Risk Factors for Below-the-Knee Amputation in Diabetic Foot Osteomyelitis After Minor Amputation

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Background: Below-the-knee amputation (BKA) can be a detrimental outcome of diabetic foot osteomyelitis (DFO). Ideal treatment of DFO is controversial, but studies suggest minor amputation reduces the risk of BKA. We evaluated risk factors for BKA after minor amputation for DFO.

Methods: This is a retrospective cohort of patients discharged from Denver Health Medical Center from February 1, 2012, through December 31, 2014. Patients who underwent minor amputation for diagnosis of DFO were eligible for inclusion. The outcome evaluated was BKA in the 6 months after minor amputation.

Results: Of 153 episodes with DFO that met the study criteria, 11 (7%) had BKA. Failure to heal surgical incision at 3 months ($P < .001$) and transmetatarsal amputation ($P = .009$) were associated with BKA in the 6 months after minor amputation. Peripheral vascular disease was associated with failure to heal but not with BKA ($P = .009$). Severe infection, bacteremia, hemoglobin A_{1c}, and positive histopathologic margins of bone and soft tissue were not associated with BKA. The median antibiotic duration was 42 days for positive histopathologic bone resection margin (interquartile range, 32–47 days) and 16 days for negative margin (interquartile range, 8–29 days). Longer duration of antibiotics was not associated with lower risk of BKA.

Conclusions: Patients who fail to heal amputation sites in 3 months or who have transmetatarsal amputation are at increased risk for BKA. Future studies should evaluate the impact of aggressive wound care or whether failure to heal is a marker of another variable. (J Am Podiatr Med Assoc 109(2): 91-97, 2019)

Diabetic foot infection (DFI), including diabetic foot osteomyelitis (DFO), is the most prevalent infection in diabetic patients and places a heavy burden on our health-care system.[1,2] Patients with DFO have prolonged hospitalizations and are more likely to require amputation. Major amputation, including below-the-knee amputation (BKA) or above-the-knee amputation, is an undesired outcome of DFO, affecting approximately 3 to 4 per 1,000 diabetic patients annually.[3] There are a variety of reasons why patients may progress to major amputation after DFO, including inappropriate antibiotic drug choice or duration, residual osteomyelitis, microvascular disease, and impaired neutrophil function from uncontrolled diabetes.[4] Controversy remains whether optimal treatment of DFO includes surgical intervention in conjunction with an appropriate antibiotic drug course or if DFO can be best treated with antibiotic agents alone. Multiple studies have suggested, however, that early surgical intervention with minor amputation (ie,

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amputation of toe[s] or metatarsal[s]) reduces the risk of major amputation.[5,6]

The appropriate choice and duration of antibiotics after minor amputation for DFO is also a debated topic. In the 1980s, nearly all patients with DFI were hospitalized and treated with prolonged broad spectrum antibiotics.[7] More recently, in North America, antibiotic drug therapy recommendations have changed to focus on gram-positive bacteria, particularly β-hemolytic streptococcus and *Staphylococcus aureus*, with less focus on *Pseudomonas aeruginosa* and anaerobic bacteria for most patients.[8-10] The duration of antibiotic drug therapy also continues to evolve. The Infectious Diseases Society of America (IDSA) guideline recommends bone culture and histologic analysis to be the most definitive way to diagnose DFO. The guideline recommends 2 to 5 days of treatment when there is no residual infected tissue or bone; 1 to 3 weeks for residual infected soft tissue; 4 to 6 weeks for residual but viable infected bone; and 3 months or longer for residual necrotic bone.[8] The International Working Group on Diabetic Foot recommends a similar duration of antibiotic drug therapy except for stating 6 weeks to be sufficient treatment when there is residual necrotic bone.[11]

Historically at our hospital, osteomyelitis has been treated surgically, and limb salvage rates for DFO have been almost 95%, although local recurrence rates are approximately 36%.[12] The purpose of this study was to evaluate current rates of local recurrence and BKA and to identify risk factors for BKA after minor amputation for DFO. We hypothesize that positive histopathologic bone resection margins are associated with increased risk of both local recurrence and BKA.

Methods

Study Setting and Population

This is a retrospective cohort of patients discharged from Denver Health Medical Center (Denver, Colorado) from February 1, 2012, through December 31, 2014. Denver Health Medical Center has a multidisciplinary musculoskeletal infections team of providers who care for patients with orthopedic and podiatric infections. All of the patients referred to the musculoskeletal infections consult service are entered into a clinical tracking database. Patients were identified for inclusion in this study by querying the clinical tracking database for patients with diabetes and a foot infection. Manual medical record review was used to determine whether the patient met the criteria for DFO (see the definition later herein). Patients who had DFO of both feet during the study period were included for both incidents. Patients were excluded for loss to follow-up at 6 months or death unrelated to DFI in the 6 months after minor amputation. The primary outcome evaluated was BKA in the 6 months after minor amputation.

Data Collection

Data were collected manually from the electronic medical record. Variables of interest included demographic information, social history, laboratory values, microbiology, established primary care within the 6 months preceding minor amputation, DFI severity by IDSA criteria,[8] type of minor amputation, antibiotic drug therapy duration, histopathologic evaluation of bone and soft-tissue surgical resection margins, wound healing within 3 months, unplanned surgery within 6 months for contiguous spread of infection, and BKA within 6 months.

Definitions

Diabetic foot osteomyelitis was defined by both the IDSA DFI criteria and the National Healthcare Safety Network criteria for osteomyelitis. The IDSA defines mild infection as infection including the skin and subcutaneous tissues without involvement of deeper tissue and erythema between 0.5 and 2.0 cm. Moderate infection is defined as infection involving structures deeper than the subcutaneous tissue and erythema greater than 2 cm. Severe infections are defined as local infection plus at least two signs of systemic symptoms, including temperature greater than 38°C or less than 36°C, heart rate greater than 90/min, respiratory rate greater than 20/min, or leukocyte count greater than 12,000 or less than 400 cells/μL.[8] The National Healthcare Safety Network defines osteomyelitis as 1) organism cultured from bone, 2) evidence of osteomyelitis on direct examination of the bone through invasive or histopathologic examination, or 3) the presence of at least 2 signs of infection (temperature >38°C, localized swelling, tenderness, and heat or drainage at the suspected site of bone infection), in addition to an organism cultured from blood, a positive laboratory blood test result, or an imaging study with evidence of bone infection.[13]

Histopathologic assessments were performed per routine patient care by a pathologist. Soft-tissue margins were defined as positive if there was one or

more of the following at the soft-tissue margin: 1) acute inflammation or mixed acute and chronic inflammation, 2) identification of an abscess, or 3) soft-tissue necrosis on microscopic examination. Bone margins were defined as positive if there was acute inflammation associated with either bone necrosis (nonviable bone) or bone resorption on microscopic examination. Peripheral vascular disease (PVD) was evaluated with ankle brachial indexes and toe pressures. Patients who had vascular studies completed were categorized by disease severity by an interventional cardiologist's interpretation of these results.[14] Only the vascular status of the surgical side was included in the evaluation. Patients with noncompressible ankle brachial indexes and no assessment of toe pressures were considered to be indeterminate.

Statistical Analysis

The primary outcome was ipsilateral BKA in the 6 months after minor amputation for DFO; secondary outcomes included failure to heal the surgical wound within 3 months and unplanned surgery within 6 months for contiguous spread of infection. Descriptive statistics were used to characterize the population. The Wilcoxon rank sum nonparametric test, the χ^2 test of association, and the Fisher exact test were used to determine bivariate relationships between the patient and treatment characteristics and the outcomes of interest. Statistical analyses were performed using SAS software version 9.3 (SAS Institute Inc, Cary, North Carolina). This study was approved by the Colorado Multiple Institutional Review Board of the University of Colorado Denver.

Results

A total of 154 patients were evaluated for inclusion, and 16 were excluded for loss to follow-up (n = 14) and death in the 6 months after minor amputation unrelated to DFO (n = 2). The remaining patients had 153 episodes of DFO included in this study. The median patient age was 54 years (interquartile range [IQR], 49-77 years), and the median hemoglobin A_{1c} level was 8.4 mg% (IQR, 6–11 mg%). Twenty-six patients (17%) were homeless, and 47 (31%) had tobacco dependence. Only 54 patients (36%) had formal evaluation of their vascular circulation beyond the presence of palpable foot pulses. The most common bacteria isolated from bone and deep-tissue culture was *Streptococcus* species (44%), followed by *Staphylococcus aureus* (37%). Of the patients with *S aureus*, 14 (23%) had methicillin-resistant *S aureus*. Moderate DFI was most common (n = 97, 63%), and 24% of patients (n = 37) had severe infection. The remaining 13% of patients had chronic DFO that was considered uninfected by the IDSA DFI severity classification. Eight patients (5%) were bacteremic during initial presentation, with an organism isolated from the foot and bloodstream.

Osteomyelitis in this cohort was primarily of the forefoot. Minor amputations included a single toe or metatarsal (n = 121, 79%), multiple toes or metatarsals (n = 22, 14%), and transmetatarsal (TMA) (n = 10, 7%). Histopathologic evaluation was performed at both the soft-tissue and bone surgical resection margins. A total of 108 patients (70%) had positive soft-tissue margin or signs of soft-tissue infection, abscess, or necrosis at the resection margin. Forty patients (27%) had negative soft-tissue margin. There were signs of residual osteomyelitis in the histopathologic analysis of 58 patients (38%), and 95 patients (62%) were deemed to have no evidence of osteomyelitis at the resection margin.

There were 11 BKAs (7%) in the follow-up period. Age, homelessness, tobacco use, bacteremia, hemoglobin A_{1c} level, severe PVD, initial C-reactive protein elevation, leukocytosis, and DFI severity were not associated with increased risk of BKA in the 6 months after minor amputation (Table 1). In addition, there was no increased risk of TMA in patients with severe vascular disease, yet those undergoing TMA were more likely to have BKA in the subsequent 6 months (odds ratio [OR] = 7.23; 95% confidence interval [CI], 1.57–33.37). Patients who had a primary care physician visit in the 6 months before the pathology date were also more likely to undergo BKA (OR = 10.00; 95% CI, 1.25–80.19).

Sixty-eight patients (44%) failed to heal the surgical incision within 3 months, and 33 (22%) required return to the operating room for an unplanned surgery due to contiguous spread in the 6 months after minor amputation. Repeated surgery within 6 months was not a risk factor for BKA; however, failure to heal the surgical incision within 3 months after minor amputation was associated with BKA (OR = 31.00; 95% CI, 1.79–536.9). Furthermore, severe PVD was not associated with BKA, but patients with severe vascular disease were less likely to heal within 3 months (OR = 5.65; 95% CI, 1.41–22.62).

Residual infection or inflammation by microscopic histopathologic examination of the resection margin, what we considered a positive margin, of soft tissue or bone was not associated with BKA or

Table 1. Characteristics of Patients Undergoing Minor Amputation for DFO

Variable	BKA (n = 11)	No BKA (n = 142)	OR (95% CI)	*P* Value
Demographics				
Age (median [years])	59.0	54.9	–	.54
Hemoglobin A_{1c} (median [mg%])	9.2	9.5	–	.40
Tobacco abuse (No. [%])	2 (20)	45 (32)	0.54 (0.1–2.6)	.72
Homeless (No. [%])	2 (20)	24 (17)	1.23 (0.2–6.2)	.68
Peripheral vascular disease (No. [%])				
None	0	18/53 (34)	3.71 (0.74–18.71)	.12
Mild/moderate	3/7 (43)	21/53 (40)		
Severe	4/7 (57)	14/53 (26)		
Primary care provider visit within the previous 6 months	10 (91)	71 (50)	10.00 (1.25–80.19)	<.01[a]
Illness severity				
Bacteremia (No. [%])	1/10 (10)	7 (5)	2.14 (0.24–19.36)	.49
C-reactive protein at presentation (median [IQR] [mg/dL])	113.5 (31.9–246.5)	78.7 (27.6–144.0)	–	.28
Leukocyte count at presentation (median [IQR] [cells/dL])	8.4 (7.3–13.0)	8.9 (6.8–10.9)	–	.62
IDSA classification (No. [%])				
Uninfected DFO	1 (9)	18 (13)	–	.23
Moderate DFI	5 (45)	92 (65)		
Severe DFI	5 (45)	32 (23)		
Incisional characteristics (No. [%])				
Type of minor amputation				
Single toe/metatarsal	8 (73)	113 (80)	7.23 (1.57–33.37)	.009[a]
Multiple toes/metatarsals	0	22 (15)		
Transmetatarsal	3 (27)	7 (5)		
Not healed at 3 months	11 (100)	57/134 (43)	31.00 (1.79–536.9)	<.001[a]
Repeated surgery within 6 months	4 (36)	29/134 (22)	2.07 (0.57–7.56)	.26
Antibiotic treatment (No. [%])				
0–3 weeks	6/10 (60)	58/136 (43)	1.34 (0.37–4.86)	.65
>3 weeks	5/10 (50)	78/136 (57)	1.61 (0.47–5.55)	.53
Resection margin (No. [%])				
Skin margin positive	10 (91)	98 (69)	3.98 (0.49–32.14)	.29
Bone margin positive	5 (45)	53 (37)	1.40 (0.41–4.81)	.75

Abbreviations: BKA, below-the-knee amputation; CI, confidence interval; DFI, diabetic foot infection; DFO, diabetic foot osteomyelitis; IDSA, Infectious Diseases Society of America; IQR, interquartile range; OR, odds ratio.
[a]Statistically significant.

lack of healing at 3 months. Intraoperative deep bone and tissue cultures were used to guide antibiotic drug choice but not duration. The median duration of antibiotic drug therapy for those with positive (26 days; IQR, 8–42 days) and negative (27 days; IQR, 12–42 days) soft-tissue margins was similar. In contrast, the median duration of antibiotic drug therapy was 42 days for those whose histopathologic bone resection margin was positive for residual osteomyelitis (IQR, 32–47 days) and 16 days for those with a negative bone resection margin (IQR, 8–29 days). Patients with positive bone margins who did not receive longer durations of antibiotic drug therapy were not more likely to have BKA than those with positive bone margins who received longer durations of antibiotic drug therapy (Table 2).

Discussion

Although minor amputation is likely to decrease the risk of BKA, BKA still occurred in 7% of our patients with DFO. Although limited numbers are available, this study suggests that patients with established primary care who fail to heal within 3 months of

Table 2. Incidents of Below-the-Knee Amputation Within 6 Months Stratified by Bone Margin and Antibiotic Drug Therapy Duration

Bone Margin	Amputations (No. [%]) 0–3 Weeks of Antibiotic Treatment	Amputations (No. [%]) >3 Weeks of Antibiotic Treatment	*P* Value
Positive (n = 56)	2 (40)	3 (60)	.21
Negative (n = 91)	4 (67)	2 (33)	>.99

minor amputation or who have TMA are at increased risk for BKA. Severe vascular disease seems to be a contributing condition to why patients do not heal at 3 months, although this was not a direct risk factor for BKA.

We were surprised to see that having a primary care physician visit in the 6 months before surgery was a risk factor for BKA. The patient-centered medical home has been a favored model for taking care of diabetic patients and been shown to decrease inpatient hospitalization and readmission rates. Studies have found that patient-centered medical home interventions are most successful in patients with the poorest diabetes management.[15,16] We suspect that the present findings were due to unmeasured comorbid conditions in this patient population. We did not formally collect information on previous hospitalizations, heart disease, kidney disease, and lung disease and hypothesize that there were underlying differences in the patient populations that made those who had BKA more likely to already have a medical home.

Multiple studies have found PVD to be a predictor of limb loss and have shown improved rates of limb salvage with revascularization procedures.[4,17,18] Although the present study did not find severe vascular disease to be a predictor of BKA, it did coincide with previous data that patients with severe vascular disease were more likely to have delayed healing of the surgical incision. Given that almost two-thirds of the present patients did not have formal vascular evaluation, we were unable to distinguish the effect of mild and moderate vascular disease on wound healing. Our institution formalized a clinical care guideline for the treatment of DFI in late 2014. The guideline consists of evidence-based recommendations for antibiotic drug therapy, radiologic studies, and vascular evaluations. We expect that the prevalence of vascular evaluation has increased since the advent of this guideline, and we look forward to studying its effect on wound healing and BKA in the future.

In addition to PVD, we found TMA to be a risk factor for BKA. This was not unexpected because patients who develop DFO after TMA may have fewer options for additional surgical resection. In addition, previous studies have reported that TMAs have had higher rates of progression to BKA compared with other minor amputations.[19-21]

Previous studies have reported that inadequate surgical resection is a cause for repeated operation in DFO.[6,8,22] Histopathologic examination and bone cultures are the recognized gold standard for the diagnosis of osteomyelitis. Positive results of additional tests, such as probe to bone, radiography, magnetic resonance imaging, and serum inflammatory markers, have also been found to make the diagnosis of osteomyelitis more likely.[11] Both the IDSA and the International Working Group on Diabetic Foot guidelines recommend histopathologic examination to guide the duration of antibiotic drug treatment,[8,11] We expected that patients with a positive bone margin, and thus residual osteomyelitis at the surgical resection margin, would be more likely to progress to BKA. We were surprised to find that positive bone resection margin was not associated with BKA. We hypothesize that this is due to the different durations of postoperative antibiotic drug therapy. In the present cohort, patients with residual osteomyelitis at the bone resection margin were treated for a median of 42 days, and those without evidence of osteomyelitis at the bone resection margin were treated for a median of 16 days. It is unclear why a small number of patients with a positive bone margin did not receive a longer duration of antibiotic drug therapy but it is hypothesized that this was secondary to nonadherence and social factors. It is unknown whether any regimens were stopped short of initial recommended duration because of signs of early healing. It is possible that patients with residual osteomyelitis would have had a higher rate of BKA than we observed if they had been treated with fewer days of antibiotics. A randomized controlled trial would be needed to assess this theory.

Nonsurgical management of DFO is a debated topic. Some authors have shown that certain patients who receive prolonged antibiotic therapy without surgical intervention have similar outcomes to those who undergo minor amputation.[23-25] The present study included only patients who were managed surgically; however, in this patient cohort, a longer duration of antibiotic drug therapy was typically given to patients who had residual osteomyelitis noted at their resection margins and thus ongoing bone infection. Small numbers of patients with negative margins also received prolonged courses of antibiotic agents. We suspect that this is because they were showing early signs of poor wound healing and treatment failure. Patients who received a longer course of antibiotics (up to 6 weeks) did not have a lower rate of BKA. It is hypothesized that although some patients may experience clinical cure of DFO with antibiotics alone, perhaps prolonged antibiotic use is not helpful in patients showing early signs of delayed wound healing. Alternatively, perhaps 6 weeks of antibiotic drug therapy was insufficient to prevent BKA, and several more weeks would have been required.

Lipsky et al[26] found that patients with leukocytosis on initial presentation, and thus signs of systemic infection by IDSA guidelines, were more likely to have treatment failure. In contrast, initial leukocytosis was not predicted with bacteremia or classification of severe DFI. We hypothesized that those presenting with bacteremia or severe DFI would be more likely to go on to BKA because of the severity of their initial presentation, yet neither was found to be a risk for treatment failure in the present patient cohort. However, it is difficult to interpret how these findings compare with patients in the Lipsky et al study because they did not necessarily undergo amputation.

The strengths of this study include the overall success of limb salvage in patients with forefoot osteomyelitis at our institution and the trend toward decreasing the rate of reoperation for contiguous spread of infection (36% historically to 26% currently).[12] The musculoskeletal infection program's success is attributed to the multidisciplinary team philosophy, implementation of standardized clinical treatment guidelines, and the execution of quality improvement projects. Weaknesses of this study include the single-center retrospective nature, inability to distinguish patients with neuropathy and Charcot's neuroarthropathy, and incomplete evaluations of vascular disease in many of the patients. In addition, erythrocyte sedimentation rate has been shown to have predictive value in diagnosis and possible resolution of osteomyelitis, and this was not evaluated in this study.[11]

Conclusions

The results of the present study suggest that patients who fail to heal their amputation sites within 3 months of minor amputation or who have TMA are at increased risk for BKA. Severe vascular disease seems to be a contributing factor to nonhealing. Additional studies should define the effect of aggressive wound care techniques and assess whether failure to heal is a marker of other unmeasured variables.

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