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MAJOR ARTICLE

Outcomes of Limb-Sparing Surgery for Osteomyelitis in the Diabetic Foot: Importance of the Histopathologic Margin

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Background. Diabetes mellitus affects up to 14% of Americans. Infection of the diabetic foot is a common complication, which may lead to amputation. If infection extends to involve bone, the risk of amputation is increased 4-fold. Presence of osteomyelitis at the histopathologic margin of resection portends a poor prognosis in osteomyelitis outside the setting of the diabetic foot. We aimed to assess the association of a positive histopathologic margin with the outcome of osteomyelitis in the diabetic foot.

Methods. Medical records were reviewed for all patients who underwent below-ankle amputation for osteomyelitis of the diabetic foot. Patients who had at least 1 year of follow-up, a histopathologic diagnosis of osteomyelitis, and a comment on whether the margin was involved were included.

Results. Thirty-nine of 66 (59%) cases had remission of osteomyelitis at 12 months. When comparing cases with remission with those who experienced recurrence in the 12 months of follow-up, there were no statistically significant differences in age, glycosylated hemoglobin, duration of antimicrobial therapy, Infectious Diseases Society of America class, or presence of osteomyelitis at the histopathologic margin. Among cases with a negative histopathologic margin, 29/48 (60.4%) were free of disease at 1 year, compared with 10/18 (55.6%) cases with a positive histopathologic margin ($P = .72$). Remission was significantly more frequent in cases undergoing amputation at the digit level (66.7%) compared with amputation at the metatarsal level (40.7%) ($P = .045$).

Conclusions. Osteomyelitis of the diabetic foot at the histopathologic margin of resection was not associated with increased risk of treatment failure. Resection at the level of the digit was associated with a lower risk of failure than at the metatarsal level.

Keywords. osteomyelitis; diabetes mellitus; histology; diabetic foot; amputation; pathology.

Recent data from the US Centers for Disease Control and Prevention show that 12%–14% of Americans have diabetes mellitus [1]. As diabetes progresses, patients may develop a number of pathologies including cardiovascular disease, nephropathy, retinopathy, neuropathy, and diabetic foot infections. Among patients with diabetes mellitus, 15%–25% develop foot ulcerations [2]. These wounds can progress to an infection both in the soft tissue and bone. Osteomyelitis occurs in 20%–60% of patients with foot ulcerations [3]. Many of these cases require hospital admission, and if the patient has a confirmed case of osteomyelitis, the risk of surgical amputation is 4 times higher than with soft tissue infection alone [4].

The traditional method of therapy for osteomyelitis is surgical resection followed by a long course of intravenous antibiotics [5–7]. Most of the data supporting this approach are drawn from case series that include few cases involving the diabetic foot. In those series, when wide resection is performed, leaving a negative histopathologic margin, outcomes are improved [8]. Recent case series of osteomyelitis of the diabetic foot have shown that nonsurgical management with a long course of antibiotics alone is often successful [9, 10]. When a surgical approach is taken, analysis of the histopathologic margin for evidence of osteomyelitis is frequently undertaken. Infectious Diseases Society of America (IDSA) guidelines state that when all infected bone has been removed, a prolonged course of antibacterial therapy is not required. A negative histopathologic margin is often interpreted to mean that all infected bone has been removed, and a short course of antimicrobial therapy is prescribed. These guidelines were considered by the IDSA to be weak recommendations with low-quality evidence [3]. Additional evidence to support recommendations for management of osteomyelitis of the diabetic foot is needed. A study examining the histopathologic margin in osteomyelitis of the diabetic foot found no difference in the primary outcome, definite failure, between cases with a negative vs a positive histopathologic margin [11]. Therefore, the purpose of this study is to assess the association of histopathologic margin with the outcome of osteomyelitis in the diabetic foot. Furthermore, we wished to investigate other risk factors for an association with the need for

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further amputation, including age, IDSA wound classification, peripheral arterial disease, level of amputation, glycosylated hemoglobin level within 4 weeks of the surgery, and duration of antimicrobial therapy.

METHODS

We reviewed the medical records of consecutive patients with diabetes mellitus who underwent below-ankle amputation for osteomyelitis of the foot between September 1, 2014, and August 30, 2017. A standard chart abstraction tool was used to record demographic variables, glycosylated hemoglobin level measured within 4 weeks before or after the index osteomyelitis, date of surgery, level of amputation, histopathological findings, duration of antimicrobial therapy following surgical therapy, and presence or absence of peripheral arterial disease. Duration of antimicrobial therapy before surgical treatment and culture results were not recorded. Bone pathology was assessed by the general surgical pathologist on duty in a rotating fashion. A scoring system was not used. Clinical care was determined by the treatment team. The surgical approach did not vary according to whether the patient had been previously treated with antibiotics before presenting with osteomyelitis requiring surgical resection. Severe soft tissue infection was managed by resection of nonviable tissue, and other tissue as needed, to produce an adequate soft tissue envelope for healing. The study was approved by the University of Colorado Combined Institutional Review Board.

Patient Ascertainment and Selection

Operating room schedules and pathology reports for the study period were reviewed to identify all cases of below-ankle amputation for osteomyelitis in persons with diabetes. A patient could be included more than once if 1 year of follow-up had been completed for the first episode and the second case was on the contralateral side. Cases were excluded if the patient was not followed up for at least 1 year or if the pathologist's report did not include an assessment of the presence of osteomyelitis at the margin of resection.

Table 1. Risk Factors for Treatment Failure in Participants With Remission or Relapse

Variable	Remission (n = 39)	Relapse (n = 27)	*P*
Age, y	65.0	66.4	.53
Positive margin, No. (%)	10/39 (25.6)	8/27 (29.6)	.7
IDSA class	3.1	3.1	.98
Peripheral Artery Disease, No. (%)	13/39 (33.3)	14/27 (51.9)	.13
Digit-level resection, No. (%)	26/39 (66.7)	11/27 (40.7)	.045
Glycosylated hemoglobin	8.1	8.9	.22
Duration of antibiotics, d	18	30	.12

Abbreviation: IDSA, Infectious Diseases Society of America.

Definitions

Osteomyelitis was defined by histopathologic findings. If the pathologist's report indicated osteomyelitis, inflammation of bone, or leukocyte infiltrate of bone, the case was considered to have osteomyelitis.

Positive Histopathologic Margin

Cases with a pathologic report of osteomyelitis, inflammation of bone, or leukocyte infiltrate at the margin of resection were considered to have a positive histopathologic margin. If none of the above were included within the descriptors of the surgical margin in the report, the margin was found to be negative. If the report did not comment on the surgical margin, the case was excluded.

Amputation was defined as surgical removal of bone for therapy of osteomyelitis.

The primary outcome was remission of osteomyelitis at 1 year. Remission of osteomyelitis was defined as epithelialization of any overlying soft tissue defect and absence of repeated amputation for osteomyelitis on the index foot.

Statistical Analysis

Categorical variables were analyzed with the Fisher exact test. For continuous variables, the *t* test or Mann-Whitney test was used as appropriate. All tests were 2-tailed. All calculations were performed in GraphPad Prism, version 7.0. Statistical significance was defined at the 5% ($P \leq .05$) level.

RESULTS

Records were reviewed for 86 amputation cases in 85 patients. Twelve patients were excluded because they had <1 year of follow-up. Eight patients were excluded because the pathology report did not comment on whether the surgical margin was free of osteomyelitis. Sixty-six amputation cases in 65 patients met all inclusion criteria and no exclusion criteria.

Thirty-nine of 66 (59%) cases had remission of osteomyelitis at 12 months. When comparing cases with remission with those who experienced recurrence in the 12 months of follow-up, there were no statistically significant differences in age, glycosylated hemoglobin, duration of antimicrobial therapy, IDSA class, or presence of osteomyelitis at the histopathologic margin (Table 1). Peripheral arterial disease was identified in 51.9% of cases who relapsed, vs 33.3% of cases with remission, but this did not achieve statistical significance ($P = .12$). Remission was significantly more frequent in cases undergoing amputation at the digit level (66.7%) compared with amputation at the metatarsal level (40.7%; $P = .045$). Among 48 cases with a negative histopathologic margin, 29 (60.4%) were free of disease at 1 year, compared with 10/18 (55.6%) cases with a positive histopathologic margin ($P = .72$). Further analysis of outcomes according to histopathologic margin at each anatomic level yielded no statistically significant differences. Cases

with a positive histopathologic margin received a significantly longer duration of antimicrobial therapy than cases with a negative histopathologic margin (Table 2). A course of antimicrobial therapy of at least 4 weeks was administered to 14/48 cases with a negative margin; 9/14 (64.3%) were free of disease at 12 months, vs 24/34 (70.1%) who received <4 weeks of antimicrobial therapy (P = .15).

DISCUSSION

In this series of cases of diabetic foot osteomyelitis managed with limb-sparing surgery, 59% of cases were in remission at 1 year. There was no need for further operative management in these cases. This represents an improvement over the historically poor outcomes reported by Nehler et al., in which 34% of patients experienced complete healing [12]. More recent case series have reported similar outcomes to our study, with remission without additional surgery in 58%–64% of cases with long-term follow-up [13–15]. This is consistent with data from the Centers for Disease Control and Prevention, suggesting that minor amputations have been substituted for major amputations in many cases [16].

Histopathologic evidence of osteomyelitis within 5 mm of the surgical margin of resection has been considered a risk factor for treatment failure [8, 11]. In our study, a positive histopathologic margin was found in 10/39 (25.6%) patients who achieved remission and in 8/27 (29.6%) patients who relapsed (P = .7). This is similar to the study by Kowalski et al. [11], which showed no difference between patients with a negative vs positive histopathologic margin in the primary outcome of definite failure, defined as pathologically or microbiologically confirmed infection relapse at the proximal amputation site. A secondary outcome of the Kowalski et al. study, the need for more proximal amputation, was more frequent in patients with a positive margin. Our results are similar to the recent study by Barshes et al. [14], in which a positive histopathologic margin was not associated with increased risk of failure in patients who received a course of antimicrobial therapy of >5 days' duration. Beieler et al. [13] also found no statistically significant difference between patients with a positive vs negative histopathologic margin. These results are consistent with a recent study showing poor interrater reliability for bone histopathology [17]. These data support a less aggressive surgical resection than the traditional approach. This aligns well with studies showing that medical therapy alone may be sufficient for osteomyelitis in the diabetic foot [10].

In our study, remission was significantly more frequent in digital amputations than in amputations through the metatarsal. This is similar to the outcomes reported by Svensson et al. Future studies should explore strategies to improve the prognosis of metatarsal amputation. IDSA class has been shown to correlate with higher risk of amputation in patients with diabetic foot infection [3]. Our study, which was limited to patients with osteomyelitis, showed no difference in IDSA class between patients with relapse vs those with remission. This is likely due to the exclusion from our study of patients with diabetic foot infection who did not have osteomyelitis. As a result, all of the patients studied had IDSA Class 3 or Class 4 disease. A recent study of diabetic foot infection showed that the presence of osteomyelitis was associated with a 4-fold increased risk of amputation [4]. Thus, a potent risk factor for amputation was present in all of the patients in our study, which limited the discriminative power of the IDSA classification system.

Cases with a positive histopathologic margin received a longer course of antimicrobial therapy, 37.6 days, than cases with a negative margin, 17.7 days (P = .001). This is consistent with the community standard of care and the belief that a positive margin portends a poorer prognosis. Among cases with a negative histopathologic margin, a course of antibiotic therapy longer than 4 weeks was not associated with a better prognosis than a shorter course. These results should be interpreted with caution, because the duration of antibiotic therapy was not randomly assigned.

This study has several limitations. The retrospective design prevents assignment of causality to any of the identified risk factors for poor outcome. The population was limited to veterans and was predominantly male, limiting the generalizability to other populations. Cases were included based on the histopathologic definition of osteomyelitis. The definition of remission was based on healing at 1 year, without need for further amputation. Although this definition is commonly employed, absence of osteomyelitis on a repeat bone biopsy at 1 year could be viewed as a more rigorous end point. We chose not to take this approach because of ethical concerns with performing bone biopsy of a healed limb for research purposes.

The strength of the study is the patient-level review of clinical details of each case. The results, consistent with other recent studies [13, 14], call into question the clinical dogma that the histopathologic margin predicts outcome in osteomyelitis of the diabetic foot. Future studies should be performed to determine the optimal duration of antimicrobial therapy for osteomyelitis in the diabetic foot, regardless of the histopathologic margin. The observation that osteomyelitis in the diabetic foot that is proximal to the digit is associated with poorer prognosis

Table 2. Participant Characteristics and Outcome at 1 Year

Variable	Positive Margin (n = 18)	Negative Margin (n = 48)	*P*
Age, y	65.1	65.8	.76
Male gender, %	100	94	
Glycosylated hemoglobin	8.8	8.2	.35
Antibiotic duration, mean ± SD, d	37.6 ± 24.1	17.7 ± 29.6	.001
Remission at 1 y, No. (%)	10/18 (55.6)	29/48 (60.4)	.72

should be studied further, with consideration of intensification of therapy.

In summary, the overall prognosis of osteomyelitis of the diabetic foot that is managed with limb-sparing below-ankle amputation is good. The presence of osteomyelitis at the histopathologic margin was not associated with an increased risk for further amputation. Amputation at the digit level was associated with a lower risk for additional amputation than amputation at the metatarsal level.

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Author contributions. Johnson, Shumway, Bivins: data collection, data analysis, manuscript draft writing and editing. Bessesen: study design, data analysis, manuscript writing and editing.

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