-8.3%)

*Totals 902 fractures, 51 infections (5.7%), and 55 delayed unions or nonunions (6.1%).

and foot and ankle (Table 5). In all tables, the number of fractures for each OTA/AO fracture at the bone-plus-segment level and Gustilo-Anderson open fracture classifications are provided, along with cumulative point estimates and 95% CIs at 12 months for rates of SSI (superficial plus deep/organ space) and delayed union/nonunion. For pelvic fractures (OTA/AO classification 61s), the only injury category with >10 fractures was Gustilo-Anderon type 3A (n = 25). At 12 months, there were 8 SSIs, resulting in a cumulative SSI rate of 32% (95% CI, 11% to 48%) and no delayed unions/nonunions. Notably, there was only 1 open acetabular fracture in the data set, which had neither an SSI nor delayed union/nonunion. Figure 1 shows a heat map of 12-month SSI and delayed union/nonunion event rates.

Further Data Granularity

Appendix Tables S1 and S2 break down the OTA/AO fracture classification to include type-A, B, and C morphology categories for each anatomic region. They also provide a breakdown of SSI by superficial and deep/organ space and cumulative point estimates for both SSI and delayed union/nonunion, with 95% CIs at 3, 6, and 12 months. Finally, these Appendix tables contain all data, including those combinations of OTA/AO fracture and Gustilo-Anderson open

Table 4. Cumulative 12-Month Surgical Site Infection and Delayed Union/Nonunion Rates in Tibial Fractures*

OTA/AO Fracture Classification	Gustilo Classification	No. of Fractures	Infection Rate *(N [%; 95% CI])*	Delayed Union/Nonunion Rate *(N [%; 95% CI])*
Proximal tibia, 41	1	38	5 (13.2%; 1.7%-23.3%)	1 (2.6%; 0%-7.6%)
	2	79	9 (11.5%; 4.1%-18.2%)	5 (6.4%; 0.8%-11.7%)
	3A	93	13 (14.1%; 6.7%-21%)	9 (9.8%; 3.5%-15.8%)
	3B	22	8 (39.8%; 14.1%-57.9%)	4 (20%; 0.4%-35.7%)
Tibial shaft, 42	1	265	17 (6.5%; 3.5%-9.4%)	13 (5%; 2.3%-7.6%)
	2	468	59 (12.7%; 9.6%-15.7%)	32 (7%; 4.6%-9.3%)
	3A	485	81 (16.8%; 13.4%-20.1%)	48 (10%; 7.3%-12.7%)
	3B	156	53 (34.7%; 26.7%-41.9%)	28 (18.4%; 12%-24.4%)
	3C	10	5 (50%; 7.1%-73.1%)	2 (20%; 0%-41.3%)
Distal tibia, 43	1	136	19 (14%; 8%-19.7%)	9 (6.7%; 2.4%-10.9%)
	2	308	54 (17.9%; 13.4%-22.1%)	26 (8.7%; 5.5%-11.9%)
	3A	269	62 (23.2%; 17.9%-28%)	38 (14.4%; 10.1%-18.5%)
	3B	52	15 (29%; 15.5%-40.4%)	6 (11.8%; 2.5%-20.2%)

*Totals 2,381 fractures, 400 infections (16.8%), and 221 delayed unions or nonunions (9.3%).

Table 5. Cumulative 12-Month Surgical Site Infection and Delayed Union/Nonunion Rates in Foot and Ankle Fractures*

OTA/AO Fracture Classification	Gustilo Classification	No. of Fractures	Infection Rate *(N [%; 95% CI])*	Delayed Union/Nonunion Rate *(N [%; 95% CI])*
Malleolar segment, 44	1	87	6 (7%; 1.4%-12.2%)	1 (1.2%; 0%-3.4%)
	2	248	33 (13.6%; 9.2%-17.9%)	5 (2.1%; 0.3%-3.9%)
	3A	212	33 (15.9%; 10.7%-20.7%)	7 (3.4%; 0.9%-5.8%)
	3B	25	6 (24%; 5.3%-39%)	0 (0%; 0%-0%)
Distal fibula, 4F3	1	15	1 (6.7%; 0%-18.5%)	0 (0%; 0%-0%)
	2	27	3 (11.1%; 0%-22.2%)	1 (3.7%; 0%-10.6%)
	3A	25	6 (24%; 5.3%-39%)	1 (4%; 0%-11.4%)
Talus, 81	2	31	5 (16.1%; 2.1%-28.1%)	1 (3.2%; 0%-9.2%)
	3A	58	10 (17.2%; 6.9%-26.4%)	0 (0%; 0%-0%)
Calcaneus, 82	1	19	1 (5.3%; 0%-14.8%)	0 (0%; 0%-0%)
	2	34	3 (8.8%; 0%-17.9%)	2 (5.9%; 0%-13.5%)
	3A	31	6 (19.5%; 4.2%-32.3%)	1 (3.3%; 0%-9.5%)
Metatarsals, 87	1	12	0 (0%; 0%-0%)	0 (0%; 0%-0%)
	2	26	2 (7.7%; 0%-17.4%)	0 (0%; 0%-0%)
	3A	27	3 (11.1%; 0%-22.2%)	1 (3.7%; 0%-10.6%)
	3B	11	1 (9.1%; 0%-24.6%)	1 (10%; 0%-26.8%)
Phalanges, 88	1	14	1 (7.1%; 0%-19.7%)	0 (0%; 0%-0%)
	2	11	0 (0%; 0%-0%)	1 (10%; 0%-26.8%)

*Totals 913 fractures, 120 infections (13.1%), and 22 delayed unions or nonunions (2.4%).

fracture classifications with <10 fractures. A companion website containing SSI and delayed union/nonunion rates based on these data is available at https://nathan-ohara.github.io/ShinySSI/.

Appendix Tables S3 and S4 retabulate the data from Appendix Tables S1 and S2, showing numbers of events instead of numbers of fractures as the denominator. Of the 675 SSIs reported, 76.4% (516) were present by 3 months and 91.9% (620) were present by 6 months. Figure 2 shows the SSI and delayed union/nonunion event rates per time interval. Note that SSI diagnosis timing is likely close to the event timing because patients typically present with this problem acutely. However, delayed union/nonunion events resulted when the unplanned reoperation to promote bone healing occurred, and surgeons could have been monitoring fracture healing for some time prior.

Gustilo-Anderson Classification

Data were separately grouped by fracture severity, as determined by Gustilo-Anderson classification. Table 6 shows the number of fractures for each Gustilo-Anderson open fracture classification type and cumulative SSI (superficial plus deep/organ space), delayed union/nonunion, and amputation rates at 12 months, with 95% CIs. Appendix Tables S5A and S5B provide a breakdown of SSI, both superficial and deep/organ space, and delayed union/nonunion rates, respectively, with cumulative point estimates and 95% CIs at 3, 6, and 12 months.

Amputations

Appendix Table S6A provides a breakdown of amputation rates, with cumulative point estimates and 95% CIs at 3, 6, and 12 months. Amputations occur with greater frequency in Gustilo-Anderson type-3B and 3C fractures. Appendix Table S6B provides more granular detail on the 72 amputations.

Discussion

Open fractures continue to be problematic for patients, orthopaedic surgeons, society, and health-care systems. The purpose of the present study was to describe, in part, the burden of disease resulting from open fractures. The data include results from 69 sites practicing contemporary care of open fractures, providing estimates of SSI and delayed union/nonunion rates in open fractures using rigorously collected data with adjudicated outcomes. This study included a unique blend of population-level data with accurate prognostic, injury-specific details (e.g., bone and soft-tissue injury classifications and fixation methods). These data establish an envelope of SSI and delayed union/nonunion rates, which patients and surgeons may use as a basis to set expectations for recovery after open-fracture treatment.

The present data show similar rates of infection and delayed union/nonunion compared with prior large series of open fractures spanning several decades (Table 7). A recent review of >7,600 patients with >11,000 open tibial fractures from >4 decades (1977 to 2017) demonstrated no change in the rates of infection and nonunion[21]. The average rates of

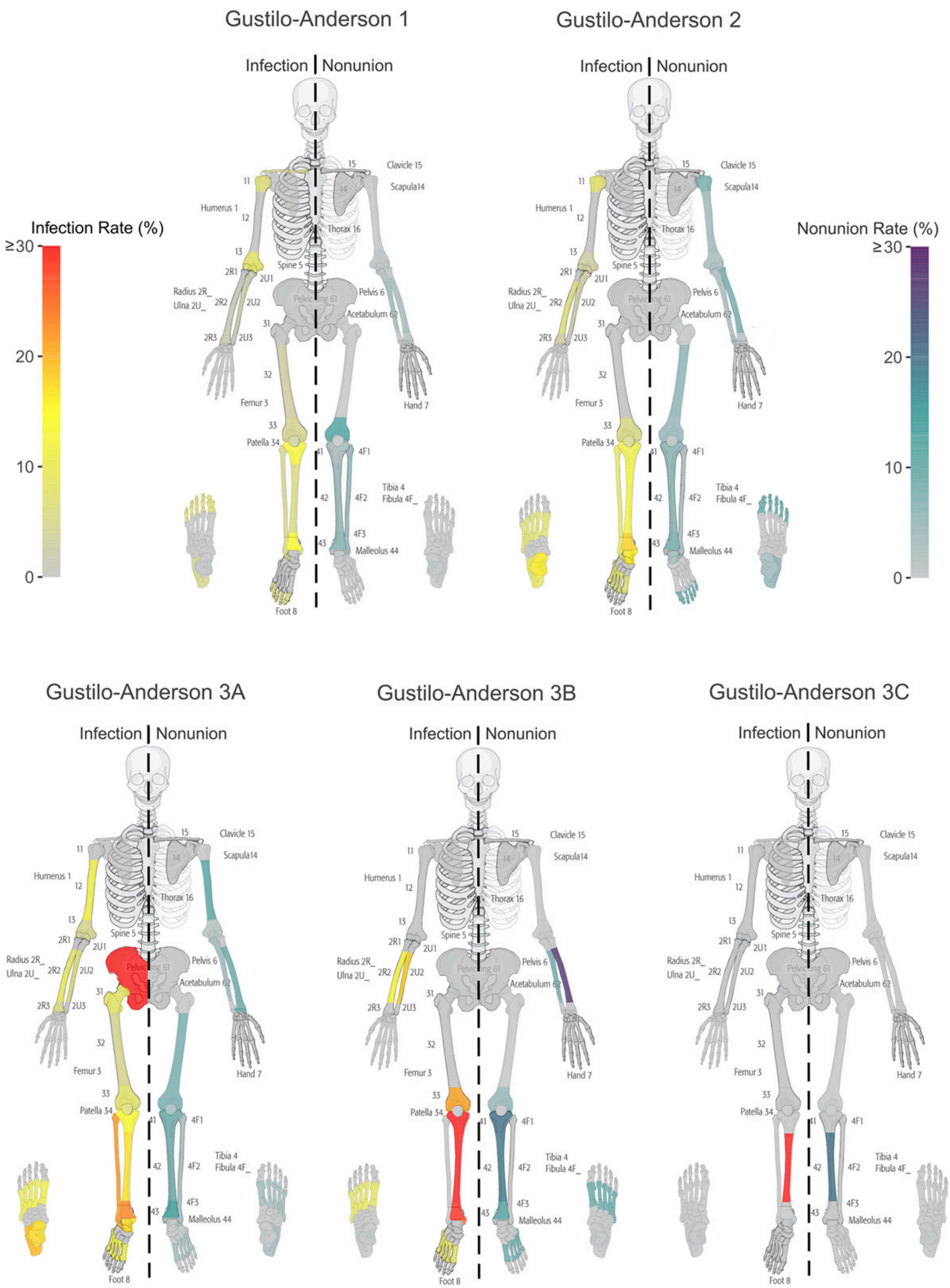

Fig. 1

Heat maps of 12-month infection rates (per the color scale at left) and nonunion rates (per the color scale at right) for each Gustilo-Anderson open fracture type. Each anatomical location is labeled according to the OTA/AO fracture classification. Data are based on Tables II through V, and combinations of OTA/AO fracture location and Gustilo-Anderson severity with <10 fractures are omitted.

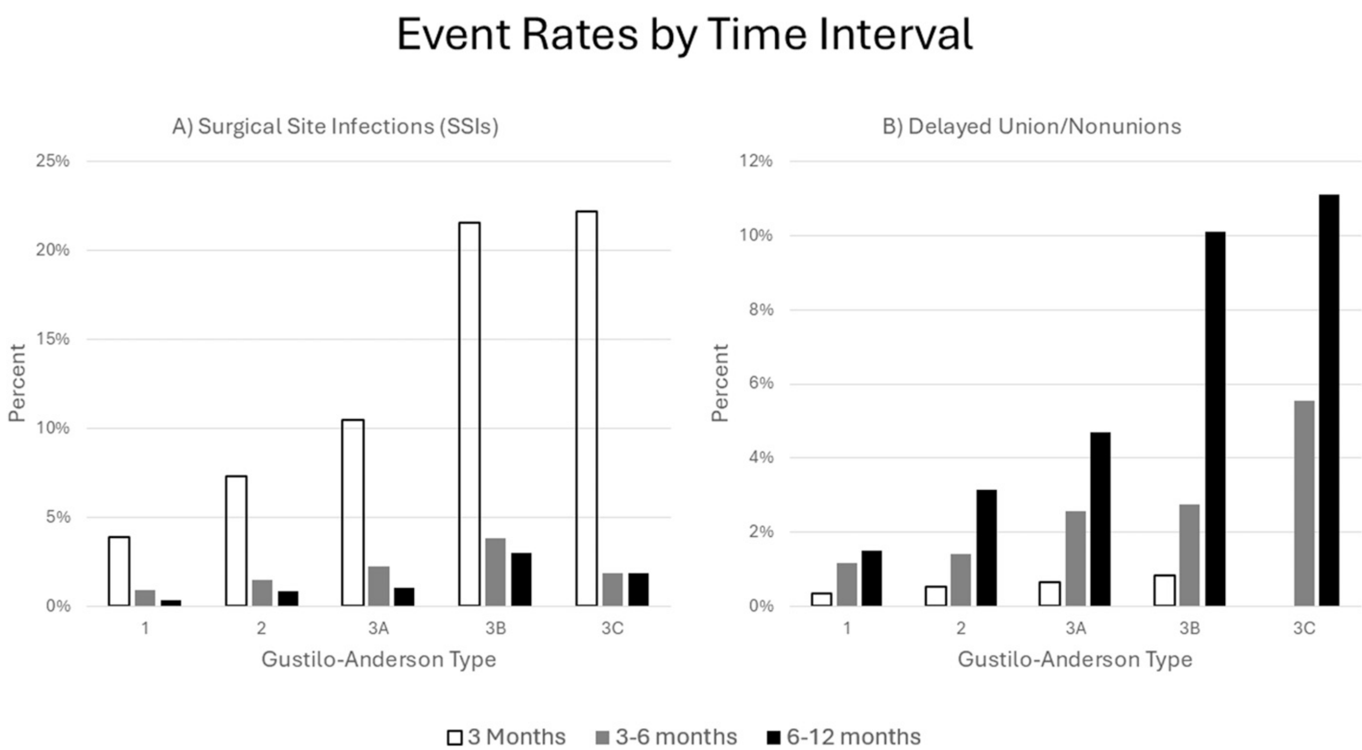

Fig. 2

Histogram of event rates by time interval for SSI (**Fig. 2-A**) and delayed union/nonunion (**Fig. 2-B**). SSIs were predominantly identified within the first 3 months, whereas delayed unions/nonunions were predominantly identified between 6 and 12 months. For each Gustilo-Anderson classification, the bars sum to the cumulative event rates provided in Appendix Tables S5A and S5B for SSI and delayed union/nonunion, respectively.

infection and nonunion were 18.3% and 14.1%, respectively. Another large review of >18,000 open fractures had an overall infection rate of 11.8%[12]. These 2 studies are limited by their retrospective nature, and neither provides a breakdown by OTA/AO fracture classification, although they provide Gustilo-Anderson open fracture classification data. A medium-sized prospective study of 739 open long-bone fractures found aggregate infection and nonunion rates of 13.4% and 17%, respectively, over 1-year follow-up[8]. That study reported both OTA/AO and Gustilo-Anderson classifications but only included long bones. The present study benefited from its prospective nature, contemporary patient cohorts, inclusion of more than just long-bone fractures, granularity that included both OTA/AO fracture and Gustilo-Anderson open fracture classification systems, and adjudicated outcomes obtained at several time points.

There were several notable findings worth mentioning from the present data. First, there was substantially less use of external fixation for definitive fracture treatment compared with early publications on open fractures[17,18]. Outside of many low- and middle-income countries, internal fixation is more commonly utilized now for definitive treatment of open fractures. Although the present study was not designed to determine if early internal fixation of open fractures affected the

Table 6. Cumulative 12-Month Surgical Site Infection, Delayed Union/Nonunion, and Amputation Rates by Gustilo Classification*

Gustilo Classification	No. of Fractures	Infection Rate *(N [%; 95% CI])*	Delayed Union/Nonunion Rate *(N [%; 95% CI])*	Amputation Rate *(N [%; 95% CI])*
1	1480	75 (5.1%; 4%-6.2%)	44 (3%; 2.1%-3.9%)	2 (0.1%; 0%-0.3%)
2	2079	199 (9.7%; 8.4%-11%)	105 (5.2%; 4.2%-6.1%)	4 (0.2%; 0%-0.4%)
3A	2063	283 (13.8%; 12.3%-15.3%)	163 (8%; 6.8%-9.2%)	34 (1.7%; 1.1%-2.2%)
3B	366	104 (28.9%; 24.1%-33.5%)	50 (14%; 10.3%-17.5%)	27 (7.5%; 4.7%-10.2%)
3C	54	14 (26.2%; 13.4%-37.1%)	9 (17%; 6.2%-26.5%)	5 (9.4%; 1.2%-16.9%)

*Totals 6,042 fractures, 675 infections (11.2%), 371 delayed unions or nonunions (6.1%), and 72 amputations (1.2%).

Table 7. Infection and Nonunion Rates Extracted from Large Series on Open Fractures Including All Gustilo-Anderson Types

Infection Rate *(%)*	Nonunion Rate *(%)*	Reference	Notes
11.2-24.3	12.3-17	21	Tibiae only
11.8	–	12	
13.4	17	8	Long bones only
2.4-52	13.6-16	17,18	Long bones only
5.1-28.9	3-17	Current	

rates of SSI or delayed union/nonunion, these complication rates at least did not appear to have increased. Perhaps definitive internal fixation is not fraught with as many complications as it was historically as a result of changes in open fracture management, such as efforts to provide more timely prophylactic antibiotic administration and the increased use of local antibiotics. Secondly, there was a predominance of plate-and-screw construct fixation for upper-extremity fractures and intramedullary nailing for lower-extremity shaft fractures, suggesting that our data are consistent with current practice experience and likely applicable to an average population of open fractures. Further supporting the generalizability of our data was the fact that only approximately 10% of SSI variation was attributable to treatment center. Thus, the findings should be transportable to other trauma centers in high-income countries treating a large population of open fractures.

Additionally, although the overall rates of infection at 12 months seemed similar between Gustilo-Anderson type-3B and 3C injuries, a close look at these rates reveals they are driven by the number of superficial infections in type-3B fractures. In contrast, Gustilo-Anderson type-3C fractures were predominantly associated with deep/organ-space infections. With respect to amputations, it bears mentioning again that acute amputations were not included, and the reported amputation rates are for those performed following attempted limb salvage. Lastly, we found that 76.4% of infections that occurred within 12 months were present at 3 months, and 91.9% were present at 6 months. This left approximately 8% of infections occurring between 6 and 12 months, similar to prior literature[29]. Based on these findings, and as previous research has suggested[30], we recommend that studies evaluating infection following open fractures should extend follow-up to at least 6 months and utilize either CDC[25] or fracture-related infection consensus[31] definitions. As delayed union/nonunion outcomes tend to occur later than surgical site infection, we would recommend a 12-month follow-up at minimum for this outcome.

The present study had several limitations. Foremost, our complication estimates were largely independent of individual demographics, patient comorbidities, and treatment choices. For example, we reported SSI rates without adjusting for the timeliness of prophylactic antibiotic administration. Although a specific treatment decision may alter the risk of infection in an individual patient, this large multicenter cohort represented the diversity of contemporary open fracture treatment. As a further example, there is no consensus definition of adequate fracture debridement, and the “aggressiveness” of debridement may affect infection and nonunion rates[32]. Open fractures from gunshot wounds were included, but only if the treating surgeon deemed a formal debridement to be warranted. Also, many categories of injuries had <10 fractures. A low number of fractures limits the accuracy of complication rate estimates. Finally, the external validity of the data beyond high-resource trauma centers participating in high-quality, prospective research is unknown; as such, these data may also be limited in their applicability to low- and middle-income countries.

Other limitations relate to classification reliability and outcomes definitions, as both could change calculated rates. We chose to utilize well accepted classifications for open fracture bone and soft-tissue injuries, although both the Gustilo-Anderson and OTA/AO classifications do not have perfect interrater or intra-rater reliability[33-37]. Classifications were obtained by pragmatic reporting according to the treating surgeon and were not adjudicated. With respect to the outcome definitions for SSI and delayed union/nonunion, the definitions we utilized have been generally considered standard, and all 3 studies were published in high-quality journals with extensive peer review of the individual trial protocols. All outcomes were adjudicated as part of the parent trials. Of note, the fracture-related infection consensus definition[31] was not available at the time of the FLOW study. For the PREP-IT studies, the fracture-related infection consensus definition was recorded for sensitivity analyses of the primary outcome, yielding a maximum 2% difference compared with the CDC definition.

In summary, the present study provided high-quality cumulative point estimates and 95% CIs for rates of SSI, delayed union/nonunion, and amputation at 3, 6, and 12 months, obtained from 3 studies published in the last decade, and included 6,042 open fractures stratified by both OTA/AO fracture location and Gustilo-Anderson open fracture severity. These data are useful for prognosis, research study design, informing public awareness, and policy implementation. These results show that despite current treatment approaches, rates of SSI and delayed union/nonunion remained high following treatment of open fractures and have not substantially improved from historical rates spanning several decades. The Gustilo-Anderson open fracture classification correlated with rates of both complications, ranging from 5.1% for SSI and 3.0% for delayed union/nonunion in Gustilo-Anderson type-1 fractures to 28.9% for SSI and 14.0% for delayed union/nonunion in type-3B fractures at 1 year. The SSI rate for Gustilo-Anderson type-3B open tibial shaft fractures was 34.7% at 1 year. Open fractures and their sequelae remain a high burden for society, and there may be opportunities to improve outcomes.

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/I841). ■

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