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Effect of Extended Prophylactic Antibiotic Duration in the Treatment of Open Fracture Wounds Differs by Level of Contamination

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Abstract

Objective: To determine the association between prophylactic antibiotic duration after the definitive wound closure of an open fracture and deep surgical site infection (SSI).

Design: Retrospective cohort study.

Setting: 41 clinical sites in the United States, Canada, Australia, Norway, and India.

Participants: Patients (N = 2400) with open fractures of the extremities who participated in the Fluid Lavage of Open Wounds (FLOW) trial.

Intervention: Extended antibiotic prophylaxis, defined as more than 72 hours of continuous antibiotic use after definitive wound closure.

Main Outcome Measurement: Deep SSI diagnosed within 1 year of enrollment.

Results: Forty-two percent of participants received extended antibiotic prophylaxis. Deep SSI prevalence was 5%, 8%, and 23% for wounds with mild, moderate, and severe contamination, respectively. In open fractures with mild contamination, extended antibiotic use showed a trend toward increased odds [adjusted odds ratio (aOR) = 1.39; 95% confidence interval (CI), 0.92–2.11] of deep SSI compared with shorter use. No association was found among patients with

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moderate contamination (aOR = 1.09; 95% CI, 0.53–2.27). By contrast, extended antibiotic prophylaxis was strongly protective (aOR = 0.20; 95% CI, 0.07–0.60) against deep SSI in patients with severe contamination. Propensity score sensitivity analysis results were consistent with these findings.

Conclusions: The evidence suggests differential effects of extended postclosure antibiotic duration on SSI odds contingent on the degree of contamination in open fracture wounds. Although extended antibiotic duration resulted in lower odds of SSI among patients with severely contaminated wounds, we observed a trend toward higher odds of SSI in mildly contaminated wounds.

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

Keywords

antibiotics; prophylaxis; open fracture; surgical site infection

INTRODUCTION

Surgical site infections (SSIs) are considered threats to the healing of open fracture wounds of the extremities.[1] The most critical wounds, designated Gustilo–Anderson grade III, have the highest risk of infection (9%–62%) compared with less severe grade II (2%–10%) and grade I (2%) fractures.[2,3] Bacteria and other contaminants enter traumatized tissues during the traumatic event, as well as during surgery to repair the wound, which can result in persistent infections.[4] SSIs present risks and costs to the patient and health care system due to unplanned reoperations, prolonged antibiotic treatment, loss of optimal functioning, and other poor healing outcomes.[5] Therefore, avoiding infection is a primary aim of the treatment of open fractures, beginning at the initial assessment and treatment of the wound.

In the acute management of open fractures of the extremities, preoperative antibiotic prophylaxis and postoperative antibiotic prophylaxis are used almost universally in high-income countries.[6] The effectiveness of this practice was evaluated in a systematic review conducted by the Cochrane Bone, Joint, and Muscle Trauma Group. In the pooled analysis of 1106 open fractures of the limbs, antibiotic use was protective against early infection compared with placebo or no antibiotics.[6] Although the debate whether to prescribe antibiotics in the early treatment of open fractures has largely been settled, controversy endures in the recommended duration for antibiotic administration after debridement and soft-tissue closure or coverage. A standardized, evidence-based protocol for antibiotic prophylaxis does not yet exist across US institutions, and there is considerable variability in the antibiotic guidelines used by different institutions.[7] International dissimilarity also exists, as evidenced by a study from India reporting over 9 days of antibiotic duration, longer than typical practice in North America.[8] Ultimately, the decision is made at the discretion of the surgeon for type, administration route, and duration of antibiotics for each patient. Guidelines for SSI prevention in nontrauma patients recommend limiting prophylaxis to 24 horns after surgery, given lack of benefit and potential harm from longer courses.[9] However, there is little evidence supporting a similar approach for traumatic fracture surgery. Several

small single-site studies have investigated the effect of antibiotic duration on SSI outcomes. Generally, the authors found that when antibiotics were administered in a timely manner after injury, shorter antibiotic regimens (48–72 hours) resulted in no increases in skin or soft-tissue infection rates.[7,10,11] However, few large studies have replicated these findings.

In this secondary analysis of clinical trial data, we assessed the association between the duration of antibiotic prophylaxis after definitive wound closure and a deep wound infection in patients with open fractures of the extremities. We hypothesized that greater antibiotic duration would be associated with a reduced risk of operative treatment for deep SSIs within 12 months of the initial surgery.

METHODS

Study Design and Procedures

This secondary analysis used data collected in the Fluid Lavage of Open Wounds (FLOW) trial, an international, randomized controlled trial conducted between 2009 and 2013.[12] Enrollment took place in 41 sites in the United States, India, Canada, Australia, and Norway. FLOW trial participants were required to be adults (18 years old or older) presenting with an open fracture of an extremity requiring operation. Eligible injuries included fractures of an arm, wrist, leg, ankle, foot, clavicle, or scapula. Fractures of the pelvic ring, axial skeleton, hands, or feet were excluded.

In the FLOW trial's 3-by-2 factorial design, patients were randomized to receive one of 6 combinations of irrigation pressure and solution during their initial surgical operation (ie, either high, low, or very low irrigation pressure and an irrigation solution composed of saline alone or a solution including castile soap). The FLOW protocol recommended that preoperative antibiotics start immediately on diagnosis and postoperative antibiotics continue for at least 24 hours after surgery.[12] The protocol also recommended specific antibiotic classes based on Gustilo–Anderson grade cephalosporin for grade I-II injuries, add aminoglycoside for grade III injuries, and add penicillin for gross contaminated injuries. Temporary local antibiotic beads were permitted until definitive wound closure. FLOW investigators collected preoperative and postoperative antibiotic use information (including whether prescriptions were intended as prophylaxis or treatment for suspected infection) and the date of definitive closure for all participants. During the 12-month follow-up period, researchers recorded whether patients underwent reoperation or received other therapies to promote wound healing or treat infections.

For the current retrospective cohort study, all patients included in the FLOW analysis were eligible for inclusion; however, participants missing data necessary for the calculation of antibiotic duration were excluded. For each participant, we calculated the number of days of continuous prophylactic antibiotic use after the date when definitive wound closure was first verified. All antibiotics prescribed to treat an infection or that were prescribed before wound closure for any reason were excluded. For 20 participants who had an SSI event while taking antibiotics, their antibiotic duration estimates were truncated at the date of the SSI event. The antibiotic duration variable was dichotomous, comparing use for greater than 72 hours versus 72 hours or less for consistency with several studies and evidence-based guidelines

on this topic.[4,13] We also assessed whether participants received an appropriate antibiotic spectrum of coverage for the severity of their wound contamination (ie, severely contaminated wounds with narrow-spectrum antibiotic coverage were considered "inappropriate").

For the main analysis, an SSI event at follow-up included reoperation (ie, irrigation and debridement) for deep wound infection, as defined in the FLOW trial supplementary materials.[12] This event was verified by an independent adjudication committee to prevent interpreter bias. For the main analysis, this outcome variable was dichotomous, indicating the presence or absence of a deep SSI during the 12 months each participant was followed. Nonoperatively treated superficial surgical site wound infections were combined with deep SSIs in a sensitivity analysis. The Centers for Disease Control and Prevention's SSI criteria state that events must occur within 30 days (if no hardware was implanted) or 90 days (with implanted hardware) after an operative procedure,[14] and in a sensitivity analysis, we restricted to 30- and 90-day SSI events. Several covariates were assessed, including country, age, smoking status, Gustilo–Anderson grade, presence of external fixation, degree of wound contamination (classified as mild, moderate, or severe by the surgeon; Orthopaedic Trauma Association Open Fracture Classification [OTA-OTC][15] descriptions for contamination levels in Table 1), wound location (ie, upper vs. lower extremity), wound area, diabetes mellitus, and rheumatoid arthritis.

Statistical Analysis

The demographic and surgical characteristics of our cohort were examined at each level of antibiotic duration. For continuous variables, we reported the mean values and SDs, and *P* values were obtained using *t* tests. For categorical variables, we reported frequencies and column percentages, and *P* values were obtained using χ^2 or Fisher's exact tests, where appropriate. We calculated crude and adjusted odds ratio (OR and aOR) estimates with 95% confidence intervals (CIs) and *P* values for the association between length of antibiotic duration after definitive wound closure and deep SSI using logistic regression.

In evaluating the association between extended prophylactic antibiotic delivery and deep SSI, Gustilo–Anderson wound grade, degree of wound contamination, and presence of external fixation were identified a priori as potential effect measure modifiers. To assess potential effect modification, we added interaction terms with each of these variables and the exposure to the original logistic regression model. When considering several potential confounders, we assessed whether each was associated with both the exposure and outcome, resulted in a change in OR of 10% or greater when added to the unadjusted model, and whether biological justification existed in the literature to suggest confounding.

FLOW participants were not randomized to different lengths of antibiotic use, and we suspected that participants with the most severe injuries at greatest risk of SSI would receive the longest antibiotic courses. These circumstances suggested that confounding by indication could bias our results. We conducted propensity score stratification, which would balance observed covariates between the 2 exposure groups and could remove up to 90% of the bias.[16] Several explanatory variables, including Gustilo–Anderson grade, contamination, country, wound area, wound location, smoking status, and days to definitive wound closure, were

added to a logistic regression model to calculate propensity scores. Participants with similar propensity scores were grouped into 7 strata, and we assessed whether differences in any covariates remained. In the final logistic regression model, we adjusted for the propensity score strata variable and the covariates that were not balanced by the propensity scores. In sensitivity analyses, we considered whether results differed when extended antibiotic duration was redefined as greater than 0, 24, 48, or 96 hours of continuous antibiotic use, when SSI outcomes were restricted to events occurring within 30 or 90 days of the initial surgery, and when deep SSIs were analyzed with superficial SSIs. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

In this analysis, we excluded 47 of the 2447 FLOW trial participants due to missing antibiotic (n = 45) or wound contamination (n = 2) data. Among 2400 remaining patients, 42% (n = 1008) received extended antibiotic prophylaxis, defined as more than 72 hours of antibiotic use after definitive wound closure, and 87% (n = 2088) had received antibiotics for more than 1 day after closure. Deep SSIs occurred in 7% (n = 163) of the total study population, and the prevalence was roughly even between the extended (7%, n = 67) and shorter antibiotic duration (7%, n = 96) groups. The prevalence was 5%, 8%, and 23% for wounds with mild, moderate, and severe contamination, respectively. By Gustilo–Anderson grade, the deep SSI prevalence was 3%, 6%, 10%, and 15%, for grade I, II, IIIA, and IIIIB wounds, respectively. The overall SSI prevalence, including superficial SSIs, was 12%.

The majority (n = 1,660, 69%) of participants were male, and the mean age in the population was 45 years (SD = 17.7). When patient demographic data were broken down by exposure level (Table 2), we found that patients recruited in India were more likely to receive extended duration antibiotics compared with those recruited in other countries ($P < 0.001$). Patients in the shorter antibiotic duration group were more likely to identify as current smokers ($P = 0.01$). Patients with extended antibiotic use were more likely to have several surgical characteristics consistent with more severe wounds, including Gustilo–Anderson grade IIIA or B, moderate or severe contamination, and external fixation (all $P < 0.001$; Table 3). Those with longer time to wound closure had longer overall prophylaxis but shorter postclosure antibiotic duration ($P = 0.01$). The appropriateness of the antibiotic coverage given wound contamination severity was not associated with the exposure. Those with shorter prophylactic antibiotic duration were more likely to have an upper extremity wound and a wound area of less than 200 cm^2 (both $P = 0.01$), although very few participants had a wound area of at least 200 cm^2 in the study population.

In the unadjusted analysis, we found no association between antibiotic duration and the odds of SSI (OR = 0.96; 95% CI, 0.70–1.32; $P = 0.81$). However, significant interaction ($P = 0.004$) between antibiotic duration and wound contamination led us to report stratified odds ratio estimates at each level of this effect measure modifier in subsequent models. We did not stratify according to Gustilo–Anderson wound grade or presence of external fixation due to nonsignificant interaction terms. Table 3 presents logistic regression results stratified by wound contamination and adjusting for the confounding variables: Gustilo–Anderson wound grade, days to definitive wound closure, country, and wound area. In open fractures with

mild contamination, patients with extended antibiotic use after definitive wound closure trended toward increased odds of deep SSI compared to those with shorter antibiotic use (aOR = 1.41; 95% CI, 0.92–2.11; $P = 0.12$). There was no association between antibiotic duration and deep SSI found among patients with moderately contaminated open fractures (aOR = 1.09; 95% CI, 0.52–2.27; $P = 0.81$). By contrast, extended antibiotic prophylaxis resulted in strongly decreased odds of deep SSI in patients with severely contaminated open fractures (aOR = 0.20; 95% CI, 0.07–0.60; $P = 0.004$).

Of the 5 covariates that were substantially imbalanced between the 2 exposure groups before propensity score stratification, 2 (days to definitive closure and country) remained unbalanced after adjustment for stratum. When adjusting for propensity score stratum and both unbalanced covariates, the aORs within the 3 strata of contamination were similar to the adjusted results reported above (Table 4).

In other sensitivity analyses, we observed similar trends in aOR estimates by degree of contamination when extended antibiotic duration was redefined as greater than 0, 24, 48, or 96 hours of continuous antibiotic use (see Table, Supplemental Digital Content 1, http://links.lww.com/JOT/A954), when SSI outcomes were restricted to events occurring within 30 or 90 days of the initial surgery (see Table, Supplemental Digital Content 2, http://links.lww.com/JOT/A955), and when deep and superficial SSIs were analyzed together (see Table, Supplemental Digital Content 3, http://links.lww.com/JOT/A956). When assessing only the deep SSIs that occurred within 30 and 90 days of the initial surgery, the aORs in the moderate stratum became nonsignificantly protective (likely due to very few events). When the outcome was expanded to include superficial and deep infections, the aOR indicating increased odds of SSI with extended antibiotic duration in the mild stratum became statistically significant.

DISCUSSION

In this study, we found that the association between extended prophylactic antibiotic duration (ie, greater than 72 hours of continuous use after definitive wound closure) and SSI differed by the level of contamination of open fracture wounds of the extremities. Participants with mildly contaminated wounds trended toward increased odds of deep SSI (borderline significant result), and those with moderately contaminated wounds had no difference in deep SSI odds associated with greater antibiotic duration. Conversely, longer antibiotic use was associated with a substantial decrease in deep SSI in the population with severely contaminated wounds. This qualitative effect modification in the main association due to contamination severity was seen in unadjusted, adjusted, and propensity score–stratified models.

Our hypothesis that prolonged antibiotic duration after definitive wound closure would reduce deep SSI odds was confirmed only in the severe contamination stratum. The mild and moderate strata results contradicted our expectations. Similarly, there is conflicting evidence on this topic found in the scientific literature. Multiple studies, including a meta-analysis of 3 randomized controlled trials, found that extended antibiotic administration (3–5 days) was not superior to a 1-day course to prevent SSI after open fractures of all grades.[11,17,18]

Messner et al[13] recently published a meta-analysis of 6692 open fractures that stratified by Gustilo–Anderson severity grade and reported no difference in infection rates by duration (dichotomized at 4-day cut point). In a large single center trial, Gatell et al found that a single dose of antibiotics was less effective compared with longer duration prophylaxis in preventing deep SSI, although the statistical significance was marginal and the effect disappeared in some sensitivity analyses.[19,20] There are key similarities and differences among these previous works. Many focused on prophylactic antibiotics prescribed after definitive wound closure. Some used a 72-hour duration cut point as we did, while others used a 24-hour cut point or focused on the number of individual antibiotic courses administered to each patient over time. Several studies restricted the outcome of interest to deep SSIs only. Although the main results focus on deep SSI, we also highlight analysis where the outcome was redefined to include superficial and deep infections. Confounding variables also varied among these studies, although many included Gustilo–Anderson grade, the anatomical location of the wound, and some measure of whether the wound was closed during the first surgery. Messner et al stratified by Gustilo–Anderson grade a priori, but it is unclear whether significant interaction was found in the analysis to justify this decision. We did not find statistical evidence to treat Gustilo–Anderson grade as an effect measure modifier. To the best of our knowledge, no previous studies stratified the effect estimates based on the severity of wound contamination. Another notable difference between our study and its predecessors is sample size, with most (excluding the meta-analyses) having considerably fewer open fracture patients, leading to insufficient power to assess the specific effects of antibiotic duration.[20]

The reason behind the unexpected result of borderline significant increased odds of deep SSI with extended antibiotics in the mild contamination group remains unclear. One possible explanation could be related to the time from injury to first antibiotic administration. There is some evidence that less severe open fractures receive antibiotics up to 1.5 hours later than more severe injuries.[21] A delay in antibiotic delivery greater than 3 hours after injury has been shown to increase infection rates.[22,23] Although 99% of FLOW patients received antibiotics within 24 hours, the exact timing of administration in relation to injury or hospital arrival is unclear.[12] It is possible that the least contaminated open fracture patients were more likely to experience delays in antibiotic delivery that would contribute to higher SSI risk. However, this theory is untested. Another factor that may contribute to the unexpected result among mildly contaminated wounds involves the appropriateness of antibiotic coverage within this group. Only 31% (n = 569) of patients in this stratum received broad-spectrum antibiotics. Although the FLOW protocol recommended gram-positive only antibiotics for the least severe wounds (grade I/II wounds usually being least severely contaminated), it is possible that broad-spectrum coverage would contribute to better outcomes in this group. Without culturing data available, we were unable to evaluate antibiotic appropriateness based on the organisms found in the wounds at definitive closure or confirm that gram-negative organisms were responsible for SSIs.

Key limitations of this secondary data analysis include the lack of hourly antibiotic duration data and the inability to account for antibiotics prescribed to patients for reasons unrelated to the randomized fracture. Revised confirmatory criteria for diagnosing fracture-related infection, as described by Metsemakers et al[24] in 2018, were not used by the FLOW

investigators to confirm SSI. Surgeons' wound contamination level assessments were not directly validated by FLOW investigators. An article assessing interobserver reliability among 8 surgeons who independently evaluated the contamination severity of injuries using OTA-OFC classifications demonstrated "fair" agreement (κ= 0.35; interpreted per Landis and Koch's guideline).[25,26] Owing to relative subjectivity and low agreement for this assessment, we recognize the potential for misclassification in this key variable in our study. However, we assume wound contamination misclassification to be nondifferential between the treatment groups, therefore, biasing the treatment effect toward the null hypothesis.[27] Also, the severe contamination group was comparatively small (n = 128), which limits confidence in the results for that stratum. The degree of contamination is also closely aligned with Gustilo–Anderson severity; most (80%) severely contaminated wounds were grades IIIA or IIIB. We lacked culture information before and at SSI diagnosis to assess whether organisms found in the wounds at definitive closure resulted in infections. Cultures would also elucidate whether the gram-positive antibiotics recommended in the FLOW protocol for the least severe wounds provided appropriate coverage for the bacteria commonly found in the wounds of this study population. Finally, we used propensity score analysis to mitigate the effect of unobserved confounding. However, we recognize that despite the benefits of this approach, it is possible that unmeasured prognostic balance continues to confound our treatment estimates.

The use of data from the FLOW trial is a strength of this study. This secondary analysis addresses several limitations of previous works, including longer follow-up time to assess the outcome, a larger sample size for increased power, and the inclusion of 41 multinational institutions to expand external validity. FLOW investigators implemented safeguards against misclassification of the outcome: the use of an independent adjudication committee to verify SSI events.[12] In this study population, the overall SSI prevalence was 12%, consistent with a recent pooled infection rate from 27 observational studies with more than 5400 open fracture patients.[13] In addition, deep SSI prevalence estimates by Gustilo–Anderson grade were consistent with previously published work.[2] Although this research is based on a clinical trial, participants were not randomized in relation to duration of antibiotic prophylaxis. Hence, propensity score stratification helped to address threats to validity due to confounding by indication. The trends remained consistent after incorporating propensity scores and several other sensitivity analyses.

In summary, we found evidence that the association between antibiotic prophylaxis and deep SSI differs by level of wound contamination. This study has the potential to inform the design of a definitive study to determine an optimal antibiotic prophylactic regimen based on contamination severity. In future research, it will be important to consider finer detail (hourly intervals) for antibiotic duration, the timing of prophylactic administration, wound culturing over time, and a validated measure of wound contamination. Ultimately, these findings would be useful in the development of an evidence-based antibiotic protocol for open fractures of the extremities.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1.

Description of Wound Contamination Severity Levels

Contamination Levels	Description
Mild	No or minimal contamination
Moderate	Surface contamination that is easily removed
Severe	Massive contamination that is due to high-risk environmental contaminants, such as clothes, grass, or fecal matter, or any contaminates deeply imbedded in bone or deep soft tissues[14]

TABLE 2.

Patient Demographics by Level of Prophylactic Antibiotic Duration, N = 2400

	>72 h of Antibiotic Use (n = 1008)	≤72 h of Antibiotic Use (n = 1392)	*P**
Age—years, mean (SD)	45 (17.5)	45 (17.9)	0.99
Sex—male, n (%)†	704 (69.8)	956 (68.7)	0.54
Country			<0.001
India, n (%)	211 (20.8)	23 (1.6)	
Other, n (%)	797 (79.1)	1369 (98.4)	
Smoker—yes‡, n (%)	298 (29.7)	476 (34.5)	0.02
Diabetic—yes, n (%)	67 (6.6)	109 (7.8)	0.51
R. arthritis—yes, n (%)	6 (0.6)	13 (0.9)	0.48

**P* values calculated using *t* test for age, Fisher's exact test for arthritis, and by χ^2 for all other variables.

†Percentages shown are column percents. R. arthritis, rheumatoid arthritis.

‡Current smokers versus never and quit smokers; 16 missing observations.

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TABLE 3.

Surgical Characteristics by Level of Prophylactic Antibiotic Duration, N = 2400

	>72 h of Antibiotic Use (n = 1008)	≤72 h of Antibiotic Use (n = 1392)	*P**
Days to definitive closure			0.01
0–5 d, n (%)†	944 (93.7)	1261 (90.6)	
>5 d, n (%)	64 (6.3)	131 (9.4)	
Surgical site infection (SSI)			0.10
None n (%)	872 (86.5)	1229 (88.3)	
Superficial n (%)	69 (6.9)	67 (4.8)	
Deep n (%)	67 (6.7)	96 (6.9)	
GA grade			<0.001
I and II, n (%)	662 (65.7)	1013 (72.8)	
IIIA and IIIB, n (%)	346 (34.3)	379 (27.2)	
Wound location			0.01
Lower, n (%)	721 (71.5)	931 (66.9)	
Upper, n (%)	287 (28.5)	461 (33.1)	
Wound area			0.01
<200 cm^2, n (%)	993 (98.5)	1386 (99.6)	
≥200 cm^2, n (%)	15 (1.5)	6 (0.4)	
Contamination			<0.001
Mild, n (%)	726 (72.0)	1123 (80.7)	
Moderate, n (%)	221 (21.9)	202 (14.5)	
Severe, n (%)	61 (6.1)	67 (4.8)	
Inappropriate antibiotic type, n (%)	14 (1.4)	19 (1.4)	0.99
External fixation n (%)	42 (4.1)	29 (2.1)	0.003

*P values calculated using the Fisher exact test for inappropriate antibiotic type and by χ^2 for all other variables.

†Percentages shown are column percents.

GA, Gustilo–Anderson fracture grade.

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TABLE 4.

Association Between Duration of Prophylactic Antibiotic Use and Deep SSI Stratified by Severity of Wound Contamination Based on Unadjusted, Adjusted, and Propensity Score–Stratified Models, N = 2400

				Unadjusted		Adjusted		Propensity Score–Stratified	
Contamination	**Antibiotic Use**	**Deep SSI (n = 163) n (%)**	**No Deep SSI (n = 2237) n (%)**	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Mild	> 72 h (n = 726)	43 (5.9)	683 (94.1)	1.20 (0.80, 1.81)	0.38	1.39 (0.92, 2.11)	0.12	1.35 (0.89, 2.05)	0.16
	≤ 72 h (n = 1123)	56 (5.0)	1067 (95.0)	1.0 (ref)		1.0 (ref)		1.0 (ref)	
Moderate	> 72 h (n = 221)	17 (7.7)	204 (92.3)	0.85 (0.43, 1.70)	0.65	1.09 (0.53, 2.27)	0.81	1.17 (0.57, 2.43)	0.67
	≤ 72 h (n = 202)	18 (8.9)	184 (91.1)	1.0 (ref)		1.0 (ref)		1.0 (ref)	
Severe	> 72 h (n = 61)	7 (11.5)	54 (88.5)	0.27 (0.10, 0.68)	0.006	0.20 (0.07, 0.60)	0.003	0.23 (0.08, 0.65)	0.005
	≤ 72 h (n = 67)	22 (32.8)	45 (67.2)	1.0 (ref)		1.0 (ref)		1.0 (ref)	

Odds ratios (ORs), confidence intervals (CIs), and *P* values calculated using logistic regression. Percentages shown are row percents. Adjusted model includes Gustilo–Anderson wound type, days to definitive closure, country, and wound area. Propensity score–stratified model adjusts for propensity score stratum, days to definitive closure, and country.