

# Low Adherence to Recommended Guidelines for Open Fracture Antibiotic Prophylaxis

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**Background:** Prompt administration of antibiotics is a critical component of open fracture treatment. Traditional antibiotic recommendations have been a first-generation cephalosporin for Gustilo Type-I and Type-II open fractures, with the addition of an aminoglycoside for Type-III fractures and penicillin for soil contamination. However, concerns over changing bacterial patterns and the side effects of aminoglycosides have led to interest in other regimens. The purpose of the present study was to describe the adherence to current prophylactic antibiotic guidelines.

**Methods:** We evaluated the antibiotic-prescribing practices of 24 centers in the U.S. and Canada that were participating in 2 randomized controlled trials of skin-preparation solutions for open fractures. A total of 1,234 patients were evaluated.

**Results:** All patients received antibiotics on the day of admission. The most commonly prescribed antibiotic regimen was cefazolin monotherapy (53.6%). Among patients with Type-I and Type-II fractures, there was 61.1% compliance with cefazolin monotherapy. In contrast, only 17.2% of patients with Type-III fractures received the recommended cefazolin and aminoglycoside therapy, with an additional 6.7% receiving piperacillin/tazobactam.

**Conclusions:** There is moderate adherence to the traditional antibiotic treatment guidelines for Gustilo Type-I and Type-II fractures and low adherence for Type-III fractures. Given the divergence between current practice patterns and prior recommendations, high-quality studies are needed to determine the most appropriate prophylactic protocol.

Prompt administration of prophylactic antibiotics substantially reduces the rate of infection in open fractures<sup>1-5</sup>. The Gustilo-Anderson classification<sup>6,7</sup> is the most widely utilized system for classifying open fractures<sup>8</sup> and is used to guide antibiotic choice<sup>7,9-12</sup>. The traditional recommendation for antibiotic choice has been a first-generation cephalosporin for Gustilo Type-I and Type-II open fractures, with the addition of an aminoglycoside for Type-III fractures and penicillin for soil contamination.

In 2011, the Eastern Association for the Surgery of Trauma (EAST) recommended a more conceptual approach for antibiotic

prophylaxis, with gram-positive coverage for Type-I and Type-II fractures, the addition of gram-negative coverage for Type-III fractures, and additional penicillin for the presence of fecal or clostridial contamination. They also recommended that for Type-III fractures, antibiotics should be discontinued within 72 hours after the injury or 24 hours after soft-tissue coverage had been achieved<sup>1</sup>. Although the importance of prophylactic antibiotics is widely accepted, the type and duration of antibiotics prophylaxis remain controversial<sup>13</sup>, and compliance rates have been found to be as low as 10%<sup>14</sup>. Furthermore, concerns over the nephrotoxicity and ototoxicity

\*A list of the PREP-IT Investigators is given in a Note at the end of the article.

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A **data-sharing statement** is provided with the online version of the article (<http://links.lww.com/JBJS/G279>).

of aminoglycosides, the changing patterns of bacterial speciation in fracture-related infections<sup>15</sup>, and the rising prevalence of methicillin-resistant *Staphylococcus aureus*<sup>16</sup> have led some surgeons to investigate alternative antibiotic choices<sup>17-21</sup>.

We sought to evaluate the level of adherence to guidelines regarding antibiotic choice and duration in the treatment of open fractures by analyzing data collected as part of 2 ongoing multicenter studies on open fracture care. Secondly, we explored the association of Gustilo type, wound contamination, and multifracture injuries with antibiotic choice and duration of prophylaxis.

### Materials and Methods

This is a substudy of 2 ongoing multicenter randomized controlled trials known as the Program of Randomized Trials to Evaluate Preoperative antiseptic skin solutions In orthopaedic Trauma (PREP-IT; clinicaltrials.gov: NCT03385304 and NCT03523962)<sup>22</sup>. Patients were included who were  $\geq 18$  years old and who underwent open reduction and internal fixation of an open extremity fracture. Patients were excluded if they were initially managed at an outside hospital, had an active infection at the time of injury, had terminal injuries, were incarcerated, or were unable to follow up. Once enrolled, demographic and medical, characteristics and open fracture characteristics for both the Gustilo classification and the OTA classification were recorded<sup>23,24</sup>. Fractures were classified by the attending orthopaedic surgeon at the time of initial debridement. Details of the initial debridement, fracture fixation, type of wound closure, and antibiotic use were prospectively collected. We defined a prophylactic antibiotic as any antibiotic that was started on the same calendar day as admission, including preoperative and postoperative antibiotics. The duration of antibiotic use was calculated by noting each calendar day that the patient received at least 1 dose of the same medication.

### Statistical Analysis

Patient and injury characteristics were described with counts and proportions for categorical data and means and standard deviations or medians and interquartile ranges (IQRs) for continuous variables, depending on the data distribution.

Counts and proportions were also utilized to describe the common antibiotic regimens. Our primary comparison described differences in common antibiotic regimens for Type-I and Type-II fractures compared with Type-IIIA, Type-IIIB, and Type-IIIC fractures with use of mixed-effects models in which we accounted for between-hospital differences with a random intercept.

We developed separate regression models for 4 common antibiotic regimens in order to explore the association between the Gustilo type, Orthopaedic Trauma Association-Open Fracture Classification (OTA-OFC)<sup>25</sup> contamination, and number of fractures with each regimen. We also fit models

TABLE I Patient and Fracture Characteristics (N = 1,234)

Characteristic	
Age* (yr)	45.34 $\pm$ 18.50
Male sex†	764 (61.9)
Race†	
White	925 (75.1)
Black	244 (19.8)
Asian	20 (1.6)
Other/mixed	43 (3.5)
Body mass index* (kg/m <sup>2</sup> )	28.87 $\pm$ 7.02
Comorbidity score*	1.25 $\pm$ 1.63
Health insurance†	975 (79.1)
Mechanism of injury†	
Motor vehicle accident	656 (53.2)
Fall	336 (27.2)
Other	242 (19.6)
Lower-extremity fracture†	882 (71.5)
Tibial fracture†	562 (45.5)
Gustilo-Anderson classification†	
I	300 (24.5)
II	404 (33.0)
IIIA	424 (34.7)
IIIB/IIIC	95 (7.8)
OTA-OFC overall*	6.77 $\pm$ 2.00
OTA-OFC components†	
OTA-OFC skin	
1	1,057 (86.5)
2	91 (7.4)
3	74 (6.1)
OTA-OFC muscle	
1	842 (69.0)
2	326 (26.7)
3	52 (4.3)
OTA-OFC arterial	
1	1,138 (93.3)
2	59 (4.8)
3	23 (1.9)
OTA-OFC contamination	
1	762 (62.4)
2	345 (28.3)
3	114 (9.3)
OTA-OFC bone	
1	735 (60.2)
2	165 (13.5)
3	321 (26.3)

\*The values are given as the mean and standard deviation. †The values are given as the number of patients, with the percentage in parentheses.

to explore the associations of the Gustilo type, OTA-OFC contamination, and number of fractures with the duration of antibiotics from admission and the duration of antibiotics from wound closure. Gustilo type was coded as Type I, II, IIIA, and a combined Type IIIB and IIIC according to previously described differences in infection event rates<sup>7,26</sup>. A dummy hospital variable was included as a random intercept in all models to account for between-hospital variance. The relative effect of each included factor was reported as an odds ratio (OR) with a 95% confidence interval (CI). The model variance attributed to hospital-level differences was reported as the intraclass correlation coefficient (ICC).

We performed a subgroup analysis of the aforementioned models that included only patients with an Injury Severity Score (ISS) of <10. Because the musculoskeletal portion of the Abbreviated Injury Scale is rarely >3 for an open fracture and the ISS is calculated by the sum of the squares of the Abbreviated Injury Scale scores<sup>27</sup>, it was likely that these patients had isolated musculoskeletal injuries. All statistical analyses were performed with use of R (version 4.0.0; R Foundation for Statistical Computing).

## Results

### Antibiotic Choice

A total of 1,234 patients from 24 medical centers across the U.S. and Canada were included. Patient demographics and injury characteristics are described in Table I. All patients received antibiotics on the day of admission. The most commonly prescribed antibiotic was cefazolin (1,135 patients; 92.0%), followed by ceftriaxone (217 patients; 17.6%) and gentamicin (102 patients; 8.3%) (Table II). Cefazolin was the most commonly prescribed cephalosporin, followed by ceftriaxone, cefepime (10 patients; 0.8%), and cefoxitin (3 patients; 0.2%).

The most commonly prescribed antibiotic regimen was cefazolin monotherapy (661 patients; 53.6%). Fifty-four different combinations of prophylactic antibiotics were prescribed. The 10 most commonly prescribed combinations are shown in Figure 1, with the remaining combinations each comprising <1% of patients.

Gustilo classification was recorded in 1,223 patients. In the combined Type-I and Type-II group, the most commonly prescribed systemic antibiotic regimen was cefazolin monotherapy (430 patients; 61.1%) in accordance with traditional recommendations, followed by cefazolin and an aminoglycoside with or without penicillin (42 patients; 6.0%), intravenous vancomycin (40 patients; 5.7%), ceftriaxone monotherapy (14 patients; 2.0%), and intravenous piperacillin/tazobactam (15 patients; 2.1%) (Table III). In the Type-III group, the most commonly prescribed antibiotic regimen was cefazolin (231 patients; 44.5%), followed by the traditionally recommended dual therapy of cefazolin and aminoglycosides with or without penicillin (89 patients; 17.2%), intravenous vancomycin (49 patients; 9.4%) intravenous piperacillin/tazobactam (35 patients; 6.7%),

TABLE II Prophylactic Antibiotics Prescribed

Antibiotic	No. of Patients (%)
Cefazolin	1,135 (92.0)
Ceftriaxone	217 (17.6)
Gentamicin	102 (8.3)
Tobramycin	89 (7.2)
Vancomycin	89 (7.2)
Clindamycin	76 (6.2)
Piperacillin/tazobactam	50 (4.1)
Penicillin	19 (1.5)
Ampicillin/sulbactam (Unasyn)	19 (1.5)
Keflex	14 (1.1)
Metronidazole	12 (1.0)
Levofloxacin	11 (0.9)
Cefepime	10 (0.8)
Ciprofloxacin	8 (0.6)
Ampicillin	6 (0.5)
Ciprofloxacin	5 (0.4)
Augmentin	4 (0.3)
Doxycycline	4 (0.3)
Trimethoprim/sulfamethoxazole	3 (0.2)
Ertapenem	3 (0.2)
Cefoxitin	3 (0.2)
Levofloxacin	3 (0.2)
Aztreonam	3 (0.2)
Fluconazole	2 (0.2)
Nafcillin/oxacillin	2 (0.2)
Polymyxin B	1 (0.1)
Moxifloxacin	1 (0.1)

and ceftriaxone (11 patients; 2.1%). When EAST guidelines were considered, 31.0% of Gustilo Type-I and Type-II fractures inappropriately received gram-negative coverage. Conversely, 54.9% of Gustilo Type-III fractures did not receive any recommended gram-negative coverage. Differences in antibiotic regimens based on Gustilo fracture type are described in Appendix 1.

An ISS was available for 696 patients, with 301 patients having an ISS of <10. Among patients with an ISS of <10, those with Gustilo Type-I and Type-II fractures were more likely to receive cefazolin monotherapy (59.8%) compared with those with Gustilo Type-III fractures (45.1%; adjusted difference, -16.4%; 95% CI, -28.8% to -4.0%). Patients with Gustilo Type-I and Type-II fractures were less likely to receive cefazolin and an aminoglycoside with or without penicillin (5.0%) compared with those with Gustilo Type-III fractures (11.0%; adjusted difference, 5.4%; 95% CI, -2.1% to 12.9%) (Table IV, Appendix 2).

The exploratory analysis suggests that cefazolin monotherapy was less likely to be prescribed for patients with Gustilo

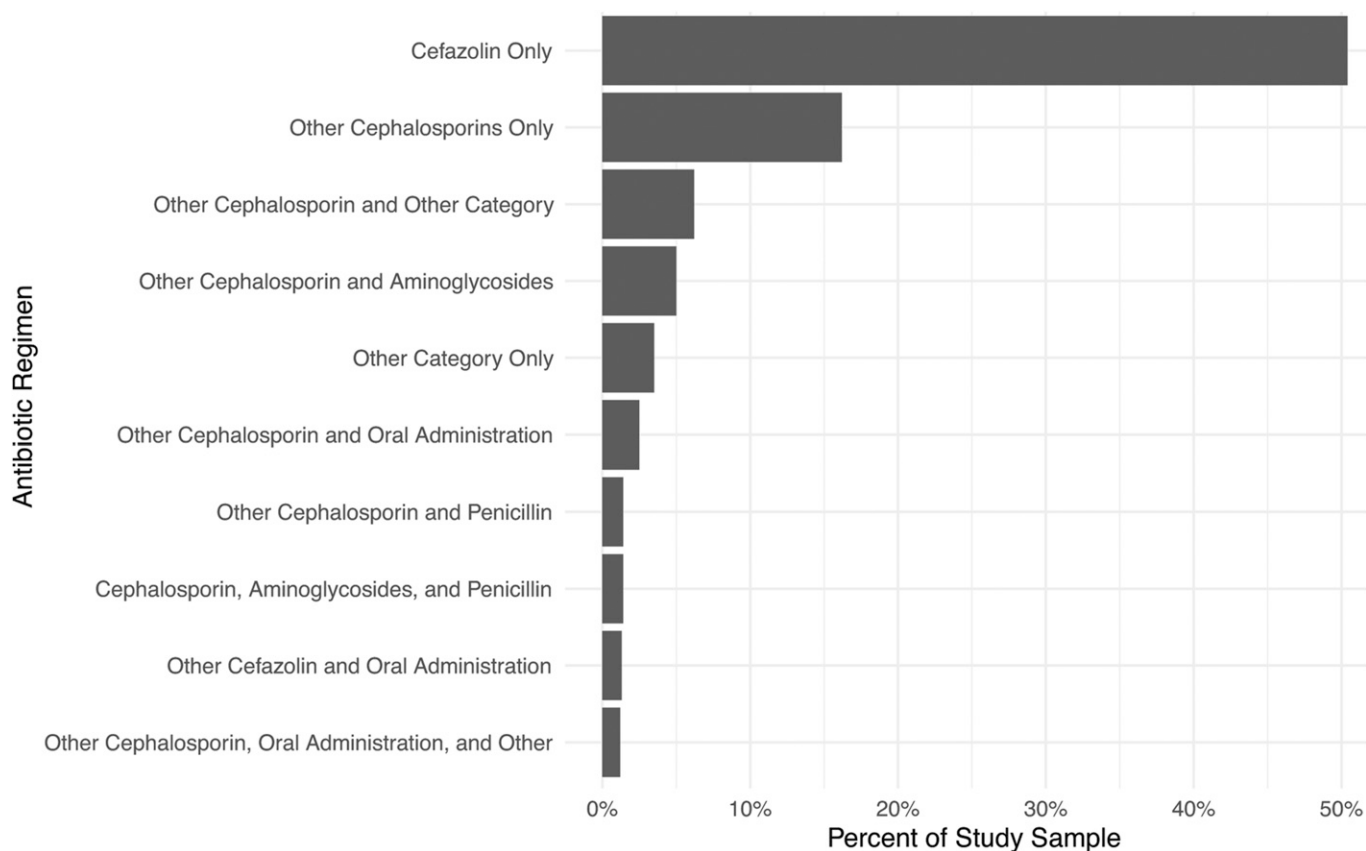


Fig. 1  
Distribution of the top 10 most commonly prescribed antibiotic prophylactic combinations for open fractures.

Type-IIIA (OR, 0.52; 95% CI, 0.36 to 0.76), Gustilo Type-IIIB or Type-IIIC (OR, 0.46; 95% CI, 0.26 to 0.80), and multiple fractures (OR, 0.56; 95% CI, 0.35 to 0.91). Patients with Gustilo Type-IIIB or Type-IIIC fractures did not have an increased likelihood of being prescribed cefazolin with an aminoglycoside

with or without penicillin (OR, 2.69; 95% CI, 0.40 to 8.11) (Appendix 3 and Appendix 4). When EAST guidelines were considered, 42.1% of patients with Gustilo Type-IIIB or Type-IIIC fractures did not receive gram-negative coverage, in violation of the recommended guidelines.

TABLE III Antibiotic Choice by Gustilo Type and Use of Local Adjuvants\*

	Types I and II (N = 704)	Type III (N = 519)	P Value
Systemic antibiotics			
Cefazolin monotherapy	430 (61.1%)	231 (44.5%)	<0.001
Clindamycin monotherapy	16 (2.2%)	5 (1.0%)	0.08
Cefazolin and aminoglycosides (± penicillin)	42 (6.0%)	89 (17.2%)	<0.001
Ceftriaxone monotherapy	14 (2.0%)	11 (2.1%)	0.87
IV vancomycin	40 (5.7%)	49 (9.4%)	0.01
IV piperacillin/tazobactam	15 (2.1%)	35 (6.7%)	<0.01
Local antibiotics			
Topical powder	252 (35.9%)	150 (28.9%)	0.01
Antibiotic-impregnated cement	10 (1.4%)	42 (8.1%)	<0.01
Bioabsorbable delivery	1 (0.1%)	3 (0.6%)	0.19

\*11 patients did not have Gustilo classification recorded and were not included in this secondary analysis. Type-III fractures include those with classifications of Type IIIA, IIIB, and IIIC. The values are given as the number of patients, with the percentage in parentheses. IV = intravenous.

TABLE IV Antibiotic Choice by Gustilo Type and Use of Local Adjuvants in Patients with an ISS of &lt;10\*

	Types I and II (N = 219)	Type III (N = 82)	P Value
Systemic antibiotics			
Cefazolin monotherapy	131 (59.8%)	37 (45.1%)	0.02
Clindamycin monotherapy	10 (4.6%)	3 (3.7%)	0.73
Cefazolin and aminoglycosides (± penicillin)	11 (5.0%)	9 (11.0%)	0.06
Ceftriaxone monotherapy	4 (1.8%)	0 (0%)	0.22
IV vancomycin	14 (6.4%)	10 (12.2%)	0.10
IV piperacillin/tazobactam	7 (3.2%)	10 (12.2%)	<0.01
Local antibiotics			
Topical powder	70 (32.0%)	24 (29.3%)	0.65
Antibiotic-impregnated cement	2 (0.9%)	7 (8.5%)	<0.01
Bioabsorbable delivery	0 (0.0%)	1 (1.2%)	0.10

\*Type-III fractures include those with classifications of Type IIIA, IIIB, and IIIC. The values are given as the number of patients, with the percentage in parentheses. IV = intravenous.

### Antibiotic Duration

The median time to wound closure from admission was 1 day (IQR, 1 to 3 days). The median duration of prophylactic antibiotics following wound closure was 2 days (IQR, 2 to 3 days) (Fig. 2-A). Patients with an ISS of <10 had a similar distribution of the number of days on antibiotics (Fig. 2-B). In the multivariable regression analysis of antibiotic duration, an OTA-OFC contamination grade of 3 was associated with a 1.36-day mean increase in the duration of antibiotics following wound closure (95% CI, 0.48 to 2.2), as did the presence of multiple fractures (1.25 days; 95% CI, 0.33 to 2.18) (Appendix 5). Gustilo type was not associated with a change in duration of antibiotics following wound closure. When the ISS was added to the model, a Gustilo Type-IIIB or Type-IIIC fracture was associated with a 1.49-day increase in the duration of antibiotics after wound closure (95% CI, 0.37 to 2.61), and the degree of contamination was no longer associated with antibiotic duration (Appendix 6).

### Discussion

In the present study, 100% of patients with open fractures received antibiotics on the day of admission, with the majority receiving at least a first-generation cephalosporin; however, there was substantial variation in the combination and duration of antibiotics when stratified by Gustilo fracture type. There was particularly low compliance with traditional recommendations for Gustilo Type-III fractures. Even when alternative antibiotics were considered, nearly half of these fractures did not receive gram-negative coverage, with only a slight improvement in adherence among patients with Type-IIIB or Type-IIIC fractures.

One possible reason for this departure from the recommended guidelines is the mixed and evolving nature of the original pivotal studies. In 1974, Patzakis et al. found that patients who received a first-generation cephalosporin had significantly fewer infections compared with those who

received penicillin with streptomycin or no antibiotic<sup>3</sup>. Later, in their seminal cohort comparison study of 1,025 patients, Gustilo and Anderson reported that the use of prophylactic oxacillin-ampicillin resulted in a substantial decrease in the rate of infection, from 12% to 2% in Type-I and Type-II fractures and from 44% to 9% in Type-III open fractures<sup>6</sup>. A follow-up study in 1984 found that in Type-III open fractures, 77% of infections were caused by gram-negative organisms, a substantial increase from their earlier cohort, which had only 24% of infections caused by gram-negative organisms<sup>7</sup>. This prompted a modification of the Gustilo classification to the current version with subtypes IIIA, IIIB, and IIIC, and the recommendations for gram-negative coverage with either an aminoglycoside or third-generation cephalosporin<sup>7</sup>.

Given the largely observational nature of the literature guiding existing antibiotic recommendations and a growing incidence of methicillin-resistant *S. aureus* infections following open fracture<sup>16</sup>, some surgeons have advocated for alternative agents, including vancomycin, ceftriaxone, piperacillin/tazobactam, and aztreonam for Type-III fractures<sup>21,28</sup>. Although more recent publications generally support the use of some sort of gram-positive coverage<sup>11</sup>, there is little high-quality evidence that evaluates the role of gram-negative coverage for high-energy fractures<sup>11,29,30</sup>. Additionally, pathogens have changed over time<sup>15,16</sup> and evidence that there may be regional or even seasonal variation in causative organisms<sup>31</sup> supports the rationale for a more customized antibiotic protocol rather than a dogmatic approach. Furthermore, despite the lack of clarity on the role of gram-negative coverage, there appears to be increasing interest in more comprehensive antibiotic prophylaxis, with 20% of published recommendations suggesting broad-spectrum coverage regardless of injury severity<sup>20</sup>.

This change in attitudes appears to be consistent with the present data. We found that the rate of usage of first-generation cephalosporins and aminoglycosides in patients with Gustilo

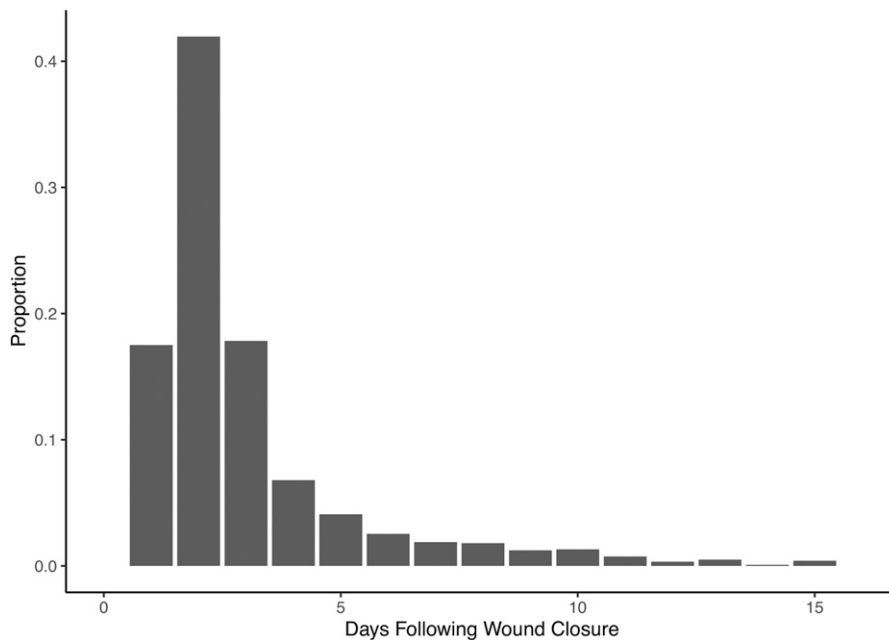


Fig. 2-A

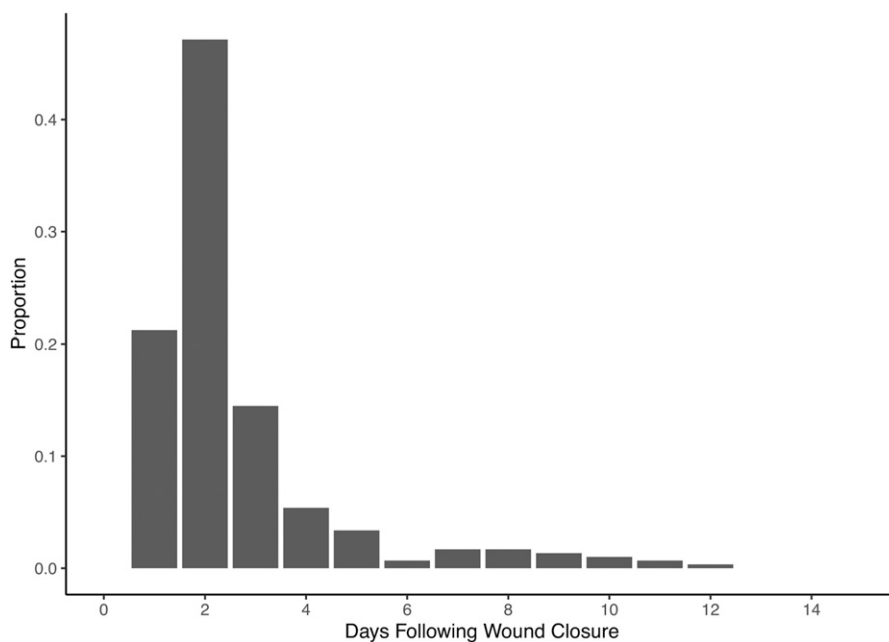


Fig. 2-B

**Figs. 2-A and 2-B** Graphs showing the duration of antibiotic prophylaxis following wound closure in all patients (**Fig. 2-A**) and in those with an ISS of >10 (**Fig. 2-B**).

Type-III fractures was very low, at only 17%, with 45% of patients receiving ceftazolin monotherapy and 10% of patients with Gustilo Type-I or Type-II fractures receiving broad-spectrum coverage. Even when the broader EAST guidelines were considered, 45% of patients with Type-III fractures received only gram-positive coverage. It is possible that hypotension resulting in renal insufficiency and the surprisingly high use of intraoperative topical antibiotics all combined to create

clinical and logistical barriers to traditional protocol adherence and a reduction in the use of appropriate gram-negative agents. It is also possible that initial uncertainty over the classification of an open fracture would lead a practitioner to select the most comprehensive bacterial coverage regardless of formal classification, or even that some centers or individual practitioners may be using broad-spectrum antibiotics for all fractures to simplify protocols<sup>30</sup>.

Beyond the choice of prophylactic agent, there is very little literature regarding the duration of prophylaxis for open fractures. Descriptions of antibiotic duration in the literature range from 48 hours<sup>32</sup> to 7 to 10 days<sup>6</sup>. The most widely recommended duration in the orthopaedic literature is 3 days after wound closure<sup>8,33</sup>, which is in contrast to the <24 hours recommended by the EAST guidelines<sup>1</sup>. A recent systematic review of randomized controlled trials found no difference between a duration of 1 versus 3 to 5 days<sup>30</sup>. In our study, the majority of patients received antibiotics for 2 days, which likely represented a 24-hour postoperative course; however, a substantial proportion of patients received antibiotics for a longer period of time, with 25% of patients receiving antibiotics between 4 and 15 days.

Although it was not the focus of this study, we were also able to describe the use of local antibiotic agents. We found that >30% of patients received a topical antibiotic as part of the prophylactic regimen. Patients with Gustilo Type-III fractures were more likely to receive local antibiotic delivery via cement beads. A recent meta-analysis on the use of local antibiotic prophylaxis found a reduced rate of infection with either direct application of antibiotics or antibiotic-impregnated cement; however, the authors also found that the quality of literature was poor with considerable risk of bias, and that the majority of the literature involved antibiotic-impregnated cement and not direct application of antibiotic powder<sup>34</sup>. The common use of local antibiotic agents warrants further study.


We studied the antibiotic-prescribing practices of 24 trauma centers actively enrolled in a large prospective randomized controlled trial that was focused on different skin-preparation solutions for open fractures<sup>22</sup>. Because initial antibiotic management was left up to the treating physicians and not dictated by the study protocol, this allowed us to closely observe the antibiotic-prescribing practices of multiple different institutions, with detailed information on antibiotic type and duration. Although we had detailed antibiotic data, because this was an opportunistic study of data collected for a larger trial and not an a priori goal, we were not able to delineate clearly if the antibiotics delivered were solely for the purposes of open fractures. For example, we could not identify, and therefore exclude, patients with penetrating abdominal injuries or active sepsis at the time of trauma. It is also possible that patients were prescribed nontraditional antibiotics for unique circumstances that were not captured in the study data collection. However, we were able to assess patients according to their ISS, and because an ISS of 9 is most typically assigned to open fractures, it is unlikely that the subgroup of patients with an ISS of <10 had any other injuries that would require prophylactic antibiotics.

Additionally, as we were not able to determine the indications for the antibiotics prescribed, we defined a prophylactic antibiotic as any antibiotic that was started on the day of admission, which could include multiple antibiotics if they were added later that day. We felt we could reasonably presume that any antibiotics started at the time of admission in patients with a primary admission for trauma would not

have conditions requiring therapeutic antibiotics. However, we were unable to detect any crossover events—for example, if a patient was initially classified as having a Gustilo Type-I or Type-II fracture at the time of admission but then reclassified later that day to Gustilo Type III with additional antibiotics added, or if a patient was erroneously started on a broad-coverage regimen but then narrowed. Similarly, as the treatment of open wounds and bone defects was at the discretion of the treating surgeon, we did not have detailed information regarding the form of antibiotic spacer used. Nonetheless, given that the choice and administration of antibiotics were at the discretion of the providers, we feel that this observational study provides valuable information on how antibiotics for open fractures are currently prescribed in clinical practice.

Despite these limitations, the results of the present study provide valuable insight into the current clinical practice regarding antibiotics for open fractures. Even among academic trauma centers, we found substantial departure from guidelines in both the choice and duration of antibiotics. These data suggest that the orthopaedic community may need to reevaluate how best to prevent infection in open fractures—particularly with high-risk Gustilo Type-III fractures—just as Gustilo et al. did when they reevaluated the Type-III subgroup 2 decades after the original series<sup>7</sup>. Regardless, the low adherence to recommended guidelines in antibiotic usage suggests that high-quality trials are needed to determine how we may achieve the best patient outcomes and most appropriate antibiotic stewardship.

## Appendix

 Supporting material provided by the authors is posted with the online version of this article as a data supplement at [jbjs.org \(http://links.lww.com/JBJS/G278\)](http://links.lww.com/JBJS/G278). ■

### Note:

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