The International Journal of Lower Extremity Wounds
1–10

DOI: 10.1177/1534734616661058
ijl.sagepub.com
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Treatment Failure and Leg Amputation Among Patients With Foot Osteomyelitis

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Abstract

We sought to identify factors associated with treatment failure and leg amputations among those patients who presented with foot osteomyelitis. Characteristics, treatments, and outcomes for all patients treated for probable or definite foot osteomyelitis (per consensus definition) between January 2011 and March 2015 were reviewed. Multivariate Cox regression models were used to identify risk factors for treatment failure (unanticipated resection of additional bone *or* leg amputation) and of leg amputation alone. A total of 184 episodes of foot osteomyelitis met inclusion criteria. Treatment failure occurred in 53 (28.8%) and leg amputation in 21 (11.4%). Risk factors for treatment failure included severe/unaddressed peripheral artery disease, homelessness, *Pseudomonas aeruginosa* or *Escherichia coli* bone isolates, serum albumin <2.8 mg/dL, hallux involvement, insulin therapy, 60 or more pack-years smoking, and <7 days of directed antibiotic therapy for a positive bone margin. Delayed primary wound closure (ie, staged operations) had significantly lower treatment failure risk. Unanticipated resection of bone was not associated with leg amputation. Foot osteomyelitis treatment failure is common. Various factors can help identify those at risk for treatment failure and/or leg amputation, and further studies should focused whether initial management or follow-up should change when these factors are present.

Keywords

osteomyelitis, diabetes, gangrene

Foot osteomyelitis complicates approximately 20% to 30%[1] of all foot ulcers in patients with diabetes and confers a 2-fold higher incidence of leg amputation.[2] Incidence rates obtained from Medicare data[3] would predict approximately 300 000 cases of foot osteomyelitis occurring annually in the United States. Management of foot osteomyelitis is costly, with estimated inpatient costs of $37 860 for antibiotic infusion therapy and $53 779 for leg amputations in the United States in 2010.[4]

Large nonrandomized series and the one randomized trial specific to foot osteomyelitis report treatment failure rates ranging from 20% to 35%.[5-13] Evidence-based guidelines addressing the management of foot osteomyelitis in the diabetic foot have been published but focus predominately on the diagnosis of osteomyelitis,[14] as the previously-published reports have not yet identified clear reasons why treatment failure occurs so frequently. Efforts to improve the outcomes of foot osteomyelitis management will be limited until these fundamental concepts are better understood.

We performed a retrospective review to identify factors associated with treatment failure among those treated for foot osteomyelitis. Our objectives in identifying such factors were 2-fold: first, to provide the foundation for a risk stratification system that may help clinicians identify those patients at risk for treatment failure, including leg amputation; and second, to identify factors that would merit further study as potential targets for improving outcomes among patients with foot osteomyelitis.

Methodology

Study Subjects and Categorization of Outcomes

We included all episodes of foot infections that reached International Working Group for the Diabetic Foot consensus definition[15] of either "probable" or "definite" foot

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osteomyelitis and were initially evaluated at the Michael E. DeBakey Veterans Affairs Medical Center between January 1, 2011 and March 1, 2015. Osteomyelitis associated with podiatric or orthopedic hardware was excluded from this analysis. Patients meeting these criteria were identified using the admission logs and operating room records of the consolidated inpatient clinical service that provided care for patients during this time period. Foot osteomyelitis was defined as bone infection distal to the malleoli. The primary unit of analysis for this study was an initial and unique episode of osteomyelitis. As such, patients with multiple episodes of foot osteomyelitis were included in the analysis, though only if occurring at a location that was not contiguous or adjacent to previous sites of foot osteomyelitis (eg, fifth metatarsal osteomyelitis in a patient who was previously treated for osteomyelitis of the first distal phalanx or osteomyelitis occurring in the contralateral foot).

Outcome was categorized based on clinical status at the patient's most recent follow-up appointment. *Treatment failure* was defined as either (*a*) unanticipated resection of additional bone in an area contiguous with or adjacent to the initial location of osteomyelitis or (*b*) major (above-ankle) amputation. A *complete response* was defined as a completely intact epithelial surface (ie, complete wound healing) without any further clinical signs of soft tissue or bony infection. Foot osteomyelitis episodes that were without clinical signs of soft tissue or bony infection but had not achieved complete reepithelialization were classified as being *in remission*. Definitions of additional variables utilized in this study are included in the appendix.

Description of Management Algorithm Used for Management of Foot Osteomyelitis

Patients identified as having moderate or severe foot infections—involving either soft tissue and/or bone, with or without the presence of peripheral artery disease (PAD)—were admitted to a consolidated vascular surgery inpatient service for administration of parenteral antibiotics (typically vancomycin and ertapenem). Surgical management was generally performed within 24 to 48 hours of admission and done by surgeons with board certification in either vascular surgery, orthopedic surgery, or podiatric surgery. Operations were performed in the operating theater under regional anesthesia. The initial suspicion for osteomyelitis was based on history, physical examination findings, and plain films of the foot. Magnetic resonance imaging was obtained selectively.

Surgical management was the predominant treatment modality during this study period. The extent of bone resection was based on the radiographic findings and the gross appearance of bone as assessed by the operative surgeon. The goal was a bone margin that appeared grossly healthy (intact cortical bone with a smooth contour, trabecular bone with punctate bleeding). The decision for continuing antibiotics after discharge from the hospital was made by the staff surgeon, often with input from an infectious disease consultant. Oral antibiotics were preferred unless microbiology demonstrated organisms identified in bone culture were susceptible only to parenteral antibiotics. A post hoc review performed by a board-certified infectious disease specialist (C.M.) categorized discharge antibiotic regimens as good coverage, or partial coverage, or no expected coverage based on the organisms identified in bone culture.

Statistical Analysis

Nonparametric analyses were used for all comparisons between groups, including the Mann-Whitney rank-sum test for continuous variables and chi-square or Fisher's exact test for binary variables. Cox regression was used to estimate hazard ratios for multivariate models using time-to-event data, with final models created through backward selection. A P value $<.05$ was considered statistically significant for all analyses. Intercooled Stata version 8.2 (StataCorp, College Station, TX) was used for all statistical analyses.

Results

Baseline Characteristics

In total, 184 episodes of foot osteomyelitis met inclusion criteria. The median age was 65 years (range 42-94 years). Most episodes (141, or 76.6%) were solitary occurrences, while 43 episodes (23.4%) occurred in patients with one or more other foot osteomyelitis episode included in this study. Diabetes mellitus was present in 170 (92.4%, (Table 1), and the median hemoglobin A1c level among these patients was 8.4%. Most patients (146, 79.3%) were living independently and walked with either no assistance or with minimal support (eg, cane or walker).

Characteristics of Foot Osteomyelitis Episodes

Leukocytosis was the single most common systemic inflammatory response syndrome (SIRS) criteria present (49 episodes, 26.6%) followed by tachycardia (30 episodes, 16.3%; see Table 2). Most episodes (97, or 52.7%) presented with no SIRS criteria, while 59 episodes (32.1%) presented with 1 criterion, 22 (12.0%) with 2 criteria, and 5 (3.2%) with 3 or more criteria. Hypotension was present in only 1 episode (0.5%). Cellulitis was present in 159 episodes (86.4%), abscess in 126 (68.5%), and septic arthritis in 38 (20.7%). In the majority of episodes (178, 96.7%) the instigating ulcers was located on the forefoot, and the remaining six (3.2%) were located on the midfoot or heel. The median area of the associated foot ulcers was 4.9 cm^2 (25%-75% interquartile range of

Table 1. Baseline Characteristics of Patients Included in the Study.

Variable	Overall (n = 184)	No Treatment Failure Occurred (n = 130)	Treatment Failure Occurred (n = 54)	*P*
Age, years, median (IQR)	65 (58-69)	65 (58-68)	64 (58-69)	.82
Body mass index, kg/m^2, median (IQR)	28.7 (23.9-32.9)	28.6 (23.9-32.6)	28.8 (23.8-33.0)	.42
Diabetes mellitus, n (%)	164 (89.1)	113 (86.9)	51 (94.4)	.14
Hemoglobin A1c, %, median (IQR)	8.4 (7.1-10.3)	8.2 (7.1-9.7)	8.7 (7.1-11.1)	.15
Insulin therapy, n (%)	115 (62.5)	74 (56.9)	41 (75.9)	.02*
Chronic kidney disease,[a] n (%)				
Stages 0, 1, and 2	111 (60.3)	81 (62.3)	30 (55.6)	.39
Stage 3a	20 (10.9)	17 (13.1)	3 (5.6)	.14
Stage 3b	27 (14.7)	18 (13.9)	9 (16.7)	.62
Stage 4	13 (7.1)	7 (5.4)	6 (11.1)	.17
Stage 5/ESRD	13 (7.1)	7 (5.4)	6 (11.1)	.17
Active tobacco use, n (%)	64 (35.0)	44 (33.9)	20 (37.7)	.62
Coronary artery disease, n (%)	53 (28.8)	34 (26.2)	19 (35.2)	.22
Congestive heart failure, n (%)	28 (15.2)	16 (12.3)	12 (22.2)	.09
PAD, n (%)				
P0, no significant PAD	146 (79.4)	106 (81.5)	40 (74.1)	.26
P1, mild PAD	18 (9.8)	14 (10.8)	4 (7.4)	.49
P2, moderate PAD	10 (5.4)	6 (4.6)	4 (7.4)	.48
P3, severe PAD	4 (2.2)	0 (0)	4 (7.4)	<.01*
Px, incompletely assessed	6 (3.3)	4 (3.1)	2 (3.7)	1.00
Previous revascularization of index limb, n (%)	54 (29.4)	33 (25.4)	21 (38.9)	.07
Previous amputation of contralateral leg, n (%)	12 (6.5)	8 (6.2)	4 (7.4)	.75
Homeless, n (%)	9 (4.9)	4 (3.1)	5 (9.3)	.13

Abbreviations: ESRD, end-stage renal disease; IQR, interquartile range; PAD, peripheral artery disease.
[a]Chronic kidney disease stages 0-2, glomerular filtration rate >60 mL/min; stage 3a, 45-59 mL/min; stage 3b, 30-44 mL/min; stage 4, 15-29 mL/min; stage 5, <15 mL/min or ESRD.
*$P < .05$.

Table 2. Systemic and Local Infection Characteristics of Foot Osteomyelitis Episodes (n = 140).

Variable	Overall (n = 184), n (%)	No Treatment Failure Occurred (n = 130), n (%)	Treatment Failure Occurred (n = 54), n (%)	*P*
Temperature >100.5°F	12 (6.5)	8 (6.2)	4 (7.4)	.75
Heart rate >100/min	30 (16.3)	22 (16.9)	8 (14.8)	.72
White blood cells >12 ×10^3/μL	49 (26.6)	25 (19.2)	24 (44.4)	<.001*
Serum sodium bicarbonate <22 mmol/L	14 (7.6)	9 (6.9)	5 (9.3)	.59
Systemic inflammatory response syndrome	37 (20.1)	18 (13.9)	19 (35.2)	.001*
Cellulitis/erythema	159 (86.4)	108 (83.1)	51 (94.4)	.06
Abscess	126 (68.5)	80 (61.5)	46 (85.2)	.002*
Septic arthritis	38 (20.6)	30 (23.1)	8 (14.8)	.21
Location of instigating ulcer				
Toes	110 (59.8)	76 (58.5)	34 (63.0)	.57
Proximal forefoot	68 (37.0)	50 (38.5)	18 (33.3)	.51
Midfoot	3 (1.6)	2 (1.5)	1 (1.9)	1.0
Heel	3 (1.6)	2 (1.5)	1 (1.9)	1.0

*$P < .05$.

3.1-7.1 cm^2). Two episodes (1.1%) originated from puncture wounds, and 7 (3.8%) originated from decubitus pressure.

Bone histopathology was obtained in 183 of the 184 episodes (99.5%). Histopathology was consistent with osteomyelitis in 167 (90.8%) of these. Bone cultures were

obtained in 140 episodes (76.1%); these demonstrated no organisms in 6 (4.3%), monomicrobial results in 31 (22.1%), and polymicrobial results in 102 (72.9%). In total, 339 organisms were identified among the 140 episodes in which bone specimens were obtained (average of 2.4 organisms per bone culture) (see Table 3).

Treatment Details and Outcomes

Fifteen episodes (8.1%) were treated with primary antibiotic therapy—all with oral antibiotics alone. The remaining 169 (91.8%) were treated with surgical resection of bone and adjunctive antibiotics. Histopathology at the proximal-most margin of resected bone was positive in 97 patients (53.0%), negative on 58 (32.7%) and not assessed in 28 (15.3%). Culture of the bone margin was positive in 28 (15.3%), negative in 13 (7.1%), and not assessed in 142 (77.6%). Of patients receiving primary surgical therapy, 118 (69.8%) received postoperative antibiotics, including 112 (94.9%) that were treated with oral antibiotics only and 6 (5.0%) that were treated with parenteral antibiotics. The duration of antibiotic treatment was ≤7 days for 30 of these episodes (25.4%), between 8 and 28 days for 55 episodes (46.6%), between 29 and 42 days for 24 (20.3%), and between 42 and 60 days for 9 episodes (7.6%). Management of 14 episodes (7.6%) was deemed palliative (ie, done without intent for cure), including 12 episodes managed with primary surgical therapy and 2 episodes managed with primary antibiotic therapy.

Treatment failure occurred in 53 episodes (28.8%) and complete response in 77 episodes (41.8%), while the remaining 54 (29.3%) were in remission at the time of last follow-up. The median follow-up time was 264 days (range, 4-1290 days). Treatment failure occurred at a median of 60 days from the initiation of treatment. Fifteen of the 53 treatment failures (28.3%) occurred within 30 days, 21 (39.6%) within 6 weeks, 33 (62.3%) within 3 months from the initial treatment. Seventeen (32.1%) occurred between 3 and 12 months from initial treatment, and 3 (5.5%) occurred more than 1 year after (Figure 1). Twenty-one patients (11.4%) underwent major amputation (Figure 2). Only 92 episodes (50.3%) were deemed to have achieved a complete response at the time of most recent follow-up. Median follow-up time was 236 days and ranged from 4 to 1290 days.

Univariate analyses demonstrated some associations. Treatment failure occurred in 24 (23.3%) of those without significant PAD and 30 (37.0%) of those with PAD (P = .04). Treatment failure was somewhat more common among those who had previously undergone revascularization (38.9% vs 25.4%, P = .07). A trend was also seen between a severe foot infection and treatment failure (odds ratio 2.0, P = .09).

Multivariate Models for Treatment Failure and Major Amputation

The presence of *Pseudomonas* and *Escherichia coli* species strongly influence time to treatment failure in the multivariate analysis (P < .001 for both). In addition, severe unaddressed or unassessed PAD, homelessness, history of 60+ pack-years of cigarette use, serum albumin <2.8 g/dL, a history of insulin therapy, osteomyelitis located in the first toe or metatarsal were all significantly associated with time to treatment failure (Table 4). Bone margin results alone did not reach significance, but a positive margin that was not treated with at least 7 days of isolate specific antibiotic therapy was significantly associated with treatment failure. The presence of methicillin-resistant *Staphylococcus aureus* (MRSA) or methicillin-sensitive *Staphylococcus aureus* (MSSA) did not affect treatment failure (P = .55 and P = .42, respectively). The presence of 2 or more SIRS criteria at presentation also did not affect treatment failure (P = .57). Using a point system assigned to the various risk factors (Table 4), failure was seen among 6 of 60 episodes (8.6%) with 1 or fewer points, 8 of 43 episodes (18.6%) with 2 points, and 25 of 44 (56.8%) of those with3 or more points.

Major amputation was independently associated with palliative management, severe or unaddressed PAD, fungal isolates on bone culture, homelessness, end-stage renal disease (ESRD), first and fifth toe or metatarsal locations, and elevated hemoglobin A1c (all Ps <.05; see Table 5). Unplanned further resection of bone, number of SIRS criteria at presentation, and margin pathology were not associated with amputation (P = .87, P = .20, and P = .79, respectively). Using a point system assigned to various risk factors (Table 5), major amputation occurred among 5 of 134 episodes (3.7%) with ≤1 points, 6 of 28 episodes (21.4%) of those with 2 or 3 points, and 10 of 22 episodes (45.5%) of those with 4 or more points.

Discussion

Foot osteomyelitis is a common problem, and more high-quality data are needed to improve the outcomes of management. Insights and generalizability from previously published literature on foot osteomyelitis may be somewhat limited by several characteristics. Most are small single-center case series that use nonstandardized case definitions of "osteomyelitis" (often based on plain films and probe-to-bone test rather than bone pathology or microbiology), and many fail to report the extent or severity of any associated soft tissue infection or systemic inflammatory response. Patients without diabetes have generally been excluded, and the severity of arterial impairment is rarely quantified.

The current study attempts to address many of these limitations. First, this is the largest series to date focused

Table 3. Microbial Isolates (N = 339) Identified From Bone Specimens in 140 Episodes of Definite or Probable Foot Osteomyelitis.

Group/Family/Species	Group/Family, Frequency (%)	Species, Frequency (%)
Gram positive aerobic bacteria	208 (61.4)	
Staphylococcaceae family	95 (28.0)	
Staphylococcus aureus, methicillin-resistant		32 (9.4)
Staphylococcus aureus, methicillin-sensitive		30 (8.8)
Staphylococcus epidermidis		20 (5.9)
Staphylococcus simulans, *anginosus, haemolyticus, lugdenensis*		13 (3.8)
α- and β-hemolytic *Streptococcaceae* family	36 (10.6)	
group B *Streptococci*		18 (5.3)
α-hemolytic *Streptococci*		13 (3.8)
Streptococcus group F, group G, *intermedius, mitis*		5 (1.5)
γ-hemolytic *Streptococcaceae* family	37 (10.9)	
Enterococcus faecalis		19 (5.6)
Enterococcus avium, faecium		2 (0.6)
Enterococcus species not otherwise specified		16 (4.7)
Corynebacterium species	30 (8.8)	
Additional gram positive species	13 (3.8)	
Brevibacillus spp		1 (0.3)
Other gram-positive organisms not otherwise specified		12 (3.5)
Gram-negative aerobic bacteria	77 (22.7)	
Enterobacteriaceae family	56 (16.5)	
Proteus mirabilis		16 (4.7)
Escherichia coli		15 (4.4)
Morganella morganii		5 (1.5)
Citrobacter freundii		4 (1.1)
Citrobacter diversus, kerosi, and *youngae*		4 (1.1)
Enterobacter aerogenes and *clocae* complex		3 (0.9)
Providencia rettgeri and *stuartii*		3 (0.9)
Klebsiella pneumonia		2 (0.6)
Kluyvera species		1 (0.3)
Serratia marcescens		1 (0.3)
Other lactose-negative gram-negative rods		2 (0.6)
Pseudomonadaceae/*Moraxellaceae* families	11 (3.2)	
Pseudomonas aeruginosa		8 (2.4)
Pseudomonas putida and other spp.		2 (0.6)
Acinetobacter baumanii		1 (0.3)
Other families	10 (2.9)	
Alcaligenes fecalis		4 (1.1)
Stenotrophomonas maltophilia		4 (1.1)
Haemophilus parainfluenzae		1 (0.3)
Achromobacter spp		1 (0.3)
Anaerobic bacteria	44 (13.0)	
Bacteroides fragilis		9 (2.7)
Bacteroides bivius, caccae, distasonis ovatus, tectum, thetaiotamicron uniformis, vulgatus		12 (3.5)
Peptostreptococcus species		7 (2.1)
Prevotella spp (including *bivia, melaninogenica, loeschii*)		8 (2.4)
Actinomyces spp		2 (0.6)
Lactobacillus, Veillonella, Fusibacterium, Propionibacterium spp		4 (1.1)
Gram-negative anaerobic rods		2 (0.6)
Fungi	7 (2.1)	
Candida parapsilosis		4 (1.2)
Candida glabrata		2 (0.6)
Candida guilliermondii		1 (0.3)

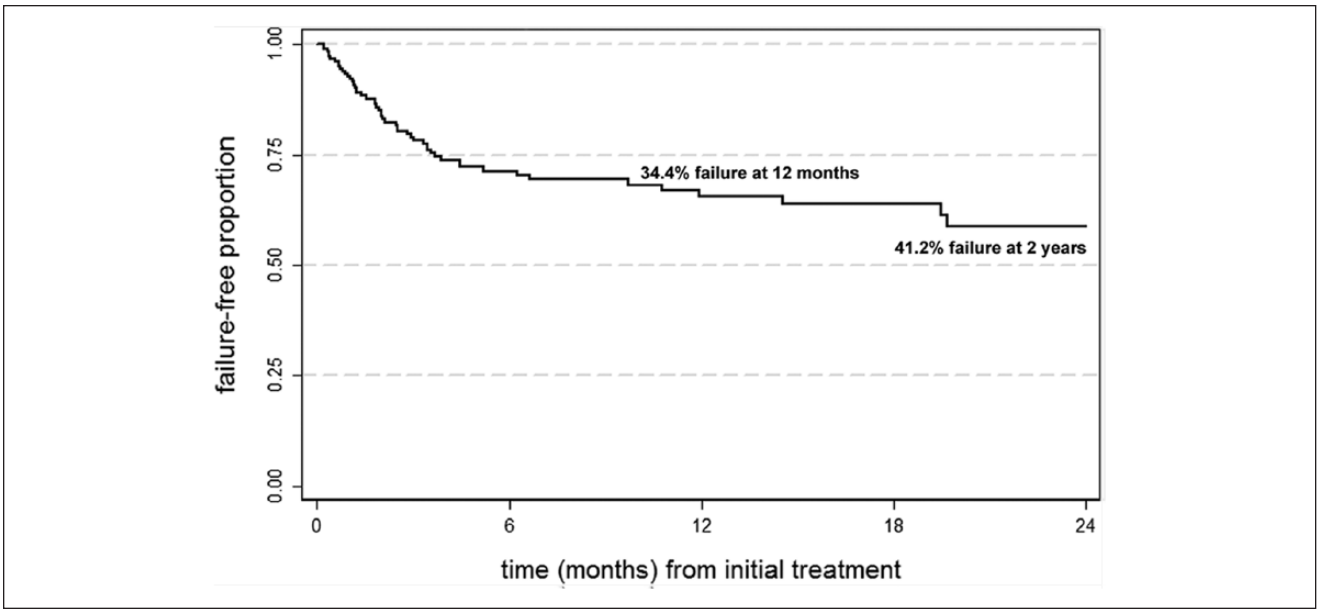

Figure 1. Kaplan-Meier analysis of time to treatment failure (unplanned resection of bone *or* major amputation; n = 184).

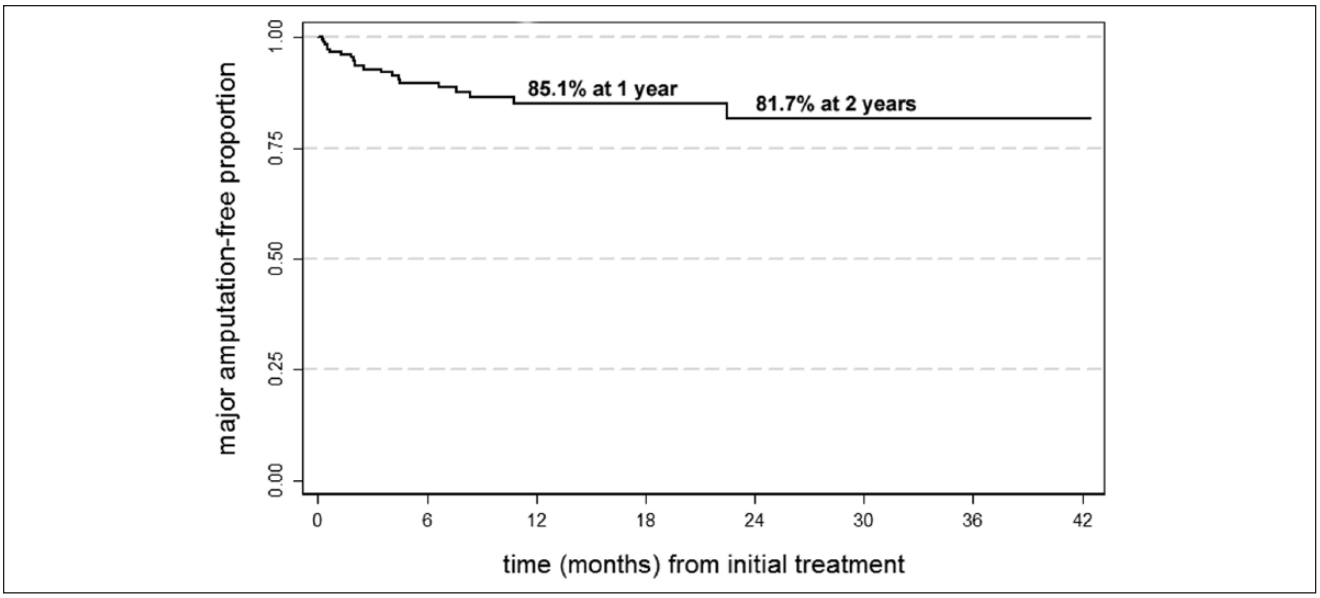

Figure 2. Kaplan-Meier analysis of time to major amputation (n = 184).

exclusively on those reaching the "probable" or "definite" consensus case definition of foot osteomyelitis.[15] Those without diabetes and those with PAD were included because there has been no firm basis to date to assume the treatment response of these patients would be different. We used a strict definition of outcomes which were evaluated with time-to-event analyses. Finally, we assessed a robust number of detailed variables from a variety of domains.

Two notable observations can be made from the results of the current study. First, a wide range of factors from multiple domains influence foot osteomyelitis treatment failure. We note that these factors are more than what is typically addressed by any one particular medical or surgical specialty, and it is perhaps for these reasons that interdisciplinary foot care teams have consistently demonstrated decreases in leg amputation rates.[16-19] Among the most influential of these factors was the presence of two particular organisms, *E coli* and *Pseudomonas aeruginosa*, were associated with increased treatment failure rates, a finding consistent with another study that examined diabetic foot

Table 4. Multivariate Model for Treatment Failure With Risk Stratification Scoring System.

Variable	Hazard Ratio	95% CI	*P*
Severe additional risk (+4 points)			
Pseudomonas aeruginosa without adequate antibiotic therapy for >7 days	21.3	5.2-87.2	<.001
Pseudomonas aeruginosa with adequate antibiotic therapy for 7+ days	12.2	1.5-100	.02
Moderate additional risk (+3 points)			
Homeless	9.5	3.3-27.3	<.001
Severe or unaddressed peripheral artery disease	8.2	3.9-17.6	<.001
Escherichia coli	7.9	3.1-20.6	<.001
Mild additional risk (+1 point)			
Insulin therapy	3.9	1.8-8.1	<.001
Serum albumin <2.8 g/dL	3.7	2.0-7.0	<.001
60+ pack-year history of cigarette smoking	3.6	1.5-9.1	.006
First toe or metatarsal location vs all other locations	3.1	1.7-5.7	<.001
Positive margin and isolate-specific antibiotic therapy <7 days[a]	2.3	1.1-4.6	.03
Mild decreased risk (−1 point)			
Delayed primary (staged) wound closure vs primary closure or secondary	0.4	0.2-0.8	.01

[a]Excluding episodes with *Pseudomonas aeruginosa*.

Table 5. Multivariate Model for Major Amputation With Risk Stratification Scoring System.

Variable	Hazard Ratio	95% CI	*P*
Severe additional risk (+3 points)			
Palliative management	13.5	3.1-58.2	<0.001
Severe peripheral artery disease	14.0	4.5-43.3	<0.001
Moderate additional risk (+2 points)			
Fungus in bone culture	11.3	2.1-61.3	0.005
Homelessness	11.1	2.5-50.5	0.002
End-stage renal disease	9.2	2.0-42.2	0.004
Mild additional risk (+1 points)			
Fifth toe or metatarsal location	6.7	1.9-23.2	0.003
First toe or metatarsal location	4.9	1.4-17.4	0.013
Additional not included in scoring system			
Hemoglobin A1c	1.3	1.1-1.7	0.008

soft tissue and bone infections.[2] *E coli* and *P aeruginosa* were found in 10.0% and 7.8% of episodes in which bone microbiology was performed, respectively—rates very comparable to other North American and European series.[8,11,13] A significant benefit was seen for antibiotic therapy that was both isolate-directed and continued for at least 7 days only when the bone margin specimen was positive on either histology or microbiology. Although the data from this study could not demonstrate a benefit for longer duration of antibiotic therapy that have been recommended, they do at least support the utility of bone margin testing.

Homelessness and malnutrition are 2 additional factors that clinicians may be able to improve outcomes. The association between treatment failure and a low serum albumin at presentation (but not other measures of inflammation/infection such as presence of SIRS or number of SIRS criteria) suggests a negative impact of malnutrition.

Most patients (62% overall) included in this study received insulin therapy for diabetes, and insulin therapy was associated with treatment failure. Consistent with findings from a recent Turkish study,[2] this more likely to represent a marker for patients with a longer duration of the disease than it is to represent a direct causal relationship. A history of more than 60 pack-years of smoking was also significantly associated with treatment failure, a finding that may not be surprising given its known negative impact on wound healing.

Delayed primary closure—that is, staged reapproximation of soft tissue with or without epithelium over remaining bone—was associated with significantly lower rates of treatment failure when compared to either primary closure or healing by secondary intent. Other groups have demonstrated that primary closure or delayed primary closure is not only reasonable but may be preferable to healing via

secondary intention.[20-22] With multiple studies demonstrating consistent findings, we suggest surgeons consider staged operations with delayed primary closure whenever feasible and look forward to further analyses on this aspect of management.

The multivariate analyses fail to corroborate many commonly held beliefs about foot osteomyelitis. Like other authors,[23] we did not find MRSA to be associated with higher rates of treatment failure. The extent/severity of any associated soft tissue infection had no significant association with treatment failure rates. Only very severe PAD (toe pressures <30 mm Hg or ankle pressures <50 mm Hg), PAD that was incompletely assessed, or those with an occluded bypass graft had higher rates of treatment failure, and no differences were seen between those that have undergone a successful revascularization and those without significant PAD. Many other patient-related factors that often beget pessimism on the part of the clinician toward long-term outcomes—including hemoglobin A1c, current tobacco use, and obesity—also did not have a significant association with treatment failure. This is not to say that managing these variables is not important to the overall health of the patient or that these variables could not have a small or indirect influence on outcomes; rather, we suggest that the focus of managing foot osteomyelitis should instead be on the other modifiable factors identified herein that appear to have a more influential association with treatment outcomes.

The second important observation is that unanticipated resection of bone does not appear to be associated with high rates of leg amputation. In our cohort, unanticipated resection of additional bone occurred in only 6 of the 21 episodes (28.6%) that ultimately underwent leg amputation. Unanticipated resection of additional bone was not significant associated with leg amputation after accounting for other factors in a multivariate model. After excluding episodes of foot osteomyelitis occurring in patients with severe or unaddressed PAD, homeless patients, those with ESRD, and those treated in a palliative fashion are excluded, leg amputation occurred in only 7 of 140 episodes (5.0%), comparable to other series that also report leg amputation rates.[7,10,12] At the very least, unanticipated resection of bone may be useful as surrogate for increased treatment costs. Findings from this study suggest, however, that it may not be appropriate to consider the need for unanticipated resection of additional bone as precursor to limb loss.

This study does have limitations. This is a retrospective observational study, so we cannot infer that any of the variables identified have a direct causal relationship with foot osteomyelitis outcomes. We did not collect data on type of diabetes mellitus (type 1 or type 2). The small number of episodes treated with primary antibiotic therapy also limits any meaningful attempts to identify factors which could be used to guide a choice between surgical or medical therapy for any given patient. Specimens for microbiology were only obtained in approximately 50% of episodes, and no consistent algorithm was used to determine for antibiotic duration. The risk scoring systems proposed should be validated at other centers before being used to identify patients at high risk for treatment failure or major amputation. Finally, the inclusion of major (above-ankle) amputation in the definition of treatment failure used in this study may be criticized. Clinicians at our hospital are aggressive in offering limb-preserving management strategies but also offer minor amputation and palliative wound care as an alternative to major amputations.[24] Nonetheless, provider and patient preferences may influence decision to proceed with major amputation as the treatment of foot osteomyelitis. Until a more objective endpoint for evaluating the outcomes of foot osteomyelitis is identified, major amputation may continue to serve as an outcome measure with limitations.

In conclusion, treatment failure is common among those with foot osteomyelitis and frequently within and up to one year of initiating management. Foot osteomyelitis treatment outcomes may be improved through a focus on addressing severe PAD, normalizing serum albumin, obtaining bone cultures to direct isolate-specific antibiotic therapy for >7 days, and performing delayed primary closure (ie, staged operations) when feasible. Unanticipated resection of additional bone does not have a clear causal relationship with leg amputation risk. Further studies should further investigate alternative management approaches for foot osteomyelitis associated the risk factors identified herein.

Appendix

Definition of Clinical Variables

Components of various classification systems were used to were used to categorize certain lesion and patient characteristics. The infection grading from the "Perfusion, Extent/size, Depth/tissue loss, Infection, and Sensation" (PEDIS) classification system[16] was used to quantify foot infection, and the modified terminology proposed in the Infectious Disease Society of America guidelines[14] was utilized. As osteomyelitis defines a grade 3 infection in the PEDIS classification system, the presence of 2 or more signs of a systemic inflammatory response syndrome (SIRS, including temperature >100.5°F, heart rate >100 beats/min, respiratory rate >22 breaths/min, white blood cell count >12 000/μL, neutrophil proportion >80%, or serum bicarbonate level <22 mEq/L) distinguished between "moderate" and "severe" foot infections. The Society of Vascular Surgery's "Wound, Ischemia, Foot Infection" threatened limb classification system[17] (roughly corresponding with the perfusion assessment in the PEDIS classification) was used to quantify severity of PAD. The area of the instigating ulcer was estimated using the elliptical method.[18] Surgical

wound management was categorized as either primary closure (closed at the time of the index operation), secondary intent (no attempt at surgical closure of skin or soft tissue), or delayed primary closure (ie, staged: initial operation to debride necrotic tissue and drain infection; planned second operation to obtain a grossly-negative margin and obtain closure of soft tissue and possibly epithelial edges).

Acknowledgments

The research reported here was supported in part by the U.S. Department of Veterans Affairs, Veterans Health Administration, Health Services Research and Development Service, at the Center for Innovations in Quality, Effectiveness and Safety (CIN 13-413), Michael E. DeBakey VA Medical Center, Houston, TX."

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.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: NRB has received $25,000 from the Michael E. DeBakey Veterans Affairs Medical Center, a federal institution, for the study of foot osteomyelitis.

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