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Outcomes of Osteomyelitis in Patients Hospitalized With Diabetic Foot Infections

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Abstract

Background—This study was conducted to evaluate the outcomes of patients with diabetic foot osteomyelitis (DFO) compared to diabetic foot soft tissue infections (STIs).

Methods—229 patients who were hospitalized with foot infections were retrospectively reviewed, identifying 155 patients with DFO and 74 patients with STI. Primary outcomes evaluated were the rates of amputations and length of hospital stay. DFO was confirmed by the presence of positive bone culture and/or histopathology.

Results—Patients with DFO had a 5.6 times higher likelihood of overall amputation ($P < .0001$), a 3.4 times higher likelihood of major amputation ($P = .027$) and a 4.2 times higher likelihood of minor amputation ($P < .0001$) compared to patients without DFO. Major amputation was performed in 16.7% patients diagnosed with DFO and 5.3% of patients diagnosed with STI. Patients with DFO complicated by Charcot neuroarthropathy had a 7 times higher likelihood of undergoing major amputation (odds ratio 6.78, 95% confidence interval 2.70–17.01, $P < .0001$). The mean hospital stay was 7 days in DFO and 6 days in patients with DFI ($P = .0082$). Patients with DFO had a higher erythrocyte sedimentation rate (85 vs 71, $P = .02$) than patients with STI, however the differences in C-reactive protein (13.4 vs 11.8, $P = .29$) were not significantly different.

Conclusion—In this study of moderate and severe DFIs, the presence of osteomyelitis resulted in a higher likelihood of amputation and longer hospital stay. Readers should recognize that the findings of this study may not be applicable to less severe cases of DFO that can be effectively managed in an outpatient setting.

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Declaration of Conflicting Interests

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Level of Evidence—Level III, retrospective comparative case series.

Keywords

diabetes; osteomyelitis; foot; outcomes; infections

Introduction

Diabetic foot infections (DFIs) are limb-threatening complications, and the prevalence of osteomyelitis in patients with moderate and severe DFI ranges from 37% to 70%.[17,29] The optimal methods of diagnosing and treating osteomyelitis (ie, diabetic foot osteomyelitis [DFO]) in DFIs remain controversial.[13,16] Various methods of treating DFO have been described to include nonsurgical (antibiotics alone), conservative surgery (no amputation), amputation, and combination therapy. Some authors feel that a positive probe to bone test and abnormal radiographs are sufficient to diagnose DFO, whereas other authors rely on bone biopsy.[5,28] The presence of radiographic bone destruction in the face of a positive probe to bone test is consistent with the diagnosis of osteomyelitis, and a negative probe to bone test is unlikely to be associated with osteomyelitis. The difficulty in diagnosing DFO remains in the setting of a positive probe to bone test in patients without signs of radiographic bone destruction. The precise duration of antibiotics remains a subject of debate as well.[28] A systematic review conducted by the International Working Group for the Diabetic Foot concluded that no significant differences in outcomes were observed when comparing different treatment protocols.[6] They questioned the need for routine operative debridement of infected bone, the precise duration of antibiotic use, and the method by which antibiotics were delivered (parenteral versus oral).[6] The purpose of this study was to evaluate the outcomes of patients hospitalized with a DFI complicated by osteomyelitis and to compare those outcomes to patients with soft tissue infections (STIs) alone. To our knowledge, few studies have been performed evaluating the impact of osteomyelitis on outcomes of hospitalized patients with DFIs. Our hypothesis was that DFO would be associated with higher rates of adverse outcomes, including prolonged hospital stays and increased risk of amputations.

Methods

Institutional review board approval was granted prior to beginning this study. This study represented a single academic medical center and included patients who were hospitalized with DFI. Inclusion criteria required the patient have an admitting diagnosis of DFI based on clinical and laboratory data. The diagnosis of infection was based on the Infectious Disease Society of America criteria and graded as moderate or severe.[21] Severe DFI was defined as having 2 or more objective findings of systemic toxicity and/or metabolic instability at the time of initial assessment based on the recommendations for systemic inflammatory response syndrome (SIRS).[29] Exclusion criteria included a mild DFI or those patients hospitalized with a foot infection who did not have a diagnosis of diabetes. For the purposes of this project, our study group was composed of patients with DFO, and the control group was composed of patients with STI. The diagnosis of osteomyelitis was confirmed by positive bone culture and/or bone histopathology, demonstrating the presence of an

inflammatory response, bone necrosis, and/or bone fragmentation.[12] Radiographs were obtained in all patients and advanced imaging such as MRI or CT scanning was used in selected cases. All patients with suspicion for DFO (ie, abnormal imaging study and/or positive probe to bone test) had a bone biopsy to confirm the presence of OM. Our outcomes of interest included the rate of amputation and length of hospital stay. Major amputation was defined as an amputation at or proximal to the ankle joint and a minor amputation was defined as removal of a part of the foot at or distal to the transverse tarsal joint. The decision to proceed with major amputation was made after seeking consultation with colleagues from infectious disease, plastic surgery, and vascular surgery. Our infectious disease consultants evaluated every patient in this study and discussed the pros and cons of long-term antibiotic therapy with the patients with DFO. In patients with large soft tissue wounds and associated DFO, plastic surgery assessed the possibility of local, regional, and distant flaps to achieve soft tissue coverage. In patients with peripheral arterial disease, vascular surgery evaluated the patient as well to determine if open or endovascular reconstruction was indicated. The senior author, an orthopaedic surgeon, determined whether osseous reconstruction was possible. Ultimately, major amputations were performed only after the lower extremity was deemed to be nonsalvageable secondary to large bone defects, inability to achieve soft tissue coverage, or vascular disease not amenable to reconstruction. Prior to undergoing major amputation, all patients had consultation with physicians from our physical medicine and rehabilitation service. These physicians, in concert with physical therapists and prosthetists, supervised our amputee clinic.

Two hundred twenty-nine patients with moderate and severe DFIs were identified and retrospectively reviewed. One hundred fifty-five patients had DFO (ie, study group) and 74 patients had STI (control group). Demographic data are recorded in Table 1. The mean length of follow-up for our DFO study group was 46.6 weeks and 48.8 weeks for our control group ($P = .41$).

Descriptive statistics were summarized as frequencies (percentages) for categorical data or as mean ± standard deviation (SD) or median and interquartile range for normally or nonnormally distributed continuous data, as appropriate. Examination of normal distribution assumption for continuous data was determined by q–q plots and histograms. Pearson chi-square or Fisher exact test, as appropriate, were used to compare the frequency distribution of categorical variables between the groups. Two-sample *t* test or Wilcoxon-Mann-Whitney test was performed to determine differences between groups for normally or nonnormally distributed continuous data, respectively. Univariate logistic regression was applied to assess the strength of association between predictor variable (group: osteomyelitis or soft tissue infection) and the dichotomous outcome of interest (eg, amputation, vascular surgery, etc). The magnitude of associations between the predictor variables and outcome was quantified using the odds ratio and the corresponding 95% confidence interval. Odds ratio (OR) and 95% confidence intervals (CI) were calculated from the beta coefficients. All tests were 2-sided and the significance level was 0.05. All analyses were conducted using SAS, version 9.3, statistical software (SAS Institute Inc, Cary, NC).

Results

The mean readmission rate between the 2 groups was not significantly different ($P = 0.65$). No significant differences between the 2 groups were found with regard to age, gender, duration of DM, type of DM, insulin use, Michigan Neuropathy Screening Index (MNSI), prevalence of Charcot neuroarthropathy (CN), history of tobacco use, need for hemodialysis, or need for arterial revascularization. Patients with DFO demonstrated a trend toward higher rates of PAD than patients with STI ($P = .06$) (Table 1). Patients with DFO had a significantly lower BMI than patients with STI ($P = .01$). There were no significant differences between the 2 groups with regard to the HbA_{1c}, admission random serum glucose, albumin, creatinine, blood urea nitrogen, and white blood cell count; however, patients with DFO had a significantly lower hemoglobin level than patients with STI ($P = .03$) (Table 2). Patients with DFO had higher elevation of the ESR ($P = .02$); however, the elevation in C-reactive protein was not statistically significant ($P = .29$). Ninety-five of 155 patients (61.3%) with DFO had an ESR ≥70 mm/h compared to 29 of 74 patients (39.2%) with soft tissue infection (odds ratio [OR] 2.24, 95% confidence interval [CI] 1.39–4.33, $P = .0019$). No significant differences were observed between the 2 groups with regard to admission vital signs or symptoms of nausea and vomiting.

The mean number of organisms identified by culture was significantly higher in DFO (1.75 ± 1.21) compared to STI (1.23 ± 1.15) ($P = .002$). No significant difference in severity of infection was observed between the 2 groups ($P = .16$). Patients with DFO underwent an average of 1.7 surgeries during their admission compared to 1.2 surgeries in patients with soft tissue infections ($P = .0003$). Patients with DFO had a 5.6 times higher likelihood of overall amputation compared to patients without DFO (95% CI 2.9–10.6, $P < .0001$), a 3.4 times higher likelihood of major amputation (95% CI 1.1–10.0, $P = .03$) and a 4.2 times higher likelihood of minor amputation (95% 2.1–8.3, $P = .0001$) compared to patients without DFO (Table 3). Twenty-five of the 155 patients diagnosed with DFO underwent a major amputation (16%) compared to 4 of the 74 patients diagnosed with STI (5.0%). The median number of operative procedures performed during the hospitalization was significantly higher ($P = .044$) in the 29 patients who ultimately underwent major amputation (median 2 [range 1–10]) compared to the 200 patients who had successful limb salvage (median 1 [range 0–6]). When evaluating only patients with DFO (n = 155), no significant difference ($P = .44$) was observed in the median number of procedures performed in the 25 patients who ultimately underwent major amputation (median of 2 procedures [range 1–10]) compared to the 130 patients who had successful limb salvage (median 1 procedure [range 0–4]). The median hospital stay was 7 days in DFO and 6 days in patients with DFI ($P = .008$). During the follow-up period (47 weeks in DFO and 49 weeks in STI), 2 patients (1.3%) in the DFO group and 1 patient (1.3%) in the STI group died ($P = 1.00$) (Table 1).

Although the rates of CN were not significantly different between patients with DFO (43 of 155 patients, 28%) and STI (17 of 74 patients, 23%) ($P = .44$), the impact on outcomes was dramatically different. The odds (OR 6.78, 95% CI 2.70–17.01, $P < .0001$) of undergoing major amputation was nearly 7 times higher in patients with DFO and CN (16 of 43 patients, 37.2%) compared to patients with DFO who did not have concomitant CN (9 of 112

patients, 8.0%). The risk of major amputation was not significantly higher in patients with STI and CN (1 of 17 patients, 5.9%) compared to patients with STI and no CN (3 of 54 patients, 5.7% [OR 1.13, 95% CI 0.11–11.57, $P = .92$]).

Discussion

Diabetic foot infections are among the most common diabetes-related causes for hospital admission.[21] A recent review by the International Working Group for the Diabetic Foot suggested that more high-quality studies were needed to guide the clinical practice of DFI.[26] The evidence guiding the specific choice of which antibiotic to prescribe and the duration of antibiotic use remained largely based on expert opinion. This review also suggested that "many" cases of DFO could be treated nonsurgically, although the authors did not provide any recommendations regarding which patients were best treated nonsurgically. No specific history and/or physical finding reliably excludes a diagnosis of osteomyelitis in patients with DFI, although ulcers >2 cm^2, a positive probe to bone test, ESR >70 mm/h, and an abnormal radiograph should raise suspicion for osteomyelitis.[7] In this study of patients hospitalized with moderate and severe DFIs, we found that the presence of DFO resulted in a higher likelihood of amputations and longer hospital stays. The odds of major amputation in patients with DFO were 7 times higher in the cohort of patients with CN compared to patients without CN. We speculate that this increased risk was likely due to the destructive osseous changes that were associated with CN, and the difficulty in eradicating infection and providing soft tissue coverage. Other risk factors for the presence of DFO include wounds that probe to bone, a history of previous foot wounds, and multiple foot wounds.[19]

Although the diagnosis of DFO was confirmed by bone biopsy and/or histopathology in this series, we do not feel that biopsy is necessary in all cases to establish the diagnosis of DFO. A biopsy is not necessary in a patient with frank radiographic changes and a positive probe to bone test. Similarly, a patient with a negative probe to bone test and no radiographic changes does not need the added risk of biopsy to exclude the diagnosis of DFO. Some clinical situations are not clear-cut; in those cases, confirmation with bone biopsy may be especially helpful in excluding DFO. Examples of confusing scenarios would be a patient with CN with an associated neuropathic ulcer that probes to bone, patients with previous treatment for DFO, or patients who have undergone prior osseous surgery (for infectious or non-infectious reasons). In these types of patients, bone culture and/or histopathology may be particularly helpful rather than relying solely on laboratory findings, imaging modalities, or the probe to bone test.[12] Postdebridement deep wound cultures, rather than superficial cultures, can also be used as a surrogate for bone cultures when bone cultures are not available.[22] Plain radiographs for the diagnosis of diabetic foot osteomyelitis have low interobserver reliability.[2]

We recognize that other centers have used the positive probe to bone test and abnormal radiographs in high risk patients to diagnose DFO.[5] Aragon-Sanchez et al[5] demonstrated that a positive radiograph and a positive PTB test had a sensitivity of 97% and a specificity of 92% in diagnosing OM. The authors found that histologically proven OM was present in only 2.5% of patients with a negative PTB test and negative radiograph.[5] Grayson et al[11] initially described the PTB and reported a positive predictive value of 89% for diagnosing

DFO with the PTB test. Other centers have found the PTB test be less reliable. Lavery et al[18] reported a positive predictive value of 57%, whereas Shone et al[27] reported a positive predictive value of 53%. Mutluoglu et al[25] reported a relatively high positive predictive value of 87% but a negative predictive value of only 62%. Similarly, we acknowledge that the diagnosis of OM by bone biopsy may be prone to inconsistencies when assessed by different pathologists.[23] The presence of elevated inflammatory markers, abnormal imaging, and/or a positive probe to bone test in a patient with DFI should heighten the suspicion for DFO. However, not all markers were significantly different between the OM and STI group of our hospitalized patients, contrary to other studies.[9,14] In our study, ESR was the only significantly different laboratory value when comparing patients with and without osteomyelitis. This finding was similar to the report by Kaleta et al[14] who reported that an ESR >70 mm/h was the optimal threshold in diagnosing osteomyelitis. Although we found that an ESR value ≥70 mm/h was associated with a 2.45-fold increased likelihood of having DFO, 60 of 155 patients (38.7%) with an ESR <70 mm/h had biopsy-proven osteomyelitis. Conversely, 29 of 74 patients (39.2%) with a soft tissue infection had an ESR >70 mm/h. Admission vital signs, presence or absence of gangrene, and severity of infection were not significantly different between patients with DFO and SFI.

This study has several weaknesses that need to be acknowledged. In general, retrospective studies rely on the accuracy of the medical records and data analysis. The nature of our operative practice potentially introduced bias into this study since our service was only consulted for the most serious DFI and we served as a tertiary referral center. Consequently, the prevalence of OM was likely to be higher than a general foot and ankle practice. A valid criticism of this study is that we did not track how many patients had undergone surgery prior to transfer and admission to our center. The overwhelming majority of patients in this study underwent surgery for their DFI, and we recognize that there was a bias toward the operative management of DFO. In this series of hospitalized patients, the wounds were generally associated with tissue undermining, necrosis, or frank abscess. Operative debridement and resection of infected bone dramatically decreased the bacterial bioburden, potentially reducing the duration of antibiotics if clean margins were obtained. Prolonged antibiotic use, as described in nonsurgical series, potentially may result in nephrotoxicity or clostridia difficile colitis. To our knowledge, no study has evaluated the risk of prolonged antibiotic use as described in nonoperative series compared to the risk of surgery in patients with DFO. This study did not address that issue and the current treatment of DFO was guided by the severity of infection, anatomic location of infection, the overall health of the patient, and the recommendations of the treating physician. Although it may be a matter of our personal opinion and bias, we view operative debridement and antibiotic therapy as synergistic treatment. We recognize that other highly respected experts in this field would disagree with this statement. At our institution, patients with less serious infections without radiographic changes are typically admitted to the medical service and do not require operative consultation. Another weakness is that we did not evaluate the specific antibiotic regimen or the duration of antibiotic use. Although patients with DFO underwent more surgeries during their admission, this potentially could represent a bias on our part. Our protocol has been to debride bone infections until a negative culture is obtained, potentially leading to more procedures. We adopted this practice based on the finding that positive

margins at the site of resection were associated with higher rates of treatment failure.[15] We also recognize that the final responsibility for recommending major amputation was made by the senior author, and this potentially introduced bias to the outcomes. Nonetheless, patients who underwent major amputation underwent twice the median number of procedures compared to patients who had successful limb salvage, and various consultants were used to formulate what we thought was the best plan for the patient. This study was further limited by our lack of differentiating patients with DFO who had bone destruction versus those who did not have bone destruction. We acknowledge that these 2 patient populations are quite different, and patients without bone destruction or abscess formation would be ideal candidates for the use of antibiotic therapy without surgery.

We recognize that antibiotic and operative treatment may have similar outcomes with regard to healing rates in patients with forefoot OM when compared to patients who are treated nonsurgically.[1,10,20] The risk of failure when using conservative surgery is increased in the presence of exposed bone, ischemia, and necrotizing soft tissue infections.[3] The severity of soft tissue involvement and ability to achieve soft tissue coverage are also very important factors in determining outcomes in patients with underlying osteomyelitis.[4] One advocate of nonsurgical treatment of DFO does not use the word *cure* but reports on remission rates.[10]

However, more studies need to be done to assess optimal treatment methods for OM involving the midfoot, hindfoot and ankle. Patients with OM of the midfoot, hindfoot and ankle may have underlying biomechanical abnormalities that may need to be addressed concomitantly when treating the bone infection.[13] Those patients with proximal OM may require more aggressive medical and operative treatment in an effort to decrease the length of stay and amputation rates. Faglia et al[8] reported on 350 patients admitted to their center for the treatment of osteomyelitis and found that independent risks factors for major amputation were osteomyelitis of the calcaneus, dialysis, and a leukocyte count >10,000/mL. Below-knee amputations were performed in 0.33% of patients with forefoot osteomyelitis, 18.5% of midfoot osteomyelitis, and 52.2% of hindfoot osteomyelitis.[8]

The outcomes in our study are similar to a report from Turkey that reviewed 73 hospitalized diabetic patients with infection.[24] In comparison to the soft tissue infection group, the DFO group had a significantly longer length of stay, longer duration of antibiotic therapy, longer duration of the wound before admission, and longer time to wound healing. There were more operative procedures in the DFO group than in the STI group during hospitalization, with 22 patients in the DFO group and 5 patients in STI group undergoing minor amputation.

Studies on DFO often stimulate more questions than they answer. The optimal diagnostic strategy and treatment of DFO remains a subject of debate. We acknowledge that our definition of outcomes (ie, rate of amputation and length of hospital stay) was arbitrary. An important question which remains unanswered by this article was whether operative or medical therapy for the same level of disease severity (ie, forefoot, midfoot, hindfoot, or ankle osteomyelitis) would result in decreased hospital stay, decreased use of healthcare resources over a long duration, or lower rates of amputation. At this point in time, we do not know if medical treatment of osteomyelitis is more likely to have a recurrence and require

additional treatment when compared to patients who undergo surgery. From an economic standpoint, we do not know if the medical treatment of patients with DFO results in more or less expenditure of health care dollars due to prolonged antibiotic therapy and a treatment in an outpatient wound clinic. Generally speaking, the majority of costs associated with treatment of diabetic foot disease have been associated with inpatient management, and this raises an important point in this era of containment of health care costs. Finally, we do not know whether medical treatment of DFO results in differences in function and health care–related quality of life when compared to operative intervention.

In conclusion, we found that the presence of DFO in patients with DFI resulted in significantly longer hospital stays and higher rates of amputation compared to patients without DFO. The only laboratory value that differed significantly between patients with and without DFO was the ESR. We were unable to distinguish osteomyelitis from soft tissue infection based on admission vital signs, laboratory findings (except ESR), severity of infection, or the presence of gangrene. Bone biopsy for culture and/or histopathology may assist in the diagnosis of DFO in patients with a confusing clinical picture. Deep soft tissue cultures after debridement may also be used to guide antibiotic therapy. Readers should recognize that our cohort of DFO patients was composed of more severe cases that required hospital admission, and that our results may not be applicable to patients without bone destruction who could be successfully managed as out-patients. The presence of CN in patients with DFO significantly increased the rate of major amputation in this series.

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Table 1

Patient Demographics.

	Osteomyelitis (n = 155)	Soft Tissue Infection (n = 74)	*P* Value
Age, y	58.8 ± 12.1	58.2 ± 13.2	.7543
Male gender, n (%)	122 (78.7)	54 (73.0)	.3357
BMI	31.2 ± 6.9	33.7 ± 7.5	.0116
Follow-up, wk	46.6 (70.1)	48.8 (90.6)	.4076
Type 2 diabetes mellitus, n (%)	140 (90.9)	61 (82.4)	.0636
Duration of diabetes mellitus, y	15.4 ± 9.8	14.8 ± 11.8	.7198
Insulin use, n (%)	119 (76.8)	56 (75.7)	.7591
Tobacco use, n (%)			
Never used	52 (70)	100 (65)	.5938
Active use	15 (20)	41 (26)	
Former use	7 (9)	14 (9)	
Tobacco pack-years	30.1 ± 17.4	27.2 ± 16.8	.4948
Michigan Neuropathy Screening Index	7.6 ± 1.6	7.1 ± 1.9	.0830
Charcot neuroarthropathy, n (%)	43 (28)	17 (23)	.4428
Peripheral artery disease, n (%)	79 (51)	28 (38)	.0625
End-stage renal disease, n (%)	27 (17)	13 (18)	.9780

Table 2

Clinical Findings on Admission.

	Osteomyelitis (n = 155)	Soft Tissue Infection (n = 74)	*P* Value Odds Ratio (95% Confidence Intervals)
HbA1c, %, M ± SD	8.9 ± 2.4	9.0 ± 2.3	.8258
Admission glucose, M ± SD	265.3 ± 137.1	254.6 ± 118.7	.5667
ESR, mm/h, M ± SD	85.4 ± 40.7	71.5 ± 38.3	.0177
ESR ≥70 mm/h	95 (61.3%)	29 (39.2%)	.0019 2.45 (1.39–4.33)
CRP, mg/dL, M ± SD	13.4 ± 10.4	11.8 ± 9.3	.2880
Admission WBC, cells/mm^3, M ± SD	12650 ± 5810	13110 ± 5680	.5737
% neutrophils, M ± SD	77.3 ± 11.4	76.5 ± 9.9	.6345
Serum albumin, g/dL, M ± SD	2.8 ± 1.0	2.9 ± 1.3	.3682
Hemoglobin, g/dL, M ± SD	11.1 ± 2.1	11.7 ± 1.8	.0317
Platelet count, cells/mm^3, M ± SD	287,900 ± 116,400	273,500 ± 117,100	.3820
BUN, mg/dL	24.0 (19.0)	20.0 (21.0)	.2148
Creatinine, mg/dL	1.3 (1.1)	1.2 (1.0)	.1422
Symptoms of nausea and vomiting, n (%)	69 (45%)	25 (34%)	.1314
Systolic BP, mm/Hg	136.0 ± 28.2	140.4 ± 21.6	.1911
Heart rate, beats/min, M ± SD	93.7 ± 18.0	91.2 ± 17.9	.3145
Admission temperature, °C	37.2 (0.9)	37.1 (0.8)	.2373
Respiratory rate, breaths/min, M ± SD	19.0 ± 3.5	18.5 ± 2.6	.1649
Gangrene, n (%)	22 (14%)	9 (12%)	.6743

Abbreviations: BUN, Blood urea nitrogen; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HbA_{1c}, glycosylated hemoglobin; M, mean; SD, standard deviation

Table 3

Results and Outcomes.

	Osteomyelitis (n = 155)	Soft Tissue Infection (n = 74)	*P* Value Odds Ratio (95% Confidence Interval)
Severe IDSA infection, n (%)	80 (51.61)	32 (43.24)	.1642
Vascular surgery, n (%)	24 (15)	6 (8)	.1228 2.08 (0.81, 5.32)
Antibiotic use after discharge, n (%)	138 (90)	68 (92)	.5849
Number of admissions after discharge, M ± SD	0.48 ± 0.89	0.54 ± 0.89	.6538
Mortality, n (%)	2 (1.3)	1 (1.3)	1.0000
Length of hospital stay in days	7.00 (6.00)	6.00 (5.00)	.0082
Any amputation, n (%)	94 (61)	16 (21.6)	<.0001 5.59 (2.94, 10.60)
Location of amputation, n (%)			
Forefoot	36 (23)	5 (7)	<.0001
Midfoot	34 (22)	7 (9)	
Transtibial	22 (14)	4 (5)	
Minor amputation, n (%)	69 (45)	12 (16.2)	<.0001 4.15 (2.07, 8.30)
Major amputation, n (%)	25 (16)	4 (5.4)	.0318 3.37 (1.13, 10.06)
Eventual major amputation, n (%)	34 (22)	10 (14)	.1476 1.76 (0.81, 3.80)