Research Article

Efficacy of Topical Antibiotic Powder Application in the Emergency Department on Reducing Deep Fracture–Related Infection in Type III Open Lower Extremity Fractures: A Multicenter Study

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ABSTRACT

Objectives: Deep fracture–related infections (FRIs) are a common complication of type III open lower extremity fractures, resulting in notable patient morbidity. The purpose of this study was to determine whether topical application of antibiotic (ABX) powder to type III open lower extremity fracture wounds upon presentation to the emergency department (ED) reduces the rate of FRI.

Methods: This is a retrospective review of ABX powder application compared with a historical cohort at 4 level 1 trauma centers. Patients with type III open lower extremity fractures from July 1, 2019, to October 1, 2022, who received topical ABX powder (1 g vancomycin and 1.2 g tobramycin) in the ED were compared with patients from a 4-year historical cohort who were treated through the same protocol without topical ABX powder. Outcomes include the development of FRI within 6 months of follow-up. Patient demographics, injury characteristics, and postoperative data were analyzed in addition to FRI.

Results: One hundred fifteen patients received topical ABX powder in the ED and were compared with 135 patients who were treated without topical ABX powder. The rate of FRI in the intervention group was 8 of 115 (6.96%) vs. 22 of 135 (16.30%) in the control cohort ($P = 0.024$). Multivariate regression analysis demonstrated higher body mass index as a risk factor for the development of FRI ($P = 0.003$). When excluding those with intraoperative ABX powder use, there was still a markedly lower rate of FRI when ED ABX powder was used on regression analysis ($P = 0.048$).

Conclusion: Antibiotic powder application to type III open fracture wounds in the ED markedly reduces the incidence of FRI in this multicenter study. Further large-scale studies are warranted.

Level of Evidence: Therapeutic Level III.

Type III open fractures are traumatic injuries plagued with complications. Deep fracture–related infection (FRI) is one of the primary drivers of these complication rates, contributing to notable patient morbidity and high economic costs to the healthcare system.[1-9] The incidence of FRI is higher in Gustilo–Anderson type III open fractures compared with types I and II, with rates of 9% to 62% reported in the literature.[10,11] FRI confers a serious burden to patients and the healthcare system, including high rehospitalization rates, prolonged antibiotic (ABX) courses, delayed recovery, and secondary amputation rates up to 3%.[12-14]

Multiple factors play a role in the development of FRI. These include patient comorbidities, injury location, and the extent of the injury. Open fractures are prone to infection from both host flora and environmental microbial contamination, with biofilm formation occurring within an hour after inoculation.[4] This biofilm confers resistance to both immune responses and antimicrobial therapies, making FRI particularly difficult to prevent and treat.[15] Greater extent of soft-tissue damage and lower extremity fractures demonstrate higher rates of FRI when compared with upper extremity fractures.[16,17]

Advances in the management of open fractures includes early administration of intravenous antibiotics (ABX) and intraoperative ABX powder administration. The use of systemic ABX has shown great clinical success in decreasing the risk of FRI, likely by impeding biofilm formation.[18-23] Similarly, the use of topical antibiotic powder in the operating room has shown promise in reducing FRI, along with being economically justifiable.[24-30] Despite these developments in treatment, the rates of FRI following open fractures remain high.[31]

More recently, the use of topical ABX powder in the emergency department (ED) on type III open lower extremity fractures has shown the potential to decrease FRI. Taylor et al[32] published a pilot study, demonstrating the use of topical vancomycin and tobramycin powder on open fractures in the ED. This study showed lower rates of FRI in the treatment group compared with the historical cohort that was treated identically besides the absence of ABX powder in the ED. This early application of ABX powder directly to the open fracture likely inhibits early biofilm formation, aiding in reducing the rates of FRI. Although this study showed decreased rates of FRI with the use of topical ABX powder in the ED, the study was underpowered, and statistically significant results were not obtained. Despite this, this study showed that the use of ABX powder in the ED was safe and economically justifiable, warranting further larger studies.[32]

The objective of our multicenter study was to evaluate the efficacy of topical ABX powder on type III open lower extremity fractures in the ED on reducing rates of FRI in a larger patient population. We hypothesize that this intervention will decrease the rate of FRI in these severe injuries.

Methods

This was an institutional review board–approved, retrospective, multicenter cohort study. Inclusion criteria included all patients >18 years of age with an index presentation of a type III open lower extremity fracture to the four level I trauma centers during the enrollment period of July 1, 2019, to October 1, 2022. Exclusion criteria included periprosthetic fractures, current infection of the lower extremity at the time of presentation, definitive fixation performed outside the study centers, patients with a known drug allergy to the trial medication, patients who underwent acute amputation (<2 weeks), and patients with <6 months of follow-up.

Historically, open fractures have been treated with a standardized institutional protocol at all centers. This consisted of saline irrigation and removal of gross debris in the ED, initiation of a broad-spectrum intravenous antibiotic regimen (vancomycin and cefepime), application of sterile saline-soaked gauze dressing, fracture reduction, and application of a plaster splint. Eventually, formal débridement and irrigation were carried out in the operating room within 24 hourrs of presentation followed by definitive versus staged fixation. The use of vancomycin and cefepime remained as the standard antibiotic protocol during the entire study period (treatment and control groups). Per institutional policy, all open lower extremity fractures presenting to the ED were initially treated as type III. Intraoperatively, the attending surgeon determined the definitive fracture classification, and the antibiotic regimen was tailored postoperatively. The final determination of fracture classification and ultimately study eligibility was based on the intraoperative assessment by the attending surgeon. All surgical procedures were performed by fellowship-trained orthopaedic traumatologists.

In 2019, the study centers modified their ED lower extremity open fracture management protocol to include the application of local antibiotic powder directly into the wounds by the orthopaedic trauma resident on call.

This antibiotic powder consisted of 1 vial (1 g) of vancomycin and 1 vial (1.2 g) of tobramycin. All other open fracture management, including dressing type, acute fracture management, and immobilization, was unchanged. If ABX powder application in the ED was not clearly documented in the on-call orthopaedic consultation note, the patient was not included in the analysis. The comparison (historical) cohort is a 4-year historical group (July 1, 2015, to June 30, 2019) of consecutive type III open lower extremity fractures that were managed identically except for not receiving the ABX powder application in the ED. All efforts were carried out to ensure that the historical cohort was identical to the intervention cohort, including matching for age, sex, race, and fracture location from all study centers.

To determine study inclusion, current procedural terminology code 11012 was used to identify patients who underwent surgical débridement of open fractures and were further reviewed to determine eligibility for inclusion in the study based on the study criteria mentioned above. The surgical note from the attending surgeon was used to objectively determine the fracture classification. Variables of interest included *patient demographics* (age, sex, ethnicity, body mass index [BMI], tobacco use, diabetes, insulin dependence, chronic kidney disease at the time of injury, immune competency status, and history of intravenous drug use), *injury characteristics* (mechanism of injury, if soft-tissue reconstruction was necessitated, and if there was a vascular injury repair), and *postoperative outcomes* (development of FRI or superficial FRI, time to revision surgery for FRI and microorganism cultured, nonunion, nonacute amputation, acute kidney injury [AKI], deep venous thromboembolism [DVT] or pulmonary embolism [PE]). All patients with deep FRI were treated with broad-spectrum antibiotics, which were further tailored according to their culture results. Patients with culture-negative results received antibiotics per the Infectious Disease Service recommendations.

The primary outcome was the development of FRI within 6 months, which was defined as clinical and radiographic signs of FRI, cultured pathogenic organisms, and elevated serum inflammatory markers.[33] These patients returned to the operating room for débridement and irrigation, and treatment with subsequent culture-specific antibiotics. Secondary posttreatment outcomes included SSSI (defined as superficial tissue infection treated with oral antibiotics), nonunion (defined as less than three bridging cortices on orthogonal radiographs at follow-up >6 months or hardware failure with no evidence of union at 3 months), nonacute amputation (amputation >2-week postinjury), development of AKI (defined as an increase in serum creatinine by ≥0.3 mg/dL or formally diagnosed by a medical provider within 48 hours of study intervention), DVT, or PE (diagnosed with appropriate imaging studies—ultrasonography or computer tomography angiography). Any discrepancies in secondary outcome measures were ultimately resolved by a senior author.

Univariate comparisons included independent *t*-tests for continuous variables and chi-square tests of independence and Fisher exact tests for categorical variables. A binary logistic regression was used to assess for variables notable at the univariate level ($P < 0.1$) with deep infection, eg, BMI, and the use of antibiotic powder. All analyses were conducted using SPSS version 27 (IBM). A post hoc power analysis was conducted on the full sample (N = 250) based on independent proportional differences using a Pearson chi-square test. With alpha level set at 0.05, the power ($1 - \beta$) of the study was 0.629.

Results

Patients

A total of 115 patients met the study criteria during the enrollment period (July 1, 2019 to October 1, 2022). These patients received documented antibiotic powder in the ED and were included in the primary analysis as the treatment (powder) cohort. The historical (nonpowder) comparison cohort consisted of a total of 135 patients.

Fracture-Related Infection

In the powder group, the FRI rate was 6.96%% (8 of 115) compared with 16.30% (22 of 135) in the historical group ($P = 0.024$) at an end point of 6 months following definitive fixation. Overall, 3 and 10 superficial FRI were observed in the powder and historical groups, respectively ($P = 0.151$). Overall, the average time to presentation of FRI was 2.9 months in the trial group and 2.4 months in the historical cohort ($P = 0.434$).

Demographic Comparisons

When comparing patient demographics and injury characteristics of the powder and historical nonpowder groups, tobacco use showed a notable difference in being more prevalent in the trial group ($P = 0.008$; Table 1). Intraoperative antibiotic was used in 32 patients (27.8%) in the intervention group, compared with 19 (14.1%) in the historical group ($P = 0.007$). However, the use of intraoperative powder was not markedly associated with decrease in the rates on deep FRI (33.3% vs. 18.6%, $P = 0.06$). In addition, no personal

Table 1. Antibiotic Powder Versus Historical Cohort: Demographic and Medical Comparisons

Factor or Variable	ABX Powder (n = 115)	Historical Cohort (n = 135)	Statistical Comparison (*P*)
Age, yr	41.3 (16.5)	40.5 (15.2)	0.691
Sex (% male)	63.5% (73)	74.1% (100)	0.071
Race/ethnicity (%)			
Black	18.3% (21)	14.1% (19)	0.723
White	57.4% (66)	57.0% (77)	
Hispanic	17.4% (20)	19.3% (26)	
Other	7.0% (8)	9.6% (13)	
BMI	29.9 (8.0)	28.4 (7.3)	0.137
Tobacco use (% yes)	58.3% (67)	41.5% (56)	**0.008**
IV drug use (% yes)	4.3% (5)	3.0% (4)	0.736
Diabetic			
%yes	13.9% (16)	8.1% (11)	0.143
%Insulin dependency	50.0% (8/16)	27.3% (3/11)	0.427
Current kidney disease	6.1% (7)	3.7% (5)	0.380
Immunocompromised (% yes)	0.9% (1)	5.2% (7)	0.073
Required coverage 3B (% yes)	7.0% (8)	11.1% (15)	0.257
Vascular injury (% yes)	4.3% (5)	5.2% (7)	0.758
Injury severity score (%)			**0.000038**
Minor	21.7% (25)	37.0% (50)	
Moderate	34.8% (40)	45.2% (61)	
Severe	43.5% (50)	17.8% (24)	
Bone fractured (%)			
Femur	21.74% (25)	21.48% (29)	0.107
Tibia	54.78% (63)	56.30% (76)	
Patella	2.61% (3)	2.22% (3)	
Ankle	18.26% (21)	10.37% (14)	
Foot	2.61% (3)	9.63% (13)	
Intraoperative ABX powder (% yes)	27.82% (32)	14.1% (19)	**0.007**

BMI = body mass index
Bold = $p<0.05$ (statistically significant).

demographic or injury characteristic varied between patients with and without FRI (Table 2).

Overall, the binary logistic regression model assessing risk factors of BMI and antibiotic powder in the development of FRI was notable ($X^2(4) = 16.741$, $P = 0.002$), with a $-2LL = 166.721$ and Nagelkerke $R^2 = 0.125$. ED powder use was negatively associated with the incidence of FRI. Those receiving ED powder were 63.3% less likely to have an FRI ($P = 0.026$). BMI was also markedly related to the incidence of FRI, such that for each unit increase in BMI, a 7.5% increase in the likelihood of developing FRI was found ($P = 0.003$). The use of intraoperative antibiotic powder, either isolated ($P = 0.107$) or in combination with ED powder ($P = 0.710$), did not markedly affect the incidence of FRI (Table 3).

The results of cultures taken at the time of revision surgery for FRI are summarized in Table 4, with higher rates of polymicrobial infections seen in the historical (nonpowder) group. No difference was detected in postoperative complication rates between the groups, including AKI, DVT or PE, nonunion, or failed limb salvage. The incidence of nonunion was 11.3% and 15.6% ($P = 0.328$) in the powder and historical nonpowder groups, respectively (Table 5). Five of the 13 nonunions in the powder group were infected nonunions.

Table 2. Comparison of Factors Related to Development of Deep Infection: Antibiotic Powder Versus Historical Cohort

Factor or Variable	Deep Infection (n = 30)	No Deep Infection (n = 220)	Statistical Comparison (*P*)
ABX powder treatment (% yes)	26.7% (8)	48.6% (107)	0.024
Age, yr	39.6 (13.4)	41.1 (16.1)	0.636
Sex (% male)	83.3% (25)	67.3% (148)	0.074
Race/ethnicity			
Black	13.3% (4)	16.4% (36)	0.810
White	53.3% (16)	57.7% (127)	
Hispanic	23.3% (7)	17.7% (39)	
Other	10.0% (3)	8.2% (18)	
BMI	32.4 (10.1)	28.7 (7.2)	0.060
Tobacco use (% yes)	50.0% (15)	49.1% (108)	0.926
IV drug use (% yes)	3.3% (1)	3.6% (8)	1.000
Diabetic			
%yes	10.0% (3)	10.9% (24)	1.000
%Insulin dependency	66.7% (2/3)	37.5% (9/24)	0.549
Current kidney disease	0.0% (0)	5.5% (12)	0.370
Immunocompromised (% yes)	3.3% (1)	3.2% (7)	1.000
Required coverage 3B (% yes)	10.0% (3)	9.1% (20)	0.745
Vascular injury (% yes)	6.7% (2)	4.5% (10)	0.642
Intraoperative ABX powder (% yes)	33.3% (10)	18.6% (41)	0.061
Fracture location (%)			
Femur	13.3% (4)	22.7% (50)	0.110
Tibia	56.7% (17)	55.5% (122)	
Patella	0% (0)	2.7% (6)	
Ankle	13.3% (4)	14.1% (31)	
Foot	16.7% (5)	5.0% (11)	
Injury severity score (%)			
Minor	46.7% (14)	27.7% (61)	0.045
Moderate	40.0% (12)	40.5% (89)	
Severe	13.3% (4)	31.8% (70)	

BMI = body mass index

Discussion

Our study detected a notable decrease in FRI with the use of topical antibiotic powder in the ED compared with a historical control cohort. When considering patient demographics and injury characteristics as contributors to FRI, the only variable with statistical significance was higher BMI on multivariate regression analyses. Notably, no identifiable difference was observed in the occurrence of AKI, DVT, or PE between the two groups, lending support to the safety of this treatment.

When comparing cultured organisms between the powder and historical cohorts, the historical nonpowder group showed higher rates of polymicrobial FRI. This is relevant because antibiotic targeting and patient outcomes may be dependent on the organism cultured during infection. Microbial culture in our study are in line with published literature.[34-36] Pradhan et al[34] demonstrated positive bacterial culture isolates among suspected orthopaedic infections in 6,201 patients of which 2,957 (47.7%) had a positive bacterial culture. The most prevalent organism identified was Staphylococcus

Table 3. Binary Logistic Regression Analysis Assessing Variables Influencing the Incidence of Deep Fracture–Related Infection

Factor or Variable	B	SE	Wald	Sig	OR	95% Lower CI	95% Upper CI
BMI	0.072	0.024	8.765	0.**003**	1.075	1.025	1.128
Male sex	0.978	0.536	3.325	0.068	2.658	0.929	7.603
ABX powder treatment	−1.003	0.451	4.942	0.**026**	0.367	0.152	0.888
No ABX powder treatment (ref)							
Only intraoperative ABX	0.938	0.582	2.604	0.107	2.556	0.818	7.991
Only ED ABX	−1.164	0.588	3.912	0.**048**	0.312	0.099	0.990
Both ED and intraoperative ABX	−0.236	0.633	0.139	0.710	0.790	0.229	2.731

ABX = antibiotic; BMI = body mass index; ED = emergency department

aureus (24.2%), followed by *Escherichia coli* (17.9%) and Klebsiella (14.1%). These results were similar to those published by Phillips et al,[35] demonstrating highest burden of Coagulase-negative *Staphylococcus*, followed by S. aureus, Enterococci, and Streptococci in patients with deep prosthetic infections. Dhanoa et al[36] showed similar results to those of Phillips et al in orthopaedic oncology patients and further highlighted successful eradication of infection in 54% patients and amputation in 2% of the patients.

This study aligns with the current literature by aiming to find new ways of managing type III open lower extremity fractures with the goal of decreasing FRI. Previous studies have shown that the use of intraoperative local antibiotics, in the form of beads or powder, have led to reduced rates of FRI.[24,30] More recently, the use of topical antibiotic powder in the ED has shown potential in lowering FRI, with the need for larger studies.[32] This study aimed at further evaluating this use of topical antibiotic powder in the ED in the setting of a larger cohort, multicenter study. The results of this study were notable, helping to corroborate the findings of this earlier pilot study but still lacking sufficient power for a definitive statement on efficacy.

Table 4. Organisms Cultured at the Time of Revision Surgery for Fracture-Related Infection

Organism	ABX Powder Cohort (n = 8)	Non-powder Historical Cohort (n = 22)
Polymicrobial	0	5
MRSA	1	2
MSSA	2	4
Gram-negative rods	2	3
Mycobacterium/ other	1	3
Culture negative/ no culture	0	5
Streptococcus	1	0
Pseudomonas	1	0

MRSA = methicillin resistent staph aureus, MSSA = methicillin sensitive staph aureus

This study has multiple limitations. A cohort study design was chosen over a randomized control trial because it is difficult to consistently enroll and properly randomize most patients with type III open lower extremity fractures. Many of these patients arrive at our institutions in critical condition, requiring immediate medical attention and intervention, making randomization impractical. As a result, a new standardized protocol involving the use of antibiotic powder was implemented for all type III open lower extremity fracture cases, and their outcomes were compared with a historic cohort. To ensure parity between the two groups, demographic and injury characteristics were evaluated, and the attending surgeon's intraoperative assessment was used for objective determination of the fracture classification and study inclusion.

Furthermore, although the ABX powder was applied immediately on patient presentation to the ED, it was challenging to record the precise timing of antibiotic powder application consistently and accurately because of the variable nature of patient presentations at busy, level 1, trauma centers. Next, a primary end point of 6 months was chosen for FRI, supported by clinical data suggesting that most FRI present within this time frame. Nonetheless, FRI can present at any time, and we also acknowledge that some patients may have presented elsewhere with FRI. Finally, standardization of treatment is a study limitation. Although institutional protocols were in place to guide management for both the historic

Table 5. Outcomes: Antibiotic Powder Versus Historical Cohort

Factor or Variable	ABX Powder (n = 115)	No ABX Powder (n = 135)	Statistical Comparison (*P*)
Deep infection (% yes)	7.0% (8)	16.3% (22)	0.024
Time to infection (mo)	2.9 (1.5) (n = 8)	2.4 (1.5) (n = 22)	0.434
AKI	7.0% (8)	11.9% (16)	0.190
DVT	2.6% (3)	2.2% (3)	01.000
PE	0.9% (1)	2.2% (3)	0.627
Superficial infection	2.6% (3)	7.4% (10)	0.151
Nonunion	11.3% (13)	15.6% (21)	0.328
Amputation (failed limb salvage)	0.9% (1)	3.7% (5)	0.222

AKI = acute kidney injury; DVT = deep venous thromboembolism; PE = pulmonary embolism

and trial cohorts, there was inevitable deviations from the standard. This included the time to IV antibiotics initiation, exact method of powder application, variability in surgical technique, and time to definitive management. In addition, with a post hoc power of 0.629, our study was underpowered and requires a future study with larger sample size and longer follow-up to validate this study's findings.

Finally, the use of antibiotic powder in the OR has been previously well-described. In this study group, 27.8% of the powder and 14.1% of the historical nonpowder group received documented ABX powder intraoperatively, which may contribute to a confounding bias despite the small total number. No notable difference was noted in incidence of deep FRI with the use of intraoperative powder (12.5% vs. 31.6%, P = 0.061), which may be because of the small number of patients with intraoperative ABX powder included in each group. However, when excluding those with intraoperative powder use, there was still a markedly lower rate of FRI in those patients when ED ABX powder was used on regression analysis (P = 0.048). Future large studies are warranted to further evaluate the use of combined ED and intraoperative ABX powder use compared with isolated ED or intraoperative application.

Conclusion

This study found a notable difference in FRIs at 6 months with the administration of intrawound antibiotic powder to type III open lower extremity fractures in the ED versus standard management. This relatively inexpensive and easily applicable modification to open fracture management has demonstrated low risk and higher efficacy in improving patient outcomes by limiting the incidence of FRI. Further, large-scale, clinical trials are warranted to corroborate the results of this study.

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