


Predictors of Outcomes in Diabetic Foot Osteomyelitis Treated Initially With Conservative (Nonsurgical) Medical Management: A Retrospective Study

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Abstract

The optimal way to manage diabetic foot osteomyelitis remains uncertain, with debate in the literature as to whether it should be managed conservatively (ie, nonsurgically) or surgically. We aimed to identify clinical variables that influence outcomes of nonsurgical management in diabetic foot osteomyelitis. We conducted a retrospective study of consecutive patients with diabetes presenting to a tertiary center between 2007 and 2011 with foot osteomyelitis initially treated with nonsurgical management. Remission was defined as wound healing with no clinical or radiological signs of osteomyelitis at the initial or contiguous sites 12 months after clinical and/or radiological resolution. Nine demographic and clinical variables including osteomyelitis site and presence of foot pulses were analyzed. We identified 100 cases, of which 85 fulfilled the criteria for analysis. After a 12-month follow-up period, 54 (63.5%) had achieved remission with nonsurgical management alone with a median (interquartile range) duration of antibiotic treatment of 10.8 (10.1) weeks. Of these, 14 (26%) were admitted for intravenous antibiotics. The absence of pedal pulses in the affected foot ($n = 34$) was associated with a significantly longer duration of antibiotic therapy to achieve remission, 8.7 (7.1) versus 15.9 (13.3) weeks ($P = .003$). Osteomyelitis affecting the metatarsal was more likely to be amputated than other sites of the foot ($P = .016$). In line with previous data, we have shown that almost two thirds of patients presenting with osteomyelitis healed without undergoing surgical bone resection.

Keywords

osteomyelitis, diabetic foot, diabetes, amputation, infection, antibiotics

Diabetic foot ulceration is one of the most common “diabetes-specific” complications resulting in hospital admission.¹ There are an estimated 6000 diabetes-related amputations per year in England alone, with the cost of diabetes-related foot disease, in particular osteomyelitis and amputation, calculated to be approximately £580 million per annum.^{2,3}

It is well recognized that osteomyelitis complicates a significant proportion of diabetic foot infections.^{4,5} However, despite this, the optimal management of diabetic foot osteomyelitis (DFO) is controversial, with limited evidence to guide the initial treatment strategy.⁶ Some authors advocate a primarily surgical approach and believe that antibiotic therapy alone may worsen outcomes with decreased wound healing and more major amputations.^{7,8} In addition, where surgery has been required, authors have shown that early intervention

improves outcomes.⁹ In contrast, several retrospective case series have demonstrated that between 58% and 80% of DFO can be successfully managed with antibiotics alone.^{10–16} However, this still leaves a proportion of patients who receive an extended period of antibiotics without benefit before eventually undergoing amputation. The ability to predict from the outset those patients likely to require surgical intervention could improve patient

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outcomes and the health economy. To date there is a paucity of data on what factors influence outcomes in patients with DFO presenting to outpatient clinics. In a retrospective review of 50 patients with conservatively treated DFO, Senneville et al¹⁴ found that only bone culture-based antibiotic therapy was a factor significantly predictive of remission. However, bone biopsy is not routinely performed in many centers. The objective of this study was to evaluate the influence of several patient variables on the outcomes of DFO where the initial approach was nonsurgical.

Patients and Methods

We carried out a retrospective study of consecutive DFO cases presenting to a tertiary diabetic foot clinic over a period from July 2008 to December 2011.

Case Selection and Definitions

Cases were identified by searching for “osteomyelitis” and “diabetes” from the comprehensive departmental electronic clinic database at our institution. A diagnosis of DFO required at least one feature of clinical suspicion: positive probe-to-bone test, visible bone at ulcer base, sausage deformity of the toe, and at least one of the following supportive radiographic features: periosteal reaction, loss of trabecular architecture, endosteal scalloping, bone destruction, or sequestered bone.¹⁷⁻²⁰ All patients had plain radiographs taken, and where this was indeterminate, a magnetic resonance imaging (MRI) scan was done. Patients with at least one supportive MRI feature of osteomyelitis including periosteal reaction, sequestrum, and characteristic alteration in bone marrow signal intensity were then included in the study. Inflammatory markers were measured at baseline. Bone biopsies were not performed in our institution. The HbA1c values were taken within a 3-month period before the diagnosis of DFO was made. Treatment was defined as nonsurgical if no surgical intervention involving the bone had taken place during the treatment episode. For each case identified, a search for discharge summaries in the hospital’s electronic patient record system (Integrated Clinical Environment (ICE), Sunquest Information Systems Ltd, Norwich, UK) was performed to identify patients who were admitted for the treatment of osteomyelitis and whether they had intravenous antibiotics or surgery.

Case Management Standards

Patients were managed by a multidisciplinary team consisting of a vascular surgeon, an orthopedic surgeon, a podiatrist, and a diabetologist with a specialist interest in diabetic feet. Patients underwent standard management with ulcer debridement and pressure off-loading. The potential need

for revascularization was considered on a case-by-case basis. Deep soft tissue samples were taken from the wound for culture and sensitivities and antibiotics were given according to local antimicrobial guidelines and culture results.²¹ Soft tissue infection was classified in line with Infectious Disease Society of America guidelines as mild, moderate, or severe depending on the degree of inflammation or cellulitis around the ulcer, response to oral antibiotics, and signs of systemic toxicity.²² In non-penicillin allergic patients with mild infections co-amoxiclav was first choice. For moderate infections ciprofloxacin and metronidazole were added in, and those with severe infections would be admitted for intravenous piperacillin and tazobactam with or without vancomycin. In our institution, the initial standard of care is antibiotic therapy, with regular clinical review in a combined foot clinic comprising concurrent (nonsurgical) podiatry, medical, and surgical (vascular/orthopedic) input. If there was no evidence of healing or deterioration, then a joint consensus on further management was made—either changing the antibiotic or progressing to surgical debridement and/or amputation. Specialist microbiological advice was sought as necessary.

Evaluation of Outcomes

The end of the osteomyelitis episode was defined as wound healing with no clinical or radiological signs of infection at the initial or contiguous sites at which point treatment with antibiotics was stopped. In those who underwent surgery, the end of episode was defined as at the point of discharge following amputation or, if they were discharged with antibiotics, the point at which antibiotics were stopped. Remission was defined as meeting the aforementioned criteria 12 months after the end of the episode without further surgical intervention, radiological changes, or the requirement for further antibiotic therapy.

Statistical Analysis

Comparisons between the groups requiring amputation and those treated nonsurgically were made according to the nature and distribution of the characteristics. Distributions were judged by inspection of histograms. For approximately normally distributed data the differences in means were calculated and tested using 2-sided *t* tests. For categorical data the number and percentages in each group were tabulated and the differences in these percentages tested using the χ^2 test (or the Fisher’s exact test where expected numbers in any cell of the cross-tabulation were less than 5). For categorical characteristics the effect size (measuring the contrast between groups) was calculated as the odds ratio for amputation versus not, comparing the index characteristic with the alternative. In the case of ulcer site with several categories, the odds for amputation were compared

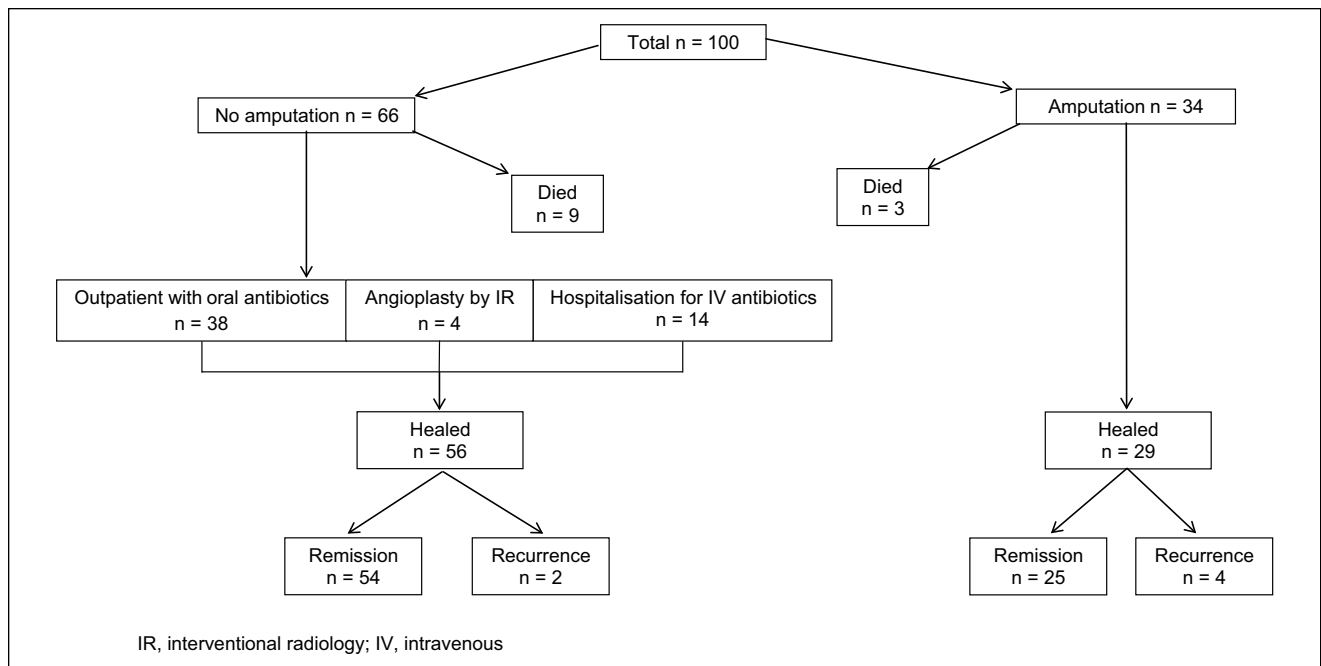


Figure 1. Flow diagram illustrating outcomes of all 100 patients diagnosed with osteomyelitis. Abbreviations: IR, interventional radiology; IV, intravenous.

for each site with those for metatarsal head (arbitrary reference category). A logistic regression analysis was performed to evaluate factors that may predict amputation.

An analysis of the length of the antibiotic treatment period (in days) was done using medians and interquartile range (IQR) to describe subgroups defined by whether or not the patient had at least one pedal pulse at diagnosis. This was done separately for those whose episode ended in amputation or not. The continuity-corrected median test was used to test the differences between the median episode lengths between pulse and no-pulse groups. All variables were stratified according to the outcome of success or failure of non-surgical management. Failure was defined as requiring amputation. Comparison of continuous variables was performed using a 2-tailed *t* test and categorical variables such as organism cultured by Fisher's exact test. The *P* value for comparison between pulses present or absent was derived from the continuity-corrected median test. Statistical significance was defined as *P* < .05. Statistical analysis was performed using SPSS software (IBM Ltd, Portsmouth, UK).

Results

Patient and Episode Characteristics

One hundred consecutive cases of DFO were initially identified. By the end of the 1-year follow-up period, 12 patients (with 15 episodes of osteomyelitis) had died and were excluded from the analysis. Causes of death were ascertained

for each patient. One patient died from sepsis, 3 from pneumonia, 6 from cardiovascular disease, 1 from cancer, and 1 from chronic renal failure. The outcomes are shown in Figure 1. Descriptive data on patients and osteomyelitis episodes are given in Table 1 according to whether the episode ended in amputation or not.

Patient Outcomes

After a 12-month follow-up period, remission was achieved in 54 (63.5%) of patients with nonsurgical management. Of these, 14 (25.9%) were admitted for intravenous antibiotics and 4 (7.4%) required percutaneous revascularization (2 underwent popliteal angioplasty, 1 bilateral femoral angioplasty, and 1 unilateral femoral angioplasty). Twenty-nine (34.5%) patients had an amputation. Of those managed without surgery, 2 (3.6%) experienced relapse at the initial or contiguous site, while 10 (17.9%) had a further episode of osteomyelitis at a distant site during the 12-month follow-up period, most being associated with the development of new foot ulcers elsewhere. This compared to 4 (13.8%) and 8 (27.6%), respectively, for those who underwent amputation (Figure 1). The decision to amputate was made after discussion between the patient and the multidisciplinary specialist foot team if the foot was failing to respond to conservative treatment.

Of the 85 patients, 84 had deep tissue samples sent for microbiological analysis at the time of initial presentation. Sixty samples grew potentially pathogenic organisms. The

Table 1. Characteristics of Osteomyelitis Cases and Comparison Between Those Whose Antibiotic Treatment Ended With Amputation or Not.^a

Characteristic	Not Amputated	Amputated	All	Effect Size (95% CI) ^b	P Value
N	56 (65.9%)	29 (34.5%)	85 (100)	—	—
Age (years), mean (SD)	69.6 (12.4)	64.4 (12.4)	67.8 (12.5)	5.17 (-0.46; 10.80) ^c	.07 ^d
HbA1c (mmol/L and %), mean (SD)	62.6/7.9 (15.2)	63.5/9 (13.2)	62.9 (14.52)	-0.7 (-7.5; 6.06) ^c	.84 ^d
eGFR <29 mL/min/1.73 m ²	6 (10.7)	0	6 (7.1)	N/A	.07
Pedal pulse detected in at least one foot	31 (55.4)	20 (69.0)	51 (60.0)	1.79 (0.69; 4.61)	.23
Location on foot					.012
Metatarsal head	8 (14.3)	13 (44.8)	21 (25.0)	— (Ref. cat)	
Proximal phalanx	10 (17.9)	7 (24.1)	17 (20.2)	0.43 (0.12; 1.59)	
Distal phalanx	26 (46.4)	7 (24.1)	33 (39.3)	0.17 (0.05; 0.56)	
Heel	3 (5.4)	0	3 (3.6)	N/A	
Mid phalanx	9 (16.1)	2 (6.9)	11 (12.9)	0.14 (0.02; 0.8)	
Previous ulcer at this site	11 (19.6)	7 (24.1)	18 (21.2)	1.30 (0.44;3.82)	.63
Previous osteomyelitis	21 (37.5)	13 (44.8)	34 (40.0)	1.35 (0.54; 3.36)	.52
Previous amputation	12 (21.4)	9 (31.0)	21 (24.7)	1.65 (0.60; 4.54)	.33
Culture result ^e	37 (67.3)	23 (79.3)	60 (71.4)	1.86 (0.65; 5.39)	.24
Streptococci	5 (9.1)	3 (10.3)	8 (9.5)	1.15 (0.26; 5.21)	.85 ^f
<i>Staphylococcus aureus</i>	23 (41.8)	12 (41.4)	35 (41.7)	0.98 (0.39; 2.46)	.97
Methicillin-resistant <i>S aureus</i>	1 (1.8)	2 (6.9)	3 (3.6)	4.0 (0.35; 46.1)	.27 ^f
Coliforms	11 (20.0)	5 (17.2)	16 (19.1)	0.83 (0.26; 2.7)	.76
<i>Pseudomonas aeruginosa</i>	7 (12.7)	1 (3.5)	8 (9.5)	0.25 (0.03; 2.10)	.25 ^f

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate.

^aData are n (%) unless otherwise indicated.

^bUnless otherwise specified, effect size is odds ratio for amputation versus not, comparing the index characteristic with the alternative. In the case of ulcer site the odds for amputation are compared for each site with those for metatarsal head.

^cEffect size is difference in means (not-amputated episodes minus amputated episodes).

^dP value from t test.

^eCulture result from deep tissue swab.

^fP value from Fisher’s exact test.

Table 2. Distribution of Pathogens Cultured From Deep Tissue Swabs From 84 Patients With Diabetic Foot Osteomyelitis.

Pathogens	n (%)
MSSA	35 (41.7)
MRSA	3 (3.6)
MSCoNS	1 (1.2)
Streptococci	8 (9.5)
Enterococci	5 (5.9)
Coliforms	16 (19.1)
<i>Pseudomonas aeruginosa</i>	8 (9.5)
Other	3 (3.6)
Polymicrobial	26 (30.6)

Abbreviations: MSSA, methicillin-susceptible *S aureus*; MRSA, methicillin-resistant *S aureus*; MSCoNS, methicillin-susceptible coagulase-negative staphylococci.

distribution of these is shown in Table 2. The median duration of antibiotic treatment given was 10.8 weeks, and the distribution is shown in Figure 2. For those achieving remission with nonsurgical management, the absence of pedal pulses in the affected foot was associated with a significantly longer duration of antibiotic therapy to achieve

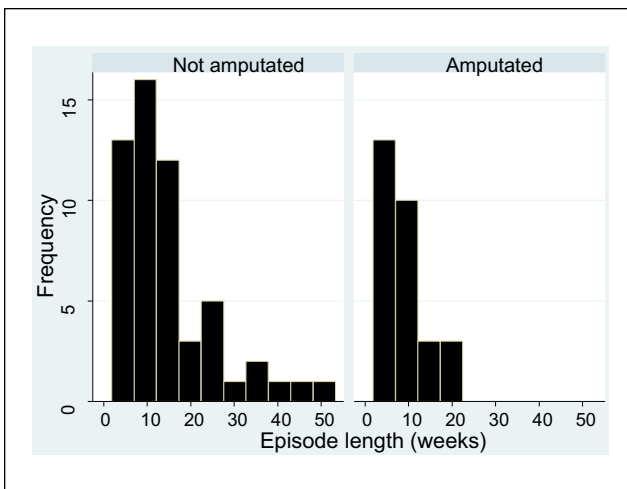


Figure 2. The median duration of antibiotic therapy.

remission. Median (IQR) therapy in patients with at least one pedal pulse on the affected side was 8.7 (7.1) versus 15.9 (13.3) weeks in those with absent pulses ($P = .003$). These data are shown in Table 3.

Factors Predicting Amputation

Logistic regression analysis was carried out as an exploratory analysis to see if there were any factors that predicted amputation. The only 2 variables that were significantly associated with amputation were ulcer site (with osteomyelitis affecting the metatarsal being significantly more likely to be amputated than other sites of the foot; $P = .016$) and the absence of pedal pulses. Combining these 2 factors produces a predictive sensitivity of 65% and a specificity of 74% for amputation.

Discussion

The present study shows that remission was achieved in 65.9% of DFO treated with nonsurgical management. To our knowledge this is only the second study to examine factors predictive of remission in DFO and has a larger sample size than the previous study. Our data are consistent with previous reports suggesting that surgery should not necessarily be considered as first-line treatment for DFO. Osteomyelitis of the metatarsal head was more likely to be amputated than at other sites in the foot. In those with absent pedal pulses on the affected foot, successful nonsurgical management was associated with a longer duration of antibiotic therapy to achieve remission. However, this subgroup was not more likely to undergo amputation than those with palpable foot pulses.

Since the data provided are a consecutive series from a single specialist center, the results are unlikely to be significantly affected by selection bias. Comparison between remission rates and factors predicting outcome are strengthened by close similarities in case definitions and standard management reported in previous studies.

Despite accumulating evidence that a majority of patients achieve remission with nonsurgical management, there continues to be discord on the optimal initial management strategy in DFO. While there are concerns about subjecting patients to long-term broad spectrum antimicrobial therapy, in this study all 85 patients managed to complete their prescribed courses without significant adverse side effects. Two previous studies have advocated an initial surgical approach to DFO based on findings that it reduces rates of more extensive bone resection. However, both of these studies focused on patients hospitalized with osteomyelitis that are likely to have more severe and late-presenting disease than an unselected cohort presenting to outpatient clinic. When surgery is required, early intervention may reduce the need for major amputations and limit exposure to prolonged antibiotic therapy and its associated risks. In a recent small randomized study of 46 patients comparing medical therapy with conservative surgery, the healing rates at 12 weeks were similar between the 2 groups.

Accepting the risks of prolonged antibiotic therapy and that those who will require amputation may benefit from an

early intervention, it is of interest to consider what factors predict failure of conservative management. Here we report that DFO affecting the metatarsal is significantly more likely to have an amputation. Combining the site of osteomyelitis with the absence of pedal pulses produced a predictive sensitivity of 65% and specificity of 74% for amputation. In line with previous work, our data show that variables such as age, HbA1C, and cultured microorganism have no influence on outcomes. Collectively, these data provide some insight in to how patient factors may influence this risk of amputation in DFO.

A recent study has shown that in a small cohort of 40 patients randomized to either 6 or 12 weeks of antibiotics, remission rates were similar between the 2 groups at 65%.²³ However, we found that there was an association between absent pedal pulses on the affected foot and the duration of antibiotic use. The study by Tone et al²³ excluded patients with no foot pulses. Despite these authors' finding, the appropriate time to stop antibiotics in DFO is often subjective. One could argue this result may in part reflect observer bias in the clinician's belief that absence of pedal pulses may require a longer duration of antibiotics. However, this association could be explained by poor tissue perfusion causing reduced penetration of the antimicrobial to the site of infection and a slowing of tissue repair, which results in a prolonged treatment with antibiotics to achieve healing in DFO.^{24,25} In addition, this group was not significantly more likely to undergo amputation. This is of particular interest as previous similar studies have excluded this patient group from their analysis. Therefore, we would expect slower progress in this group of patients and prolonged conservative management should be tried before considering amputation, particularly since following amputation the wound site is less likely to heal unless vascular insufficiency is addressed. It may well be that the differences seen in our study are due to the collective input of the MDT who all see the patients in the same room at the same time to aid decision making.

We had a small number of deaths during the study; however, the numbers were small, and the proportion of deaths in each arm was similar, 13.6% in the nonamputation arm and 9% in the amputation arm. Causes of death were similar to those previously reported.²⁶

The main limitations to our data are that it is a retrospective cohort study. A randomized controlled clinical trial would be the gold standard in comparing outcomes of primary medical versus surgical management in DFO. However, even though such a study was recently reported, it was limited by a small sample size, and a larger sample size is required to better evaluate each approach. Such a study is likely to prove difficult as it would require randomizing patients to surgery that may not be required and recruitment could be undermined by patient preferences to avoid surgery. Further work utilizing increasingly sophisticated

Table 3. Length of the Antibiotic Treatment Period in Those With and Without Palpable Foot Pulses Stratified According to the Outcome of Amputation or Not.^a

Episode Ended by Amputation	Length of Episode (Antibiotic Treatment), Median (IQR)		P Value ^b
	No Pulse Present	At Least One Pedal Pulse Present	
No	15.9 (13.3)	8.7 (7.1)	.003
Yes	7.1 (4.1)	8.3 (7.2)	.901

Abbreviation: IQR, interquartile range.

^aPulses were assessed on the affected foot only.

^bP value for comparison between pulse present and pulse not present—from continuity-corrected median test.

and accessible radiological techniques in addition to clinical characteristics may provide more contextual information to help decide on the optimal initial management of DFO.^{27,28} In addition, this was a single-center study, and while we believe this is one of the largest series reported, with the longest follow-up, the relatively small sample size makes it harder to generalize. Another limitation is that in common with previous work, this study is limited by difficulties in case definition in the absence of universally accepted criteria for osteomyelitis. However, the diagnostic methods in the study, including sausage deformity and probe-to-bone test in the presence of characteristic X-ray or MRI appearances, are used consistently within the literature.²⁹ Furthermore, these are the clinical grounds for diagnosis in much of routine practice, which strengthens the external validity of our results.

In summary, we have shown that the absence of foot pulses on the affected side in DFO is associated with requiring significantly longer duration of antibiotics to induce remission. DFO of the metatarsal is significantly more likely to undergo amputation than other sites in the foot.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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