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MAJOR ARTICLE

Evaluating Predictive Value of Surgical Resected Proximal Bone Margins in Diabetic Foot Osteomyelitis With Clinical Outcomes at 1 Year

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Background. Osteomyelitis of the diabetic foot remains a significant complication that may result in the need for amputation. Proximal surgical margin histopathology after limb-sparing amputation could be used to guide antimicrobial duration and prognostic management but remains debatable. Here we evaluate if negative proximal bone margins predict outcomes of diabetic foot osteomyelitis at 1 year.

Methods. A retrospective study assessed adults with diabetes undergoing limb-sparing foot amputations from September 2016 to September 2019. Patients required histopathology confirmation of osteomyelitis, proximal margin histopathology report, and documented electronic medical record follow-up through 12 months. The primary outcome evaluated if no further amputation at the same site was required in the following 12 months.

Results. Of 92 patients, 57 (61.9%) had pathology-confirmed negative margins for osteomyelitis. Patients with negative margins required less frequent subsequent amputations at the same site within 12 months compared to positive margins (86.0% vs 65.7%; $P = .003$). Antibiotic duration was shorter in patients with negative margins (mean, 18 vs 30 days; $P = .001$). Negative-margin patients also noted lower rates of readmission at 12 months (26.3% vs 51.4%; $P = .015$) for site-specific complications. *Staphylococcus aureus* was more predominant in patients with positive versus negative margins (57.1% vs 29.8%; $P = .017$).

Conclusions. Negative proximal bone margin by histopathology was associated with lower frequency of further amputations at the index surgical site within 12 months. This group also received shorter courses of antibiotic therapy. It was also associated with lower rates of readmission at 12 months for surgical-site complications. Proximal margin histopathology results potentially can be integrated to guide antimicrobial duration and decrease the frequency of further amputation at the original site.

Keywords. diabetes mellitus; diabetic foot; osteomyelitis; surgical margins.

According to the Centers for Disease Control and Prevention, an estimated 34.3 million people live with diabetes mellitus in the United States alone, with costs for management hovering around $327 billion in 2017 [1, 2]. Complications from diabetes range from cardiovascular, renal, ocular, and neuropathic disease, to infections and death. A major complication from diabetes with associated comorbidity is the development of diabetic foot infections (DFIs). This often presents a formidable challenge in management for healthcare providers both in the ambulatory and inpatient settings. The presentation can range from significant soft tissue infections to deep bone infections, which often require antimicrobial therapy and a multidisciplinary approach with surgical intervention.

Patients presenting with diabetic foot osteomyelitis (DFO) may require both surgical and medical interventions especially with progressive soft tissue and bone disease, or after failed antimicrobial therapy. However, evidence has been limited and with inconsistent findings on the most appropriate treatment of refractory DFI. Some studies have demonstrated that antimicrobial therapy alone without surgical intervention may still be a reasonable approach [3, 4]. Other studies have indicated that a combined surgical and medical approach may have better outcomes [5, 6]. Current guidelines have suggested surgical debridement of infected bone for further treatment and potentially further antimicrobial therapy in the setting of such infections with history of treatment failures. The now-archived Infectious Diseases Society of America guidelines noted that duration of therapy was not well defined and could be influenced by

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residual disease at the site of resection, along with any remaining soft tissue involvement. Antimicrobial duration after surgical resection could range anywhere from 2–5 days to 4–6 weeks depending on the presence or absence of residual disease either in the soft tissue or to bone at the amputation margins [7]. Current recommendations from the International Working Group on the Diabetic Foot guidelines recommend obtaining a specimen of bone at the resected margin for culture and histopathology to evaluate if there is residual bone disease in order to help guide antimicrobial therapy, but have noted that these recommendations were considered weak with moderate quality of evidence [8]. Multiple studies have further evaluated the prognostic values of proximal resected surgical margins in DFO, but results have been mixed and this recommendation remains unclear in benefit [9, 10].

Historically, the outcomes with histopathologic presence of osteomyelitis at proximal margins have had mixed results regarding outcomes. One recent study by Johnson et al reported that residual osteomyelitis at proximal margins often needed further surgical intervention or even higher mortality [11]. Kowalski et al evaluated residual osteomyelitis of surgical bone resections of DFO and found that positive margins correlated with increased treatment failures [12]. Simpson et al evaluated outcomes of chronic osteomyelitis of the lower extremities and found that necrotic and infected bone removal was the most crucial factor in cure of infection [13]. This is in contrast to other studies that have demonstrated nonsignificant differences in treatment outcome regardless of a negative or positive histopathologic margin [14, 15].

Given the mixed outcomes of evaluating the benefits of resected surgical margins, the primary purpose of this study was to evaluate the potential predictive impact of resected negative surgical proximal bone margins in DFO and the correlation with clinical outcomes at 12 months, specifically the need for further bone amputation at the same site. Furthermore, the study evaluated if margin results could guide shorter duration of antimicrobial therapy at our institution, and if there were differences in outcome with intravenous versus oral therapy. Finally the study also assessed if other risk factors were associated with clinical failure or success at 12 months.

METHODS

This was a descriptive retrospective study at a single-center safety-net county hospital (Riverside University Health System Medical Center, Moreno Valley, California). The study was approved by the institutional review board and granted a waiver for consent due to the retrospective design. We identified records of patients who underwent limb-sparing below-ankle amputations from September 2016 to September 2019 by *International Classification of Diseases, Tenth Revision* and *Current Procedural Terminology* codes through the hospital electronic medical record (EMR) database used by our surgical and podiatry services (Supplementary Table 1). Patients were manually screened to confirm a diagnosis of diabetes, and individuals with a pathology report of histopathologically confirmed osteomyelitis were included for study analysis. Only first encounters of DFO were included.

Patient Selection

Inclusion criteria were as follows: (1) age ≥18 years; (2) clinical diagnosis of diabetes mellitus; (3) having undergone limb-sparing, below-ankle amputation; (4) histopathological confirmation of osteomyelitis; and (5) documented follow-up through 12 months available in the EMR for review.

Individuals were excluded if there was inadequate histopathology descriptive assessment of the presence or absence of osteomyelitis at proximal surgical margins, deceased prior to 12 months from index surgical intervention from non-DFO-related complications, underwent definitive above/below-knee amputation, or were without documented follow-up for chart review in EMR within 12 months from surgery by surgical, infectious disease, or primary care providers. Positive histopathology was defined by noted report of osteomyelitis and/or inflammation, or leukocyte infiltration of bone. Clinical care was typically arranged by treating services, including the interval and duration of follow-up after intervention.

Definitions and Variables

We defined treatment success as individuals not requiring further surgical amputation at the same site within a 12-month period from the index surgery. The primary analysis evaluated if there were differences in the rate of successful outcomes between the negative and positive proximal margin groups. Secondary analysis evaluated if there were differences in success rate based on microbiology (specifically *Staphylococcus aureus*), duration and route of antibiotic therapy, and readmission for surgical-site complications for non-amputation-related interventions at the index site (such as repeated incision and drainage, or revisions) the following 12 months from initial surgery.

A standard chart abstraction program was utilized to record data including demographics, duration and route of antimicrobial therapy, operative microbiology, histopathology results, methicillin-resistant *S aureus* (MRSA) screen on admission, history of prior non-infection-associated surgery at the same site, frequency of readmission after surgery for surgical complications, and if infectious disease was consulted during the amputation encounter. The most recent glycosylated hemoglobin (HbA1c) value within 3 months was recorded, with HbA1c further categorized into dichotomous categorical variable (≤7 vs <7%). The most current C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and procalcitonin were collected, either at admission or prior to surgery. Comorbidities such as

vascular and microvascular disease and smoking history were recorded if ever documented in the EMR.

Statistical Analysis

Statistical analysis was performed by a biostatistician with the Comparative Effectiveness and Clinical Outcomes Research Center (CECORC) at our institution. Categorical variables were documented with absolute values and frequency, and continuous variables were documented with mean ± standard deviation. Categorical variables were analyzed as appropriate with χ^2 analysis with a Bonferroni correction or Fisher exact test when applicable. Normally distributed continuous variables were analyzed using independent *t* test. Nonparametric continuous variables were analyzed using Mann-Whitney *U* test. Variables were then assessed for bivariate correlation with the outcome of interest and controlled for in a multivariate logistic regression model. Multivariable regression analysis was thus performed in assessing the 12 month outcomes of patients while controlling for covariates that were significantly correlated with the outcome and/or are clinically significant. Variables controlled for included age, sex, initial CRP levels, bone margin, HbA1c >7%, antibiotic class, course length, smoking history, and prevalence of a previous surgery. Furthermore, a time-to-event analysis was added to assess the 12-month failures. Cox regression analysis was utilized to demonstrate the correlation between bone margin and failure at the 12-month outcome adjusting for failures at time dropoffs earlier than 12 months. All data analysis was performed using SPSS version 26 software. *P* values <.05 were considered statistically significant.

RESULTS

A total of 697 patient cases from September 2016 through September 2019 were identified for review, with 271 cases identified as first-event DFO encounters. One hundred seventy-nine cases were excluded, and ultimately 92 cases were identified for the study population (Figure 1).

Demographics and clinical characteristics of patients included in the study are noted in Table 1. Age, sex, and comorbidities including peripheral vascular disease and diabetic-associated microvascular disease (nephropathy, neuropathy, and retinopathy) were similar between the 2 groups.

Of the 92 cases, 57 had negative margins and 35 had positive margins. Forty-nine of 57 (86.0%) patients with negative margin resulted in a successful outcome compared to 23 of 35 (65.7%) in the positive-margin group. When comparing the 2 groups, this represented a statistically significant difference

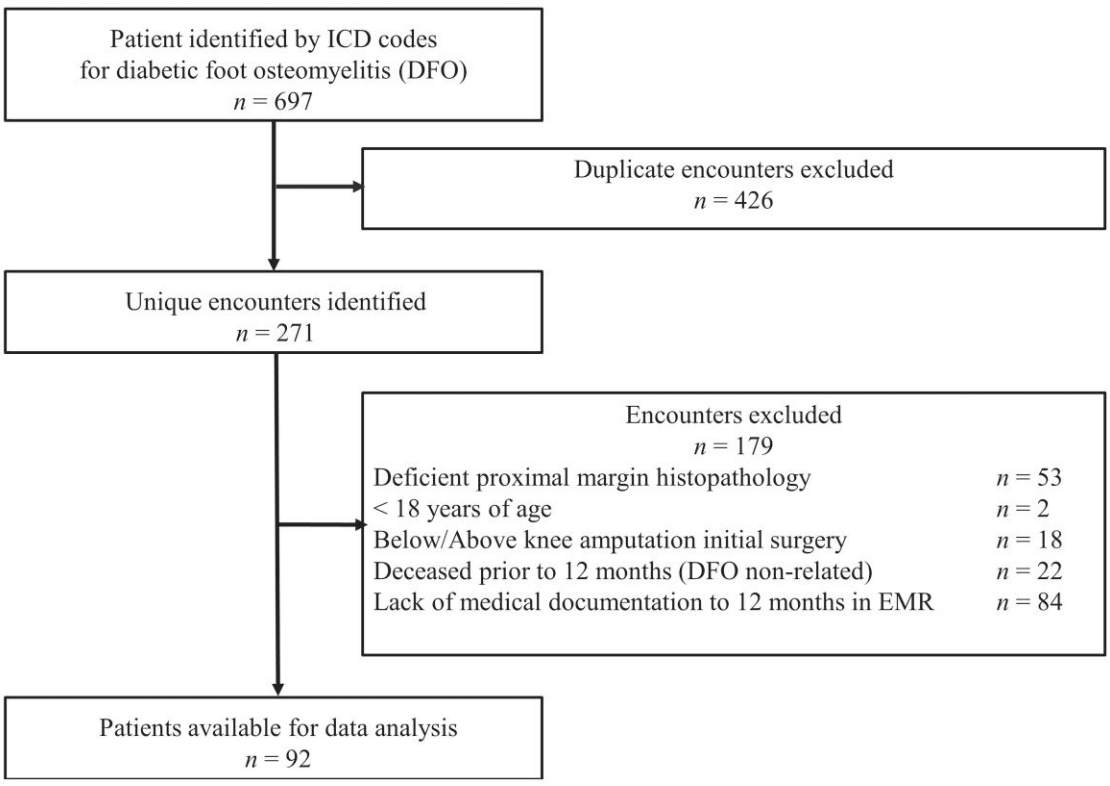

Figure 1. Study population flowchart. Abbreviations: DFO, diabetic foot osteomyelitis; EMR, electronic medical record; *ICD-10, International Classification of Diseases, Tenth Revision.*

Table 1. Univariate Analysis of Population, Outcomes, Microbiology, and Antibiotic Characteristics

Variable	Negative Margins (n = 57)	Positive Margins (n = 35)	*P* Value
Demographics and background			
Age, y, mean ± SD	53 ± 10	54 ± 10	.66
Male sex	24 (73.7)	30 (85.7)	.203
HbA1c, %	8.9 ± 2.7	8.3 ± 2.4	.298
≤7	16 (28.1)	15 (42.9)	.277
>7	41 (71.9)	20 (57.1)	.121
Vascular disease	24 (42.1)	10 (28.6)	.192
Smoking history	20 (35.1)	20 (57.1)	.038
Prior surgery same site	15 (26.3)	13 (37.1)	.273
Microvascular disease			
Neuropathy	23 (40.4)	15 (42.9)	.867
Nephropathy	17 (29.8)	11 (31.4)	.914
Retinopathy	6 (10.5)	4 (11.4)	.990
Laboratory results			
CRP[a], mg/dL, mean ± SD	10.17 ± 13.54	13.0 ± 9.95	.301
ESR[b], mm/h, mean ± SD	88 ± 31	92 ± 29	.794
Procalcitonin[c], ng/mL, mean ± SD	1.53 ± 3.72	1.9 ± 2.43	.584
MRSA screen	0 (0.0)	3 (8.6)	.004
Clostridioides difficile infection	1 (1.8)	0 (0.0)	.990
Microbiology of intraoperative surgical cultures			
Staphylococcus aureus[d]	17 (29.8)	20 (57.1)	.017
MSSA	8 (14.0)	16 (45.7)	.001
MRSA	9 (15.8)	4 (11.4)	.399
Streptococcus spp only	6 (10.5)	4 (11.4)	.574
Polymicrobial cultures without *S aureus*	9 (15.8)	3 (8.6)	.253
Aerobic gram-negative rods only[e]	5 (8.8)	2 (5.7)	.524
Coagulase-negative *Staphylococcus* spp only	2 (3.5)	1 (2.9)	.990
Negative cultures	3 (5.3)	1 (2.9)	.250
No cultures collected	15 (26.3)	4 (11.4)	.272
Further organism breakdown of all polymicrobial operative cultures			
Anaerobes	4 (7.0)	0 (0.0)	.294
Coagulase-negative			
Staphylococcus	2 (3.5)	2 (5.7)	.634
Enterococcus spp	6 (10.5)	2 (5.7)	.706
Enterobacter spp	2 (3.5)	1 (2.9)	.990
Escherichia coli	0 (0.0)	2 (5.7)	.142
Group B/G *Streptococcus*	3 (5.3)	9 (25.7)	.009
Klebsiella pneumoniae	0 (0.0)	1 (2.9)	.380
Proteus mirabilis	2 (3.5)	2 (5.7)	.634
Pseudomonas aeruginosa	4 (7.0)	0 (0.0)	.294
Providencia stuartii	1 (1.8)	0 (0.0)	.990
Streptococcus viridans	1 (1.8)	0 (0.0)	.990
Outcomes			
Successful outcome at 12 mo[f]	49 (86.0)	23 (65.7)	.033
Successful outcome at 6 mo[f]	48 (84.2)	24 (68.6)	.077
Readmission after surgery[g]	15 (26.3)	18 (51.4)	.015
Antibiotic characteristics			
Antibiotic duration, d, mean ± SD	18 ± 15	30 ± 15	.001
Antibiotic treatment			
Oral	31 (54.4)	12 (34.3)	.061
Intravenous	19 (33.3)	23 (65.7)	.002
Intravenous to oral	1 (1.8)	0 (0.0)	.062
No antibiotics	6 (10.5)	0 (0.0)	.051

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HbA1c, glycosylated hemoglobin; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; SD, standard deviation.

[a]CRP reference range: 0–0.3 mg/dL.

[b]ESR reference range: 0–20 mm/hour.

[c]Procalcitonin reference range: 0.00–0.50 ng/mL.

[d]Includes both monomicrobial and polymicrobial cultures with *Staphylococcus aureus*.

[e]*Escherichia coli* (n = 5), *Klebsiella* spp (n = 1), *Morganella morganii* (n = 1), *Proteus* spp (n = 1), *Pseudomonas aeruginosa* (n = 1).

[f]Not requiring further limb-sparing amputation at the same site.

[g]Admission specifically related to complications of treatment site.

Table 2. Multivariable Analysis of Baseline Characteristics, Outcomes, Microbiology, and Antibiotic Characteristics Assessing 12-Month Failures

Independent Variable	OR	(95% CI)	*P* Value
Bone margins (positive vs negative)	5.091	(1.26–20.571)	.022
Age, y	0.994	(.935–1.056)	.835
Sex	1.799	(.308–10.514)	.515
HbA1c >7% vs ≤7%	1.283	(.331–4.968)	.719
Smoking status	0.943	(.278–3.206)	.926
Initial CRP	1.005	(.963–1.05)	.806
Previous surgery at same site	2.81	(.836–9.452)	.095
Long vs short antibiotic course	0.434	(.093–2.028)	.289
Antibiotic treatment (IV vs PO)	2.746	(.615–12.271)	.186

Abbreviations: CI, confidence interval; CRP, C-reactive protein; HbA1c, glycosylated hemoglobin; IV, intravenous; OR, odds ratio; PO, oral.

(86.0% vs 65.7%; $P = .033$) (Table 1). HbA1c was similar between the 2 groups (8.9% vs 8.3%; $P = .298$). HbA1c was not found to be significant with univariate or multivariate analysis. Furthermore, when controlling for HbA1c in the logistic regression model, no significant correlation was observed between HbA1c and incidences of failures at 12 months (Table 2). CRP, ESR, procalcitonin, and rates of *Clostridioides difficile* infection were not statistically different between the 2 groups. Frequency of infectious disease consultation did not differ between the 2 groups, but did trend higher toward the positive proximal margin group (Table 1). Among patient clinical characteristics, tobacco history was identified as the only characteristic with a statistically significant difference that was higher in the positive margin group (35.1% vs 57.1%; $P = .038$). On further multivariable regression analysis, tobacco history did not demonstrate a significant difference in success or failure at 12 months (Table 2).

Upon evaluating operative microbiology cultures, *S aureus* was noted more frequently in individuals with positive margins compared to negative margins (57.1% vs 29.8%; $P = .017$), with methicillin-susceptible *S aureus* being more predominant in those with positive margins (45.7% vs 14.0%; $P = .001$). MRSA rates were similar between the 2 groups (15.8% vs 11.4%; $P = .399$). Negative culture results were more notable in individuals with negative margins (43.9% vs 22.9%; $P = .041$) (Table 1). Operative cultures were not consistently documented directly from proximal margins, so could not be evaluated specifically in this context.

Readmission for surgical-site complications for non-amputation-related interventions at the index site within the following 12 months was also statistically different between the 2 groups with fewer readmissions in the negative-margin group (26.3% in negative-margin group vs 51.4% in positive-margin group; $P = .015$). Despite a statistically significant difference in successful outcomes at 12 months when comparing negative- to positive-margin groups, there was no observable difference between the 2 groups at 6 months, and did not achieve statistical significance (84.2% in negative-margin group vs 68.6% in positive-margin group; $P = .077$).

Antibiotic duration was significantly shorter in the negative-margin group with a mean duration of 18 ± 15 days versus 30 ± 15 days ($P = .001$; Table 1). Comparison of outcomes with intravenous versus oral antibiotics in multivariable analysis noted no significant differences in 12-month outcomes (odds ratio [OR], 2.746 [95% confidence interval {CI}, .615–12.271]; $P = .186$). These same findings were also observed in the logistic regression model in assessing 12-month outcomes (OR, 1.577 [95% CI, .461–5.397]; $P = .468$; Table 2).

In further multivariable regression analysis, only negative bone margins were significantly associated with higher rates of success at 12 months (Table 2). In adjusting for time-to-event analysis, again only negative margins were significantly associated with higher rates of success at 12 months. Other variables including diabetic control, antibiotic duration, and antibiotic type (oral vs intravenous therapy) were not found to be significantly associated with 12-month failures when adjusting for time-to-event analysis (Table 3).

Cumulative time-to-event analysis was performed and adjusted for all success and failure events by 12 months. All failure events occurred by 8 months from initial surgical intervention (Figure 2). Further evaluation specifically comparing failure events of negative to positive bone margins observed a higher success rate in negative-margin individuals (Figure 3).

Table 3. Cox Regression Assessing 12-Month Failure (Adjusted for Time)

Independent Variable	OR	(95% CI)	*P* Value
Bone margins (positive vs negative)	3.282	(1.103–9.766)	.033
Age, y	0.987	(.937–1.04)	.623
Sex	1.882	(.385–9.187)	.435
HbA1c >7% vs ≤7%	1.214	(.397–3.718)	.734
Smoking status	0.944	(.339–2.631)	.912
Initial CRP	1.006	(.972–1.041)	.741
Previous surgery at same site	2.055	(.807–5.231)	.131
Long versus short antibiotic course	0.468	(.126–1.741)	.257
Antibiotic treatment (IV vs PO)	1.577	(.461–5.397)	.468

Abbreviations: CI, confidence interval; CRP, C-reactive protein; HbA1c, glycosylated hemoglobin; IV, intravenous; OR, odds ratio; PO, oral.

DISCUSSION

In this study evaluating the outcomes of DFO requiring surgical amputation, individuals with negative proximal bone margins for osteomyelitis were observed to have less subsequent

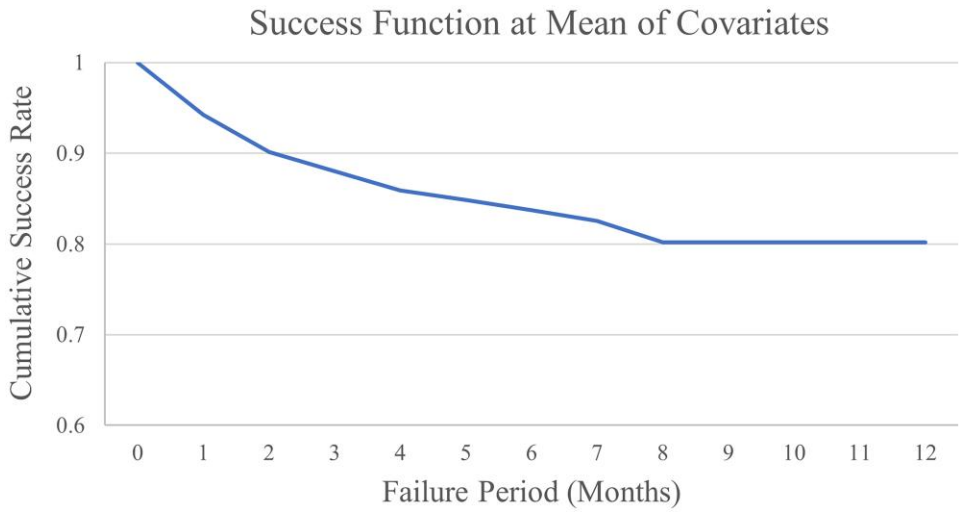

Figure 2. Time-to-event analysis of cumulative 12-month success and failure.

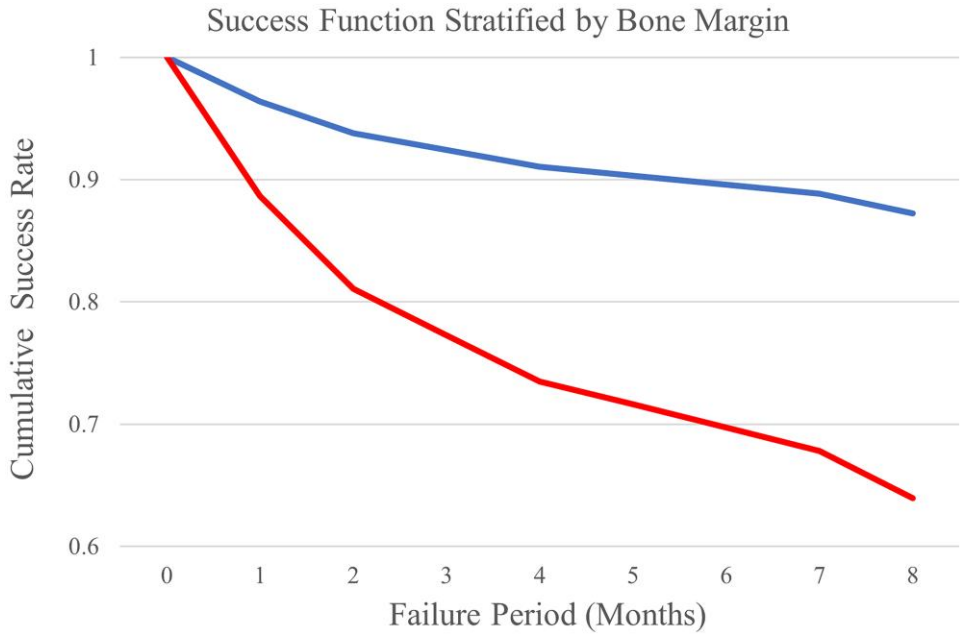

Figure 3. Time-to-event analysis of failures, stratified by proximal bone margin results.

surgical amputation at the same site within the following 12 months. This was similar to observations and results in other studies [12, 13, 16]. Secondary analysis observed that patients with negative margins also had lower rates of readmission for surgical-site complications for non-amputation-related interventions at the same site over the following 12 months.

In evaluating antimicrobial therapy, negative histopathology for osteomyelitis at proximal margins was observed to result in shorter duration of antibiotics. In individuals with positive margin, the mean treatment duration was 30 days (±15 days), but despite receiving less than the full 6 weeks of therapy on average, 65.7% of positive margin cases still had successful outcomes. Definitive conclusions could not be drawn regarding the appropriateness and outcome of shorter antimicrobial courses for individuals with positive margins, and future studies should evaluate if shorter durations of antibiotics than the typical 6-week course is a viable option in these presentations. The utilization of bone margins results could be considered in stewardship interventions directed toward optimizing duration of antimicrobial therapy [17].

Further observations of 12-month success between individuals receiving intravenous versus oral antibiotics noted no differences. This study noted only 1 instance of an individual who transitioned from intravenous to oral therapy, which had a successful outcome. No individuals switched from oral to intravenous antibiotics. This may further support the emerging evidence for utilizing or transitioning from intravenous to oral antibiotics for definitive therapy, potentially leading to lower complications and costs [18, 19].

Staphylococcus aureus was the most common organism documented in the study, consistent with prior epidemiology reports [20]. When evaluating if there was a difference in successful outcomes regardless of proximal margin results in the presence of *S aureus*, there were no observed differences. Yet the presence of *S aureus* was significantly higher in positive margins, which were observed to have more failure rates. The presence of *S aureus* with positive margins may warrant a more aggressive approach given the significant correlation with positive margins and poorer outcomes, but this study was not able to draw a definitive observation regarding this point, and further studies would need to be conducted. Interestingly when evaluating the overall microbiology of the 20 failure cases needing repeat surgical amputation by 12 months, only 2 had the same microbiology on repeat operative cultures, none which were *S aureus*.

Strengths of this study included the relevancy to our specific patient population at a safety-net county hospital where there can be barriers for access to care. There were several limitations with this study. First was the retrospective design with a relatively small sample size. Furthermore, given the single-center location and specific patient population unique to our center, the results may not be applicable to other populations. The study specifically identified the need for further surgical amputation at the same site within a 12-month period as the criteria for treatment success or failure, but persistent nonhealing wound at the surgical site, which is a frequent sign of delayed recovery, was not categorized as a treatment failure. A significant portion of identified cases also had to be excluded

(179 of 271 unique encounters), with most of them due to deficient histopathology documentation of proximal margins, or inconclusive EMR documentation records through 12 months. These individuals may have been lost to the system, established care elsewhere, or not needed further follow-up due to complete clinical resolution of infection, and thus were not accounted for in this review. Regarding differences in outcomes of individuals with histopathology versus the lack of histopathology, this was not specifically evaluated and would require further studies. Although there were no differences in outcomes when comparing oral versus intravenous antibiotics, the choice was not based on a preset guideline and was physician dependent, so this potentially introduced bias into the results. Comorbid tobacco use, which is commonly known to lead to poor wound healing in general and in DFIs, was significantly more prevalent in the positive-margin group, and this may represent a potential confounding factor [21, 22]. However, further multivariate analysis did not observe a statistically significant difference in our results.

CONCLUSIONS

In summary, our results observed that patients with negative proximal surgical resected bone margins after limb-sparing amputations in DFO lead to more successful outcomes and required less subsequent amputations at the same site by 12 months. Individuals with negative margins were observed to receive shorter courses of antimicrobial therapy. The route of antimicrobial administration did not affect primary outcomes. Proximal margin results potentially can be integrated to help predict outcomes and guide antimicrobial duration usage. Further studies are needed to evaluate the ongoing debate surrounding the clinical relevance of proximal surgical resected bone margins in DFO, along with optimal antimicrobial duration in these cases.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Patient consent. The study was approved by the local institutional review board and granted a waiver for consent due to the retrospective design.

Potential conflicts of interest. All authors: No reported conflicts.

The authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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