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Change in Gustilo-Anderson classification at time of surgery does not increase risk for surgical site infection in patients with open fractures: A secondary analysis of a multicenter, prospective randomized controlled trial

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Abstract

Introduction: Open fractures represent a major source of morbidity. Surgical site infections (SSIs) after open fractures are associated with a high rate of reoperations and hospitalizations, which are associated with a lower health-related quality of life. Early antibiotic delivery, typically chosen through an assessment of the size and contamination of the wound, has been shown to be an effective technique to reduce the risk of SSI in open fractures. The Gustilo-Anderson classification (GAC) was devised as a grading system of open fractures *after* a complete operative debridement of the wound had been undertaken but is commonly used *preoperatively* to help with the choice of initial antibiotics. Incorrect preoperative GAC, leading to less aggressive initial management, may influence the risk of SSI after open fracture. The objectives of this study were to determine (1) how often the GAC changed from the initial to definitive grading, (2) the injury and patient characteristics associated with increases and decreases of the GAC, and (3) whether a change in GAC was associated with an increased risk of SSI.

Methods: Using data from the FLOW trial, a large multicenter randomized study, we used descriptive statistics to quantify how frequently the GAC changed from the initial to definitive grading. We used regression models to determine which injury and patient characteristics were associated with increases and decreases in GAC and whether a change in GAC was associated with SSI.

Results: Of the 2420 participants included, 305 participants had their preoperative GAC change (12.6%). The factors associated with upgrading the GAC (from preoperative score to the definitive assessment) included fracture sites other than the tibia, bone loss at presentation, width of wound, length of wound, and skin loss at presentation. However, initial misclassification of type III fractures as type II fractures was not associated with an increased risk of SSI ($P = 0.14$).

Conclusions: When treating patients with open fracture wounds, surgeons should consider that 12% of all injuries may initially be misclassified when using the GAC, particularly fractures that have bone loss at presentation or those located in sites different than the tibia. However, even in misclassified fractures, it did not seem to increase the risk of SSI.

Keywords: open fracture, trauma, randomized trial, secondary analysis, surgical site infection, antibiotics

The authors report no conflict of interest.

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THE FLOW Investigators are listed at Appendix 1.

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1. Introduction

Open fractures represent a major source of mortality and morbidity across the world.[1,2] Moreover, complications after open fractures are common and are often associated with surgical site infections (SSIs).[3,4] Patients who have suffered from a SSI after an open fracture report a quality of life similar to those who have suffered from a major cardiac event.[5,6] Administration of appropriate antibiotics within 60 minutes of injury, based on fracture severity defined by the Gustilo-Anderson classification (GAC), has reliably been shown to reduce the incidence of postoperative complications due to infection.[7,8]

The GAC, first developed in 1969[9] (and modified to its current version in 1984[10]), remains the standard for evaluation of the skin and soft-tissue injuries associated with open fractures. Any open fracture of the extremity can be graded from I to III based on the length of the open wound, the amount of energy that produces the trauma, and the degree of soft-tissue injury and contamination. Although the GAC was developed as a tool to be applied after irrigation and debridement of an open fracture was completed and a definitive intraoperative evaluation of skin, soft-tissue, and periosteal injury can be performed, a preliminary GAC is also given to patients when they first present after their traumatic injury.[11] This initial GAC is often the definitive injury characteristic that guides antibiotic prophylaxis,[12] although not originally designed for this purpose.

Furthermore, given that the preoperative GAC drives initial antibiotic use, an incorrect preoperative GAC (when compared with the definitive GAC) may lead to inappropriate antibiotic administration in the immediate hours after the open injury, the most crucial period of open fracture care. With inappropriate antibiotic administration, there is a theoretical increase in the risk of both deep and superficial SSIs. This potential relationship between incorrect GAC and the risk of SSI has not yet been studied.

Moreover, no formal statistical analysis has evaluated how reliably a preoperative GAC predicts the definitive classification once formal debridement is completed, or what may predict a change in score. An understanding of how often the preoperative GAC correctly predicts the definitive GAC, along with what factors predict changes in preliminary to definitive GAC, will help evaluate the utility of assigning a preoperative GAC altogether.

Thus, the objectives of this study were (1) to determine whether a change in GAC was associated with an increased risk of SSI, with the hypothesis that a GAC that was upgraded may not have received appropriate antibiotic prophylaxis initially and, thus, increased the patient's risk of SSI; (2) to determine the injury characteristics associated with either upgrading or downgrading the preoperative GAC to the definitive classification; and (3) to determine which wound characteristics are associated with increases and decreases of the GAC.

2. Methods

2.1. Data Source—The FLOW Trial

This study presents the results of secondary data analysis performed on the Fluid Lavage of Open Wounds (FLOW) study, of which the full objectives, methods, and primary results are provided in a prior publication.[13] In brief, the FLOW study was an international, multicenter, blinded, 2×3 factorial randomized controlled trial assessing the effect of two different irrigation solutions (normal saline vs. soap) and three different irrigation pressures (high vs. low vs. gravity flow) on 1-year reoperation rates among patients with open fractures.

The FLOW study was approved by the ethics committees at the coordinating center, McMaster University (REB: 08-268).

From June 2009 to September 2013, patients 18 years and older presenting with an open fracture of an extremity requiring operative fixation were randomized to one of the six study groups, after stratification by center and GAC. For a patient with multiple fractures, the highest GAC that did not meet any exclusion criteria was considered as the fracture of consideration for the FLOW study.

Patients returned for follow-up at 1, 2, and 6 weeks and 3, 6, and 12 months. A total of 2447 patients were included in the final primary analysis, which showed that the rates of reoperation were similar, regardless of irrigation pressure, and higher in the group treated with a soap solution compared with those treated with saline.

2.2. Assessment of SSI

A blinded, independent central adjudication committee determined the occurrence of the end point of SSI based on a review of clinic notes, procedure logs, and antibiotic prescriptions, using a modified version of the Centre for Disease Control criteria.[14] SSIs included superficial incisional SSI, deep incisional SSI, and organ/space SSI. The final analysis in this study evaluated all SSIs together as a composite outcome of infection.

2.3. Accuracy of GAC Grading

As part of the FLOW trial, participants were assigned a GAC at the time of randomization, as it was a stratification variable, and then a definitive GAC on the first irrigation and debridement. The GAC was assigned by a treating surgical team member (either orthopaedic fellow or orthopaedic surgeon). As part of our analysis, the GAC change was subclassified into downgraded, upgraded, or no change to score.

2.4. Selection of Baseline Factors

We selected baseline factors associated with either upgrading or downgrading the preoperative GAC to the definitive classification a priori based on biologic rationale and previous reports in the literature. For each potential factor, we proposed a hypothesized effect for the logistic regression outcome. To avoid an overfitted or unstable model, we used a rule of thumb that there should be at least 10 times the number of observations as there are factors in a regression model.[15] Using primary outcomes data from the FLOW trial, 325 patients developed a SSI; thus, with less than 30 covariates, we were not at high risk of overfitting the model.

Baseline factors were classified into two main groups: injury characteristics and wound characteristics. Injury characteristics included preoperative GAC, location of injury (classified as tibia or elsewhere, as used in the primary study), and mechanism of injury (high or low energy). Wound characteristics included preoperative assessment of bone loss, skin loss, and muscle loss as well as amount of muscle, skin, bone, and fascia debrided intraoperatively.

2.5. Definition of Baseline Factors

2.5.1. Injury Characteristics. We analyzed preoperative GAC as an ordinal variable, creating four levels of analysis with a separate grade for GA I/II, IIIA, and IIIB. GA I/II fractures were grouped together because they often represent injuries with lower energy mechanisms, compared with those in GA class III (A + B). GA IIIC fractures were excluded from the primary study and

subsequent analysis. Location of injury and mechanism of injury were analyzed as categorical variables.

2.5.2. Wound Characteristics. The preoperative assessment of bone, skin, and muscle loss were all recorded as categorical variables (presence or absence). By contrast, the amount of muscle, skin, bone, and fascia debrided were classified in an ordinal fashion (0—no debridement, 1—small amount debrided [<1 cm^2], 2—moderate amount debrided [1–5 cm^2], and 3—large amount debrided [>5 cm^2]).

2.6. Statistical Analysis

Our statistical analysis plan was determined a priori. We included FLOW trial participants with complete data in the logistic regression model. We used descriptive statistics to summarize all factors (frequencies and percentages for categorical and ordinal variables and means, medians, and ranges for continuous variables).

For our definitive analysis, we developed a multinomial regression model, with three potential outcomes: an upgraded GAC, a downgraded GAC, and no change in GAC. This produced two regression outputs, one that identified factors associated with *upgrading* preoperative to intraoperative GAC and another to identify factors associated with *downgrading* scores. We included all factors specified above as independent variables in fixed effects.

A logistic regression model was then built with SSI as the dependent variable of interest. Change in GAC (no change, upgrade, downgrade) was the independent variable while the above-listed covariates, including initial GAC, were also incorporated as adjustment variables. Patients were compared with those in their initial GAC (eg, the risk of SSI for patients who were upgraded from GAC II to III was compared with the risk for those with initial GAC II). Regression results were reported as odds ratios (ORs) with corresponding 95% confidence intervals (CIs) and *P* values. We used R (v3.6.1 open access online) for statistical analyses.

3. Results

3.1. Participant Characteristics

Of the 2447 participants who enrolled and contributed data for the FLOW primary outcome analysis, 2420 participants were ultimately included in this secondary analysis, with 27 participants (1.1%) excluded because of incomplete data. The demographic data for this cohort are similar to the cohort reported in the initial trial (Table 1).

TABLE 1

Participant Characteristics

Variables	FLOW Cohort (N = 2420)
GAC (preoperative), n (%)	
1/2	1682 (69.5)
3a	529 (21.9)
3b	209 (8.6)
GAC (intraoperative), n (%)	
1/2	1538 (63.6)
3a	650 (26.8)
3b	232 (9.6)
Location, n (%)	
Tibia	1511 (62.4)
Elsewhere	909 (37.6)
Mechanism of injury, n (%)	N = 2419
High energy	2132 (88.1)
Presence of bone loss (preoperative), n (%)	N = 2419
	534 (22.1)
Skin loss (preoperative), n (%)	N = 2419
	426 (17.6)
Muscle loss (preoperative), n (%)	N = 2419
	345 (14.3)
Width of wound, cm (SD)	2.77 (3.77)
Length of wound, cm (SD)	4.50 (5.81)
Muscle debridement, cm^2, n (%)	N = 2415
None	1210 (50.1)
<1	913 (37.8)
1–5	237 (9.8)
>5	55 (2.3)
Skin debridement, cm^2, n (%)	N = 2416
None	751 (31.1)
<1	1327 (54.9)
1–5	282 (11.7)
>5	56 (2.3)
Fascia debridement, cm^2, n (%)	N = 2417
None	1034 (42.8)
<1	1123 (46.4)
1–5	228 (9.4)
>5	32 (1.3)
Bone debridement, cm^2, n (%)	N = 2416
None	1358 (56.2)
<1	771 (31.9)
1–5	246 (10.2)
>5	41 (1.7)

Note: A total of 2447 participants were enrolled in the trial, 2432 received a preoperative GAC and 2420 received a definitive perioperative GAC. These 2420 participants were included in the analysis. Not all patients had complete data on every factor listed.

3.2. Accuracy of GAC Grading

Of the 2420 participants included, 305 participants had their preoperative GAC changed (12.6%). In total, 229 participants (9.5%) were upgraded and 76 participants (3.1%) were downgraded after surgery. Of the 1682 participants classified as GAC I/II preoperatively, 190 participants (11.3%) were upgraded intraoperatively. Of those 529 participants classified as GAC IIIA, 39 (7.4%) were upgraded and 39 (7.4%) were downgraded. Finally, of the 209 participants classified as GAC IIIB, 37 (17.7%) were ultimately downgraded.

3.3. GAC and SSI

Forty-six participants who had their GAC upgraded suffered an SSI (20%), compared with 13 patients who had their GAC downgraded and suffered an SSI (17.1%), and 266 patients who had no change in GAC went onto having an SSI (12.5%). An upgraded GAC was not significantly associated with an increased risk of SSI when considered in the multivariate model (OR: 1.03; 95% CI: 0.99–1.07; $P = 0.14$). These results were mirrored in patients who had a downgraded GAC, which did not change their risk of SSI (Table 2).

3.4. Factors Associated with Upgrading GAC

The factors associated with upgrading the GAC (from the preoperative score to the definitive assessment) were lower initial GAC (grade I/II compared to grade IIIA OR: 7.91, 95% CI: 4.68–13.40; $P < 0.001$), fracture site other than the tibia (OR: 1.97, 95% CI: 1.45–2.67; $P < 0.001$), bone loss at presentation (OR: 1.67, 95% CI: 1.14–2.45; $P = 0.009$), width of wound (OR: 1.06 per additional cm of wound width, 95% CI:

TABLE 2

Change in GAC and SSI Association

Characteristic	OR	95% CI	P
Change in GA classification			
Same (Reference)	—	—	
Downgrade	0.98	0.92–1.04	0.5
Upgrade	1.03	0.99–1.07	0.14

Note: These results are adjusted for injury and participant characteristics.

1.01–1.12; $P = 0.02$), length of wound (OR: 1.08 per additional cm of wound length, 95% CI: 1.05–1.12; $P < 0.001$), and skin loss at presentation (OR: 1.75, 95% CI: 1.15–2.66; $P = 0.009$). Moreover, any amount of muscle debridement, 1–5 cm of skin debridement (95% CI 1.61–4.84, $P < 0.001$), and bone debridement over 5 cm^2 were associated with upgrading GAC (95% CI: 1.32–11.0, $P = 0.01$; Table 3).

3.5. Factors Associated with Downgrading GAC

The only covariate associated with downgrading the initial GAC was the actual grade assigned, with higher initial grade more likely to be downgraded (grade IIIB compared with grade IIIA, OR: 9.84, 95% CI: 5.23–18.50; $P < 0.001$; Table 4).

TABLE 3

Factors Associated With Upgrading GAC

Characteristic	OR	95% CI	P
GA classification			
Reference (GA IIIA)	—	—	
I/II	7.91	4.68–13.4	**<0.001**
IIIB/C	0.00	0.00–0.00	**<0.001**
Location of injury			
Reference (tibia)	—	—	
Injuries elsewhere	1.97	1.45–2.67	**<0.001**
Mechanism of injury	1.68	0.96–2.97	0.07
Presence of bone loss	1.67	1.14–2.45	**0.009**
Width of wound (per additional cm)	1.06	1.01–1.12	**0.02**
Length of wound (per additional cm)	1.08	1.05–1.12	**<0.001**
Presence of skin loss	1.75	1.15–2.66	**0.009**
Presence of muscle loss	1.18	0.72–1.92	0.52
Amount of skin debrided, cm^2			
Reference (no debridement)	—	—	
<1	1.44	0.95–2.17	0.08
1-5	2.79	1.61–4.84	**<0.001**
>5	2.19	0.61–7.95	0.23
Amount of muscle debrided, cm^2			
Reference (no debridement)	—	—	
<1	1.52	1.03–2.23	**0.03**
1-5	2.58	1.38–4.81	**0.003**
>5	15.1	4.08–55.6	**<0.001**
Amount of fascia debrided, cm^2			
Reference (no debridement)	—	—	
<1	1.25	0.85–1.84	0.25
1-5	0.87	0.45–1.69	0.69
>5	0.03	0.00–0.44	**0.01**
Amount of bone debrided, cm^2			
Reference (no debridement)	—	—	
<1	1.33	0.93–1.91	0.12
1-5	1.28	0.75–2.17	0.36
>5	3.81	1.32–11.0	**0.01**

4. Discussion

This FLOW trial secondary analysis identified that 12% of patients with open fractures, in a large prospective randomized controlled trial, had a change in GAC from initial preoperative assessment to final postoperative evaluation. Moreover, this study demonstrated that an upgrade in GAC was not associated with an increased risk of SSI. Finally, patients with open fractures in a location other than the tibia and with bone loss at presentation were more likely to have an upgraded GAC.

Rather than time to debridement, appropriate early antibiotic administration has been shown to be the best predictor of SSI after open fractures.[12,16] The 2011 Eastern Association for Surgery of Trauma (EAST) recommends antibiotic choice based on preoperative GAC, with first-generation cephalosporins for type I and II fractures, with the addition of an aminoglycoside for type III fractures, and penicillin for highly contaminated injuries or those occurring in farming environments.[12] This antibiotic protocol was followed in the FLOW trial.[17] In addition, antibiotic coverage postoperatively should be altered if the GAC changes after definitive operative debridement, although the use of any postoperative prophylaxis has recently come into question.[18] Moreover, the time to definitive operative debridement is often delayed by 12 or more hours as the standard of care for allowable time before operative debridement continues to increase.[19–21] Thus, with inadequate initial antibiotic administration and a longer time to definitive GAC, patients may be at a substantially higher risk of SSIs.

We found that while injuries where GAC was upgraded had a modestly increased proportion of SSI (20% vs. 17%), regression models, adjusting for confounding factors, did not show a significant association between GAC upgrade and SSI (95% CI 0.99–1.07, $P = 0.14$). Thus, treating more severe injuries with antibiotic monotherapy did not contribute to infection. However, our findings were quite fragile with a fragility index of 2—if two more patients in the upgraded GAC had suffered a SSI, the results would have been statistically significant.[22]

It has been suggested that broadened antibiotic coverage for more severe injuries—the inclusion of an aminoglycoside antibiotic—may have little role in the prevention of SSI in open fractures and that time to delivery of antibiotics, along with injury and patient characteristics, play a larger role. Lack (2015), in an evaluation of SSI risk in severe (GAC III) open tibia fractures, reported that only time to antibiotic administration was predictive of infection. In this observational study, cefazolin was the only agent given in 93.4% of cases and the overall infection rate was 17.5%. Patients who received antibiotics within 1 hour of injury had a 6.8% infection rate compared with 27.9% in those receiving antibiotics after 90 minutes. Similarly, Roddy et al[23] found that patients who did not receive antibiotics within 120 minutes were at 2.4 times greater risk of SSI, with patients who had GAC 3 injuries twice as likely to develop a SSI. Moreover, a recent publication, which included 1234 patients enrolled in an open fracture randomized trial, reported that only 61.1% of patients with GAC I/II fractures were given appropriate antibiotics (ie, a first-generation cephalosporin).[24] Thus, in addition to delayed time to antibiotics, there remains low adherence to antibiotic prophylaxis guidelines for open fractures, which may also contribute to a higher rate of SSI.

In addition, our study shows that certain factors, including bone loss on presentation, may predict an eventual change to a higher GAC after final debridement. These injuries may be classified as low GAC based on wound characteristics alone but have worrisome features of higher energy events with a higher risk of eventual soft-tissue infection. For example, the finding that

TABLE 4

Factors Associated With Downgrading GAC

Characteristic	OR	95% CI	*P*
GA classification			
Reference (GA IIIA)	—	—	
I/II	0.00	0.00 to 4.19E+13	0.59
IIIB/C	9.84	5.23 to 18.50	**<0.001**
Location of injury			
Reference (tibia)	—	—	
Injuries elsewhere	1.07	0.62 to 1.84	0.81
Mechanism of injury	0.44	0.15 to 1.27	0.13
Presence of bone loss	0.86	0.42 to 1.76	0.69
Width of wound (per additional cm)	0.92	0.85 to 1.00	0.04
Length of wound (per additional cm)	0.93	0.87 to 0.98	0.01
Presence of skin loss	0.26	0.10 to 0.64	0.004
Presence of muscle loss	0.78	0.30 to 2.01	0.61
Amount of skin debrided, cm^2			
Reference (no debridement)	—	—	
<1	0.90	0.47 to 1.73	0.76
1-5	0.53	0.18 to 1.57	0.25
>5	1.19	0.17 to 8.05	0.86
Amount of muscle debrided, cm^2			
Reference (no debridement)	—	—	
<1	0.82	0.43 to 1.55	0.54
1-5	0.31	0.09 to 1.10	0.71
>5	0.88	0.11 to 7.03	0.91
Amount of fascia debrided, cm^2			
Reference (no debridement)	—	—	
<1	0.88	0.46 to 1.70	0.71
1-5	0.68	0.22 to 2.15	0.51
>5	1.24	0.09 to 17.2	0.88
Amount of bone debrided, cm^2			
Reference (no debridement)	—	—	
<1	1.19	0.63 to 2.25	0.58
1-5	0.94	0.35 to 2.57	0.91
>5	0.63	0.07 to 5.79	0.68

fractures located in a site other than the tibia were associated with a greater chance of upgrading may be related to underestimating injuries other than those in the tibia and in particular underestimating injuries in bones that are not subcutaneous, such as the femur or humerus. Although this is an interesting finding, it remains to be seen whether there is any clinical relevance associated with a change in GAC.

There are a few limitations to this study. First, the GAC may have been assigned by different physicians at different levels of training, with the possibility of a resident, fellow, or staff physician assigned the GAC. Moreover, the preoperative and intraoperative GAC may have been assigned by different physicians, although we do not have discrete data on which physician assigned which grade. These physicians may have had varying experiences managing orthopaedic trauma, and it remains unclear whether there are underlying surgeon factors that prompt a surgeon to classify an open fracture as they do, beyond the basic assessment of wound size. In addition, while all centers used standardized antibiotic protocols with the goal of administration of antibiotics within 1 hour, there were deviations within the protocol where patients either received inappropriate or delayed antibiotics (approximately 1% each). Unfortunately, owing to limitations in data collection, it was not possible to exclude or adjust for this as a potential confounding variable affecting the risk of SSI.

Moreover, in determining the relationship between GAC change and SSI, all patients with a change in GAC were pooled together because of data limitations. This meant that patients with changes from GAC I to GAC II were treated equivalently to patients who changed from GAC II to GAC III. This prevented us from analyzing each subgroup and could have understated or overstated the importance of misclassification in the development of a SSI. In addition, for the same reason, we are unable to compare patients on a more granular level. Moreover, quantifying the amount of bone, muscle, fascia, and skin debrided can be inexact, and given this limitation, the original study chose to follow an ordinal scale for these measurements. Because an upgraded score was nearly three times more likely than a downgraded one, it is possible that the model constructed to predict downgraded GA did not include sufficient events to generate meaningful statistical findings.

Finally, the GAC classification has many potential limitations because it is based primarily on the length of the skin wound and not the extent of muscle, arterial, or other soft-tissue injury. Alternative classifications, such as the Orthopaedic Trauma Association open fracture classification, which are designed to have more inclusive criteria for rating open fracture, are becoming more prevalent and popular.[25] These alternate classifications may reduce the likelihood for change in classification of an open fracture wound between the emergency department and after definitive operative debridement.

5. Conclusion

When treating patients with open fracture wounds, surgeons should consider that when grading injuries according to the GAC and choosing the initial prophylactic antibiotic scheme or triaging care urgency, 12% may initially be misclassified. However, a misclassified GAC may not have a substantial impact on the overall risk of SSI. Fractures with any bone loss at presentation and those located in sites different than the tibia are more likely to be inappropriately underclassified. A focus on early antibiotic delivery, rather than the choice of antibiotics associated with a specific GAC classification, seems to be more important in preventing SSI. Future randomized controlled trials evaluating either limited or broad antibiotic coverage for open fractures in prevention of SSIs would build on the results from this study.

Appendix 1. The FLOW Investigators

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