Timing and Management of Surgical Site Infections in Patients With Open Fracture Wounds: A Fluid Lavage of Open Wounds Cohort Secondary Analysis

Carlos Prada, MD, MHSc,[a] Francesc A. Marcano-Fernández, MD, PhD,[b] Emil H. Schemitsch, MD, FRCSC,[c] Sofia Bzovsky, MSc,[a] Kyle Jeray, MD,[d] Brad Petrisor, MD, MSc,[a] Mohit Bhandari, MD, PhD, FRCSC,[a,e] and Sheila Sprague, PhD[a,e] on behalf of the FLOW Investigators

Background: Many studies report on the incidence or prevalence of fracture-related surgical site infections (SSIs) after open fractures; however, few studies report on their timing and management outcomes. To address this gap, we used data from the Fluid Lavage of Open Wounds trial to determine timing of diagnosis, management, and resolution of SSIs.

Methods: All participants included in this analysis had an SSI after an open fracture. Participants were assigned to a group based on the type of SSI as follows: (1) those who developed a superficial SSI and (2) those who had either a deep or organ/space SSI. Descriptive statistics characterized the type, timing, and management of each SSI.

Results: Of the 2445 participants in the Fluid Lavage of Open Wounds trial, 325 (13.3%) had an SSI. Superficial SSIs were diagnosed significantly earlier [26.5 days, interquartile range (IQR) 12–48] than deep or organ/space SSIs (53 days, IQR 15–119). Of the 325 patients with SSIs, 174 required operative management and 151 were treated nonoperatively. For SSIs managed operatively, median time for infection resolution was 73 days (IQR 28–165), and on average, 1.73 surgeries (95% confidence interval 1.58–1.88) were needed during the 12 months follow-up. There were 24 cases whose SSIs were not resolved at the time of the final follow-up visit (12 months).

Conclusions: Based on this study's findings and in contradistinction to the Centers for Disease Control and Prevention guidelines, after an open fracture, superficial SSIs were diagnosed at one month and deep/organ/space SSIs at 2 months. This information can allow for earlier infection detection. In addition, the knowledge that approximately 50% of the SSIs in our study required a reoperation and 3 months at a minimum to resolve will assist orthopaedic surgeons when counseling their patients.

Key Words: bone infections, open fracture surgical site infection, osteomyelitis, timing of infections, secondary analysis, open fracture management, surgical site infection treatment

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

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INTRODUCTION

Complications after an open fracture are associated with significantly impaired health-related quality of life and increased costs to the health care system.[1–3] The incidence of surgical site infections (SSIs) after surgical treatment of an open fracture has been widely explored and reported in many previous studies.[4–8] It is known that the incidence of SSIs differs substantially depending on the severity of the injury (Gustilo–Anderson classification type), with a reported incidence of 0%–2%, 2%–10%, and 10%–50% for Gustilo–Anderson types I, II, and III, respectively.[4–8] Nevertheless, there are few published studies on open fractures regarding the timing of SSI diagnosis, its management, and the length of time it takes to reach resolution of the SSI.[2]

Most of the scarce existing data regarding these SSI characteristics address only certain subtypes of open fractures [9,10] or retrospectively review these data based on patients who suffer complications.[11–13] Having an understanding of the timing, management, and outcome of SSIs in open fracture patients is necessary to provide better prognostic information to patients, their families, and their treating surgeons. Specifically, it will shed light on the expected timing to diagnose and resolve an SSI after an open fracture. It will also help patients manage their expectations regarding time to recovery and number of surgeries required to treat an SSI. To address this gap in the literature, we used data from the Fluid Lavage of Open Wounds (FLOW) trial to determine the timing of diagnosis, management, and resolution of SSIs.[14]

METHODS

FLOW Trial

This is a secondary analysis of the FLOW trial data set. The FLOW trial was an international, blinded, randomized controlled trial that used a 2-by-3 factorial design to evaluate

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From the [a]Division of Orthopaedic Surgery, Department of Surgery, McMaster University, Hamilton, ON, Canada; [b]Orthopaedic Department, Parc Taulí Hospital Universitari, Institut D'Investigació i Innovació Parc Taulí I3PT, Universitat Autònoma de Barcelona, Sabadell, Spain; [c]Department of Surgery, University of Western Ontario, London, ON, Canada; [d]Department of Orthopaedic Surgery, Greenville Health System, Greenville, SC; and [e]Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, ON, Canada.

The authors report no conflict of interest.

Reprints: Carlos Prada, MD, MHSc, 293 Wellington St. N, Suite 110, Hamilton, ON L8L 8E7, Canada (e-mail: pradac@mcmaster.ca).

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the effects of high versus low versus very low (gravity flow) irrigation pressures and soap versus normal saline solutions on reoperation rates among patients with an open fracture.[14] This large cohort of open fracture patients provides an ideal opportunity to address relevant clinical questions in this population.

Patients enrolled in the FLOW study were followed for 12 months after their index surgery for an open fracture at 1, 2, and 6 weeks and 3, 6, 9, and 12 months. The primary end point was reoperation, defined as surgery that occurred within 12 months after the initial procedure to treat an infection at the operative site or near it, manage a wound-healing problem, or promote bone healing. Nonoperatively managed complications were considered as secondary end points. The FLOW study was approved by the ethics committees at the coordinating center, McMaster University (REB: 08-268) and at each participating center. All patients provided written informed consent before enrollment. The trial was registered at ClinicalTrials.gov (Clinical Trials Identification Number: NCT00788398).

Surgical Site Infections

A descriptive analysis was conducted to assess the timing from the index surgery to the first SSI diagnosis for open fracture patients enrolled in the FLOW trial. As per above, clinical sites documented reported SSIs at each follow-up visit, using date of diagnosis. The FLOW Adjudication Committee reviewed each reported infection to confirm that it met the criteria for an SSI. For patients experiencing multiple SSIs, only the earliest SSI was taken into account when determining the timing to diagnosis because the FLOW Adjudication Committee assumed that most of the subsequent SSIs were related to the initial infection that likely remained unresolved.

Two orthopaedic surgeons reviewed the clinical notes of all cases where an SSI was reported and categorized them independently according to the current SSI reporting criteria by the Centers for Disease Control and Prevention's (CDC) National Health care Safety Network (superficial, deep, or organ/space).[15] The 2 orthopaedic surgeons reviewed any disagreements pertaining to the categorization and solved them by mutual agreement. When assessing the SSIs, the reviewers did not consider the following time frame criteria as per the definitions: 30 days for a superficial SSI; 90 days for a deep or organ/space SSI. In addition, although the CDC definition includes superficial, deep, and organ/space as the 3 categories for an SSI, we decided to present the results in 2 categories as follows: (1) superficial and (2) deep or organ/space. This decision to group the deep and organ/space SSI categories together was based on the fact that most of the open fracture SSIs of the cohort occurred in the lower extremity, where it is challenging and somewhat inaccurate to distinguish between these 2 categories.

The management of SSIs was reported by the clinical site personnel and included nonoperative management (eg, antibiotics and dressings) and operative management. The FLOW Adjudication Committee reviewed each reported operation to ensure that it was correctly documented.

The length of time from the index surgery to SSI diagnosis was documented in days but was presented under time interval categories. The median time from the index surgery to first SSI diagnosis was calculated for the whole cohort and for the superficial and deep or organ/space categories.

Finally, we presented the median times from SSI diagnosis to its resolution for the whole cohort by superficial and deep or organ/space as well as by treatment type (operatively or nonoperatively managed). Infection resolution information was obtained from the Case report form were the attending surgeons documented the date the infection was resolved according to their clinical judgment. We also report the number of patients whose SSI resolved by time interval and the number of patients whose SSI was still ongoing at the last follow-up (12 months postfracture).

In addition, a descriptive analysis of the participants whose SSIs were treated operatively was conducted assessing the timing from the index surgery to the first SSI diagnosis, the time until they underwent their first reoperation, the timing until infection resolution, and the number of surgeries needed during the follow-up period.

Statistical Analysis

The data analyses were conducted using SPSS software (version 25). Variables were tested for normal distribution using the Shapiro–Wilk test. For normally distributed continuous variables, we used means as central tendency measures and 95% confidence intervals (CIs) as measures of spread. A χ^2 test was used for the analysis of categorical variables. A Mann–Whitney U test was performed to compare the 2 infection groups' median times to (1) first SSI diagnosis and (2) SSI resolution. For skewed data, we used medians as a central tendency measure and interquartile ranges (IQRs) as a measure of spread. P values were considered significant if they were <0.05.

RESULTS

Patient Characteristics

All 2445 patients from the FLOW trial were eligible and included in this secondary analysis. The follow-up data were obtained for 90% of the patients. From the 2445 patients with follow-up data, 325 had an SSI. The demographical data of the included participants are in Table 1. The majority of the patients were men (69.2%), in their 40s, who had an open fracture because of a motor-vehicle accident as a driver/passenger or pedestrian or a motorcycle accident (54.8%).

Surgical Site Infections Characteristics, Classification, and Timing

From the total of 325 SSIs, 169 (52.0%) of the SSIs were superficial, 151 (46.5%) were deep or organ/space, and 5 (1.5%) were nonclassifiable. The overall SSI incidence was 13.3% (325 of the 2445). Most infections occurred in participants with lower extremity open fractures, that is, 89.2% (290 of the 325). Twelve percent (39) of the SSIs occurred in participants with Gustilo type I fractures, 33.8%

TABLE 1. Patient Characteristics and Surgical and Perioperative Management

	Superficial SSI Operatively Treated (N = 50	Superficial SSI Nonoperatively Treated (N = 119)	Deep or Organ/Space SSI Operatively Treated (N = 124)	Deep or Organ/Space SSI Nonoperatively Treated (N = 27)	SSI Cohort (N = 325)*
Age, mean (SD)	N = 50	N = 119	N = 124	N = 27	N = 325
	47.6 (17.5)	47.0 (17.6)	45.3 (17.9)	39.3 (14.0)	45.8 (17.4)
Gender, n (%)	N = 50	N = 119	N = 124	N = 32	N = 325
Male	33 (66.0)	88 (73.9)	86 (69.4)	19 (70.4)	230 (70.8)
Female	17 (34.0)	31 (26.1)	38 (30.6)	8 (29.6)	95 (29.2)
Current smokers, n (%)	N = 49	N = 119	N = 124	N = 27	N = 324
	17 (34.7)	39 (32.8)	116 (33.9)	15 (55.6)	116 (35.8)
Diabetic, n (%)	N = 50	N = 119	N = 124	N = 27	N = 325
Yes	4 (8.0)	10 (8.4)	16 (12.9)	4 (14.8)	35 (10.8)
Insulin dependent	1 (2.0)	2 (1.7)	5 (4.0)	1 (3.7)	9 (2.8)
Noninsulin dependent	3 (6.0)	8 (6.7)	11 (8.9)	3 (11.1)	26 (8.0)
No	46 (92.0)	109 (91.6)	108 (87.1)	23 (85.2)	290 (89.2)
Current recreational drug use, n (%)	N = 50	N = 119	N = 123	N = 27	N = 324
	0 (0)	3 (2.5)	1 (0.8)	1 (3.7)	5 (1.5)
Mechanism of injury, n (%)	N = 50	N = 119	N = 124	N = 27	N = 325
MVA (driver/passenger)	7 (14.0)	29 (24.4)	35 (28.2)	7 (25.9)	79 (24.3)
MVA (pedestrian)	5 (10.0)	14 (11.8)	10 (8.1)	2 (7.4)	31 (9.5)
Motorcycle accident	8 (16.0)	19 (16.0)	21 (16.9)	7 (25.9)	55 (16.9)
ATV	1 (2.0)	2 (1.7)	3 (2.4)	1 (3.7)	9 (2.8)
Crush injury	5 (10.0)	5 (4.2)	7 (5.6)	2 (7.4)	21 (6.5)
Fall from standing	10 (20.0)	15 (12.6)	11 (9.2)	0 (0)	36 (11.1)
Fall from height	9 (18.0)	22 (18.5)	30 (24.2)	3 (11.1)	64 (19.7)
Twist	1 (2.0)	1 (0.8)	0 (0)	0 (0)	2 (0.6)
Direct trauma (penetrating)	0 (0)	6 (5.0)	3 (2.4)	1 (3.7)	10 (3.1)
Direct trauma (blunt)	4 (8.0)	5 (4.2)	3 (2.4)	4 (14.8)	16 (4.9)
Explosion	0 (0)	1 (0.8)	0 (0)	0 (0)	1 (0.3)
Bicycle accident	0 (0)	0 (0)	1 (0.8)	0 (0)	1 (0.3)
Major concomitant trauma, n (%)	N = 50	N = 119	N = 124	N = 27	N = 325
Head injury	2 (4.0)	9 (8.4)	6 (4.8)	0 (0)	17 (5.2)
Chest injury	1 (2.0)	4 (3.4)	14 (11.3)	3 (11.1)	22 (6.8)
Intra-abdominal injury	1 (2.0)	3 (2.5)	4 (3.2)	2 (7.4)	10 (3.1)
Any of the above	2 (2.0)	15 (12.6)	21 (16.9)	5 (18.5)	43 (13.2)
Gustilo type, n (%)	N = 50	N = 119	N = 124	N = 27	N = 325
Type I	7 (14.0)	18 (15.1)	12 (9.7)	1 (3.7)	39 (12.0)
Type II	19 (38.0)	50 (42.0)	33 (26.6)	8 (29.6)	110 (33.8)
Type IIIA	15 (30.0)	35 (29.4)	51 (41.1)	10 (37.0)	113 (34.8)
Type IIIB	9 (18.0)	16 (13.4)	28 (22.6)	8 (29.6)	63 (19.4)
Location of fracture, n (%)	N = 50	N = 119	N = 124	N = 27	N = 325
Upper extremity	3 (6.0)	13 (10.9)	15 (12.1)	4 (14.8)	35 (10.8)
Lower extremity	47 (94.0)	106 (89.1)	109 (87.9)	23 (85.2)	290 (89.2)
Preparation solution received in emergency department	N = 49	N = 118	N = 124	N = 27	N = 323
Iodine	7 (14.3)	21 (17.8)	15 (12.1)	5 (18.5)	48 (14.9)
Alcohol	2 (4.1)	2 (1.7)	3 (2.4)	0 (0)	7 (2.2)
Chlorhexidine	3 (6.1)	4 (3.4)	5 (4.0)	1 (3.7)	13 (4.0)
Others	0 (0)	1 (0.8)	0 (0)	0 (0)	1 (0.3)

TABLE 1. (*Continued*) Patient Characteristics and Surgical and Perioperative Management

	Superficial SSI Operatively Treated (N = 50	Superficial SSI Nonoperatively Treated (N = 119)	Deep or Organ/Space SSI Operatively Treated (N = 124)	Deep or Organ/Space SSI Nonoperatively Treated (N = 27)	SSI Cohort (N = 325)*
None	39 (79.6)	93 (78.8)	104 (81.1)	22 (81.1)	262 (81.1)
Hours to first incision from injury, median (IQR)	N = 49	N = 118	N = 122	N = 27	N = 321
Gustilo type I	9.9 (6.2–14)	8.3 (6.2–14.4)	7.8 (5.1–13.4)	6.2 (4.7–8.5)	8.0 (5.8–13.1)
Gustilo type II	11.0 (9.2–18)	13.5 (8.3–17.8)	10.8 (6.4–16.8)	10.7 (9.5–11.9)	11.3 (8.0–17.9)
Gustilo type IIIA	11.0 (8–17.8)	8.8 (6.6–15.1)	8.9 (6.2–15.5)	6.1 (4.9–8.7)	9.0 (6.3–15.6)
Gustilo type IIIB	8.6 (6.8–11.3)	7.3 (5.1–9.8)	7.6 (4.9–11.0)	6.2 (2.9–7.5)	7.6 (5.0–11.0)
	3.7 (3.2–7.7)	6.0 (4.6–7.4)	5.7 (4.2–8.3)	5.7 (4.7–8.7)	5.7 (4.2–8.2)
Surgical preparation solution, n (%)	N = 50	N = 117	N = 123	N = 27	N = 322
Iodine or povidone-iodine	22 (44.0)	60 (51.3)	62 (50.4)	17 (63.0)	165 (51.2)
Chlorhexidine	24 (48.0)	54 (46.2)	54 (43.9)	10 (37.0)	143 (44.4)
Alcohol	5 (10.0)	21 (17.9)	26 (21.1)	0 (0)	53 (16.5)
Others	7 (14.0)	8 (6.8)	9 (7.3)	3 (11.1)	27 (8.4)
Solution used for irrigation, n (%)	N = 50	N = 119	N = 124	N = 27	N = 325
Castile soap	30 (60.0)	56 (47.1)	61 (49.2)	13 (48.1)	163 (50.2)
Saline	20 (40.0)	63 (52.9)	63 (50.8)	14 (51.9)	162 (49.8)
Definitive fixation, n (%)	N = 50	N = 119	N = 124	N = 27	N = 325
Intramedullary nail	23 (46.0)	48 (40.3)	40 (32.3)	8 (29.6)	121 (37.2)
External fixator	0 (0)	3 (2.5)	3 (2.4)	0 (0)	6 (1.8)
Plate	21 (42.0)	51 (42.9)	67 (54.0)	14 (51.9)	155 (47.7)
Other internal fixations	6 (12.0)	17 (14.3)	14 (11.3)	5 (18.5)	43 (13.2)
Antibiotic beads or antibiotic osteobiologics used, n (%)	N = 50	N = 119	N = 123	N = 27	N = 324
Yes	4 (8.0)	4 (3.4)	15 (12.2)	1 (3.7)	24 (7.4)
No	46 (92.0)	115 (96.7)	108 (87.8)	26 (96.3)	300 (92.6)

ATV, all-terrain vehicle; MVA, motor-vehicle accident.
*The total FLOW SSI cohort numbers are the sum of the numbers from the superficial, deep, or organ/space SSI cohort and the 5 patients who had a nonclassifiable infection.

(110) occurred in type II fractures, and 54.2% (176) of the SSIs occurred in type III fractures [34.8% (113) type IIIA and 19.4% (63) type IIIB]. The incidence of SSIs per Gustilo–Anderson fracture classification type in the FLOW trial cohort was of 6.1% (39 of the 639) for participants with type I fractures, 12.2% (110 of the 899) for participants with type II fractures, and 20% (176 of the 881) for participants with type III fractures [17.4% (113 of the 649) SSI incidence in participants with type IIIA fractures and 27.2% (63 of the 232) in participants with type IIIB fractures].

The median time to SSI diagnosis was 31 days (IQR 13–79). The median time from the index surgery to superficial SSI diagnosis was 26.5 days (IQR 12–48), and the median time to deep or organ/space SSI diagnosis was 53 days (IQR 15–119) with a significant difference between groups ($P < 0.001$) (Figure 1). Ninety-six participants (56.8%) had their superficial SSIs diagnosed within 30 days of their index surgery (Table 2); therefore, 73 patients (43.2%) in the superficial SSI group would not have been included if the CDC[15] time-based definition of 30 days was taken into account. Similarly, 103 patients (68.2%) with deep or organ/space SSIs were diagnosed within the 90-day window, and 48 patients (31.8%) patients would not have been included if the CDC time frame criteria would have been used. [15]

Management of Surgical Site Infections

One hundred fifty-one participants (46.5%) had their SSI managed nonoperatively. From this group, 119 had a superficial SSI (78.8%). On the other hand, 174 participants (53.5%) had one or more reoperations to treat an infection at the operative site or contiguous to it. In this group, the superficial SSIs represented only 28.7% (50 participants)

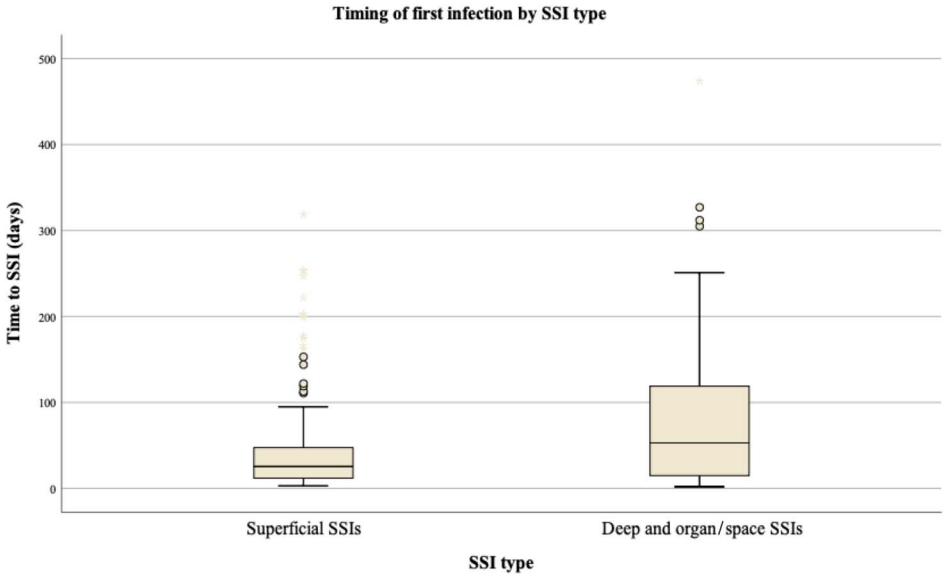

FIGURE 1. Timing of infection by the surgical site infection group. **Editor's Note**: A color image accompanies the online version of this article.

while the deep or organ/space were the majority (71.3%, 124 participants). These patients needed on average 1.73 reoperations (95% CI 1.58–1.88) during the follow-up to treat their SSI. The patients who underwent reoperation because of a deep or organ/space SSI had significantly more procedures [1.88 (1.72–2.04) vs. 1.36 (1.27–1.45)] than the ones who had a superficial SSI ($P < 0.001$). The median time until SSI diagnosis for the group of patients who underwent a reoperation was 33 days (IQR 14–97.75).

The majority of patients (58.6%) underwent their first reoperation to treat an SSI during the first 90 days after the index surgery. The details concerning the timing of reoperations by type of SSIs can be seen in Figure 2. The mean time to the first reoperation to treat an infection at the operative site or contiguous to it was of 91.1 days (95% CI 78.9–103.4). When analyzed by group, it was of 117.8 days (95% CI 92.0–143.7) and 80.4 days (95% CI 67.0–93.8) for the superficial and the deep or organ/space groups, respectively ($P < 0.001$).

Resolutions of Surgical Site Infections

Excluding the 24 cases whose SSIs were not resolved at the time of the final follow-up visit (6 cases of superficial SSIs and 17 cases of deep or organ/space SSIs and 1 case nonclassifiable), timing until resolution significantly differed between groups ($P < 0.001$). Overall, the median time to SSI resolution was 49 days (IQR 17–115). For the superficial and the deep or organ/space SSI groups, the median times to SSI resolution were 28 days (IQR 13–73.5) and 76.5 days (IQR 39–166), respectively. When we analyze this by type of management, median times to SSI resolution for the nonoperatively and operatively managed group were 34.5 days (IQR 11–73) and 73 days (IQR 28–166), respectively ($P < 0.001$).

Of the 174 participants who underwent a reoperation for an SSI, infection resolution status was unknown in 3 cases as a result of being lost to follow-up and 18 (10.3%) were still under SSI treatment at the final follow-up visit. For the remaining 153 participants, the median times until the infection was resolved grouped by type of infection were 41 days (IQR 15.5–151) for the superficial SSI group and 84 days (IQR 44–171) for the deep SSI and organ/space SSI group. These median times differed significantly ($P < 0.001$). Extensive details about the number and median time to the first reoperation categorized by type of SSI can be found in Table 3.

From the 24 cases whose SSIs were not resolved at the final follow-up visit, (1) 8 were scheduled to undergo a reoperation (3 amputations, 2 bone transport procedures, 2 bone grafting and implant exchange procedures, and one unspecified procedure), (2) 6 were still under antibiotic treatment (4 waiting for infectious disease follow-up appointments, and for 2 cases, the clinical information was unclear as to whether antibiotics would be given until suppression, for a certain amount of time, or until achieving bone healing), and (3) 10 participants were either lost during follow-up after their infection (8) or did not have enough information available in their clinical records (2) about their infection treatment.

DISCUSSION

The FLOW trial was conducted to analyze the primary end point of reoperation within 12-months after the index surgery for promotion of wound or bone healing or treatment of an open fracture wound infection. This secondary analysis intended to characterize the timing and type of SSIs in this cohort of patients as well as identify the timing and number of reoperations patients needed because of an SSI during the 12-month follow-up. We also evaluated the average time until infections were resolved since their diagnosis.

One of the findings of our analysis was that in our cohort, patients having an SSI after an open fracture wound were diagnosed around 1 month after the index surgery was performed (31 days, IQR 13–79) and, as anticipated, the

TABLE 2. Timing of First Surgical Site Infection Diagnosis

Type of Surgical Site Infection	Timing of Infection Diagnosis in Days, N = 320* (%)			
	<30 d	30–90 d	>90 d	Total
Superficial	96 (56.8)	52 (30.8)	21 (12.4)	169
Deep or organ/space	58 (38.4)	45 (29.8)	48 (31.8)	151
Total	154 (48.1)	97 (30.3)	69 (21.6)	320

*This table shows the timing for 320 patients from the total 325 participants who suffered an SSI because 5 patients had an SSI that was nonclassifiable.

timing of these infections was statistically different for the superficial and the deep and organ/space SSI groups. The median time to diagnose a deep or organ/space SSI was approximately twice the time for a superficial SSI after the index surgery. One hundred fifty-one participants of the 325 patients (46.5%) who developed an SSI were treated nonoperatively. This percentage is consistent with what has been already published by other authors.[2,16]

The overall SSI incidence of the FLOW trial (13.3%) is consistent with the published literature.[17] However, we observed a slightly increased incidence of SSIs for Gustilo type I and II open fractures compared with what is considered to be the standard rates (0%–2% for type I and 2%–10% for type II) reported in the scientific literature. The FLOW trial included a high proportion of lower extremity fractures (nearly 70% of the participants included in the FLOW trial and almost 90% of all the SSIs), which may explain this difference. In addition, the FLOW trial achieved high follow-up rates compared with previous studies. This may also help to explain the higher incidence of SSI.

Regarding reoperations because of SSI, the median time until diagnosis in the group who underwent a reoperation to treat an SSI at the operative site or contiguous to it was 33 days (IQR 14.75–106.25) after the index surgery. As expected, the median timing for SSI diagnosis because of deep or organ/space SSIs was significantly later than for superficial SSIs. Conversely, the time until the first reoperation was performed because of an SSI was higher for the participants who had a superficial SSI compared with those who had a deep or organ/space SSI. Probably, this was because some participants with superficial SSIs were treated conservatively initially, and only after this option failed were they booked for surgery. Surprisingly, although this information seems reasonable, we did not find previous literature addressing this topic. Therefore, the information gathered from our analysis could be useful during doctor–patient communication and the decision-making process when a patient experiences an SSI after an open fracture.

When suffering an SSI that required surgical treatment, the number of reoperations needed during the follow-up period was, on average, 1.73 surgeries (95% CI 1.58–1.88). The median time until the infection was solved for participants requiring reoperations to treat their SSIs was between 2 and 3 months (73 days, IQR 28–165), with the time being more than twice as long for the deep or organ/space SSI group as compared to the superficial SSI group. Unfortunately, we know that the calculated time until SSI resolution could be significantly underestimated in our cohort because there were 24 patients whose SSIs were not resolved at the time of their final 12-month follow-up visit. This is particularly relevant for the deep and organ/space SSI group because 17 participants (11.3%) had their infection ongoing at this visit. As stated previously, in this analysis we excluded those cases when calculating how much time it took for the infections to be resolved. Nevertheless, the median times will be at least the presented ones, or probably higher, because they could be underestimated. This information could help health care professionals alert patients about their prognosis and expected outcomes in the future and increase the awareness for potentially earlier infection diagnosis. As far as we know, there are currently no studies that have addressed the timing of

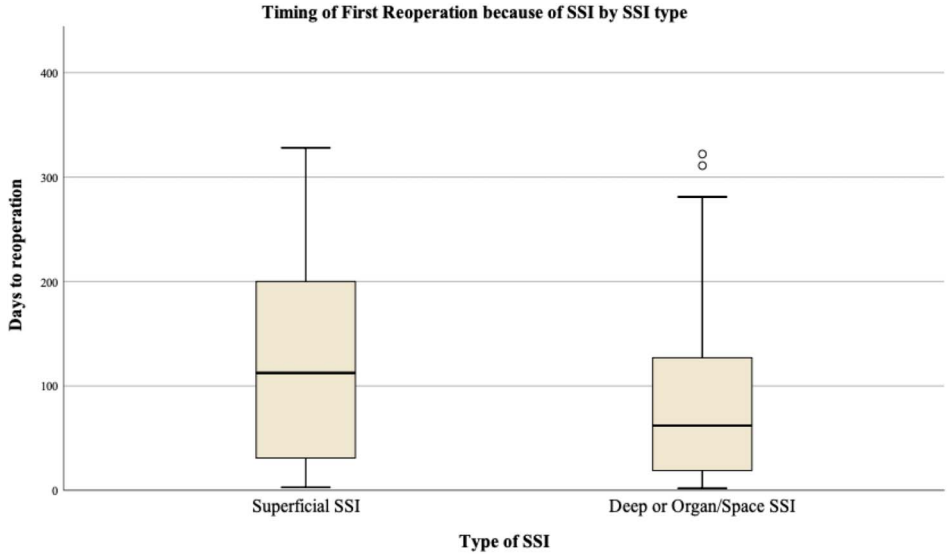

FIGURE 2. Timing of first reoperation because of surgical site infection by infection type. **Editor's Note**: A color image accompanies the online version of this article.

TABLE 3. Mean Number and Timing Until First Reoperation Because of SSI and Infection Resolution During the Follow-up by Type of SSIs

Type of SSI	Number of Patients (% of Total SSI Patients Who Underwent a Reoperation)	Mean Number of Reoperations (95% CI)	Mean Time to First Reoperation Because of Infection in Days (95% CI)	Median Time until Infection Resolution (Interquartile Range)
Superficial	50 (28.7)	1.36 (1.27–1.45)	117.8 (92.0–143.7)	41 (15.5–151)
Deep and organ/space	124 (71.3)	1.88 (1.72–2.04)	80.4 (67.0–93.8)	84 (44–171)
Total	174	1.73 (1.58–1.88)	91.1 (78.9–103.4)	73 (28–165)

infection and reoperations because of infection in open fracture patients.

The principal strengths of this study are its prospective design, its large sample size, and the robust and frequent data collection within the 12-month follow-up that allowed for precise timely documentation of SSI diagnoses. The multicentre nature of this trial provided us with a significant and diverse sample size increasing the external validity of our results and allowing us to gather new information about the following: (1) the timing and number of SSIs, (2) the timing and number of reoperations needed to resolve an SSI, and (3) the time taken until SSI resolution, when it occurs after an open fracture.

It is also important to state that the CDC SSI time frame definition has evolved over the course of time.[18] The FLOW Adjudication Committee did not use the current time frame criteria suggested by the CDC to categorize an SSI as superficial, deep, or organ/space because bone infections have some particularities that can delay SSI presentation. If the Adjudication Committee would have used the CDC SSI time frame definition, 72 (42.9%) patients in the superficial SSI group would have been included instead in the deep SSI group. In addition, 69 patients (21.2%) whose SSIs occurred after 90 days would not have fallen under one of the SSI categories. The FLOW investigators recognized the timing limitations of the CDC criteria and chose to ignore them. They still used the CDC criteria to classify SSIs as superficial, deep, and organ/space but did not consider the timing of the SSI occurrence for the purposes of classification. It is possible that current CDC guidelines do not fulfill the time frame surveillance required for fracture-related infections and orthopaedic surgeons' needs in this regard. Moreover, as previously disclosed, surgeons may find it challenging to distinguish between deep and organ/space infections using the CDC criteria; therefore, we collapsed these categories for our analysis. We also acknowledge that it may be difficult to classify infections as superficial or deep/organ/space in specific anatomic areas, such as the ankle or leg. In such cases, the signs and symptoms present were used to determine between superficial and deep/organ/space infections. This controversy is supported in the literature. In fact, only a few randomized controlled trials in orthopaedics have used a clear definition for fracture-related infections as a systematic review showed.[19] Future work should be directed toward the development of standardized definitions of fracture-related infections. Another limitation of our study is that the FLOW trial did not follow participants beyond 12 months or until their SSI was resolved because there were certain cases where their infections were still ongoing at the final follow-up visit (24 cases). In addition, SSI resolution was determined using the clinical judgment of the attending orthopaedic surgeon. Some SSIs may have seemed to be resolved; however, it is possible that some bone infections are only suppressed and potentially lie dormant for years.[20] Finally, considering the natural history of this condition, following participants for longer than 12 months would have been desirable to draw more precise conclusions regarding the number of reoperations needed after an SSI for an open fracture and what the expected times are to achieve infection control.

CONCLUSIONS

Knowing that after an open fracture and in contradistinction to the CDC guidelines, superficial SSIs and deep or organ/space SSIs are normally diagnosed around one and 2 months, respectively, can help increase surgeons' and health care professionals' awareness of potential infection during this period to allow earlier detection. In addition, knowing that around half of the SSIs underwent a reoperation because of infection, needed 2 procedures and took almost 3 months to resolve will help orthopaedic surgeons to counsel their patients who develop an SSI after an open fracture.

REFERENCES

1. Parker B, Petrou S, Achana F, et al. Economic outcomes associated with deep surgical site infection in patients with an open fracture of the lower limb. *Bone Joint J.* 2018;100B:1506–1510.
2. Doshi P, Gopalan H, Sprague S, et al. Incidence of infection following internal fixation of open and closed tibia fractures in India (INFINITI): a multi-centre observational cohort study. *BMC Musculoskelet Disord.* 2017;18:156–210.
3. Whitehouse JD, Friedman ND, Kirkland KB, et al. The impact of surgical-site infections following orthopedic surgery at a community hospital and a university hospital: adverse quality of life, excess length of stay, and extra cost. *Infect Control Hosp Epidemiol.* 2002;23:183–189.
4. Gustilo RB, Anderson J. Prevention of infection in the treatment of one thousand and twenty-five open fractures of long bones: retrospective and prospective analyses. *J Bone Joint Surg Am.* 1976;58:453–458.
5. Gustilo RB, Mendoza RM, Williams DN. Problems in the management of type III (severe) open fractures: a new classification of type III open fractures. *J Trauma.* 1984;24:742–746.
6. Gustilo RB, Gruninger RP, Davis T. Classification of type III (severe) open fractures relative to treatment and results. *Orthopedics.* 1987;10:1781–1788.
7. Patzakis MJ, Harvey JP, Ivler D. The role of antibiotics in the management of open fractures. *J Bone Joint Surg Am.* 1974;56:532–541.
8. Patzakis MJ, Wilkins J. Factors influencing infection rate in open fracture wounds. *Clin Orthop Relat Res.* 1989:36–40.

9. Redfern J, Wasilko SM, Groth ME, et al. Surgical site infections in patients with type 3 open fractures. *J Orthop Trauma.* 2016;30:415–419.
10. Hu R, Ren Y-J, Yan L, et al. Analysis of staged treatment for Gustilo–Anderson IIIB/C open tibial fractures. *Indian J Orthop.* 2018;52:411–417.
11. Aytaç S, Schnetzke M, Swartman B, et al. Posttraumatic and postoperative osteomyelitis: surgical revision strategy with persisting fistula. *Arch Orthop Trauma Surg.* 2014;134:159–165.
12. Ren M, Liang W, Wu Z, et al. Risk factors of surgical site infection in geriatric orthopedic surgery: a retrospective multicenter cohort study. *Geriatr Gerontol Int.* 2019;19:213–217.
13. Chen AT, Vallier HA. Noncontiguous and open fractures of the lower extremity: epidemiology, complications, and unplanned procedures. *Injury.* 2016;47:742–747.
14. FLOW Investigators, Bhandari M, Bhandari M, Jeray KJ, et al. A trial of wound irrigation in the initial management of open fracture wounds. *N Engl J Med.* 2015;373:2629–2641.
15. Centers for Disease Control and Prevention (CDC). *Surgical Site Infection (SSI) Event*. 2017. Available at: https://www.cdc.gov.
16. Leaper D, Fry DE, Assadian O. Perspectives in prevention and treatment of surgical site infection—a narrative review of the literature. *Wounds.* 2013;25:313–323.
17. Oliveira PR, Carvalho VC, da Silva Felix C, et al. The incidence and microbiological profile of surgical site infections following internal fixation of closed and open fractures. *Rev Bras Ortop*. 2016;51:396–399.
18. Control Centre for Disease. *Procedure-associated Module SSI Surgical*. 2019:20–31. Available at: https://www.cdc.gov.
19. Metsemakers WJ, Kortram K, Morgenstern M, et al. Definition of infection after fracture fixation: a systematic review of randomized controlled trials to evaluate current practice. *Injury.* 2018;49:497–504.
20. Prada C, Tanner SL, Marcano-Fernández FA, et al. How successful is antibiotic treatment for superficial surgical site infections after open fracture? A Fluid Lavage of Open Wounds (flow) cohort secondary analysis. *Clin Orthop Relat Res.* 2020.