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ORIGINAL ARTICLE

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Multidrug resistant organism predicts ulcer recurrence following surgical management of diabetic foot osteomyelitis

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Abstract

Diabetic foot ulcers commonly precede diabetic foot osteomyelitis (DFO) and once the latter occurs, surgical management is often performed. The presence of osteomyelitis is an independent risk factor for the development of re-ulceration. We investigated the relationship between causative organisms in osteomyelitis and 1-year diabetic foot outcomes (re-ulceration, amputation, and death) following surgical management in an observational cohort of 223 patients. Univariate and multivariate analyses were performed for available demographic, clinical, and laboratory data. In addition, random forest plots were used to identify microbiologic predictors of 1-year outcomes. Patients with osteomyelitis managed surgically were younger and exhibited more painful peripheral neuropathy than outpatients with diabetes alone (both $P < .0001$). Osteomyelitis proximal margin cultures were diverse, at times polymicrobial, and included multidrug-resistant organisms in 13.9% of the cohort. In patients who underwent surgery, 44.5% experienced a re-ulceration on the same foot within 12 months of surgery. The presence of multidrug-resistant organisms on proximal bone culture was found to be a significant predictor of diabetic foot ulcer recurrence in univariate modelling ($P < .001$) and importance rankings. This is the first study to use prediction modelling to identify a relationship between multidrug-resistant organisms and diabetic foot ulcer recurrence following DFO.

KEYWORDS

amputation, diabetic foot osteomyelitis, diabetic foot ulcer, multidrug-resistant organisms, ulcer recurrence

1 | INTRODUCTION

Diabetic foot osteomyelitis (DFO) remains a difficult clinical and surgical complication of diabetic foot ulcers (DFU). Approximately half of all DFU become infected, and 20% result in amputation.[1] Multidrug-resistant organisms (MDROs) are often present in DFU: about one-third of patients with a history of the previous hospitalisation for the same wound and 25% of patients with osteomyelitis had MDRO-positive specimens.[2] Recent evidence suggests this is a growing concern in urban areas where the reported rate of MDROs in DFU reaches 56%, and approximately 30% of cultures are resistant to recommended treatment[3]. Evidence suggests that MDROs in DFU lead to worse clinical outcomes, including poor ulcer healing, increased treatment failure, increased readmission rates, and increased mortality.[2,4-7]

DFU recurrence is common following healing and is reported to be approximately 40% within 1-year of a

healing event with wound recurrence demonstrating a near logarithmic relationship to time.[8] Osteomyelitis is an independent risk factor for DFU recurrence.[8] However, few studies have evaluated the relationship between causative organisms in osteomyelitis and recurrent DFU. Therefore, we sought to investigate the effect of MDROs on outcomes in a cohort of patients who underwent primary surgical intervention for the management of DFO.

Key Messages

- the paper examines the relationship between proximal margin culture organism and outcomes following surgery for diabetic foot osteomyelitis (DFO)
- we analysed a cohort of 223 patients who underwent surgery to manage DFO using univariate, multivariate, and random forests to predict outcomes
- recurrence of a diabetic foot ulcer is predicted by the presence of multidrug-resistant organism on proximal bone cultures

2 | MATERIALS AND METHODS

2.1 | Patients and setting

We conducted an observational study from October 2016 to October 2018 of adult patients with type 1 or type 2 diabetes mellitus (DM) who underwent ablative foot surgery by the Michigan Medicine Podiatry service for DFO. A patient database was constructed to collect admission data on consecutive patients. We excluded individuals with osteomyelitis who refused surgical intervention and those who did not have DM. This study was approved by the University of Michigan Medical Centre Institutional Review Board.

Pre-operative diagnosis of DFO was established by clinical signs/symptoms of infection (erythema, warmth, purulent drainage, and malodor), compatible laboratory values, and imaging tests following previously published guidelines.[9-11] Ablative surgery was defined as partial or total removal of ray(s) or toe(s), or a combination thereof, distal to the tarsometatarsal (LisFranc) joint,[12] and included transmetatarsal amputations. In a standardised manner, histopathology results were recorded at the surgical margin from the resected bone (ie, dirty margin) in a binary fashion as either "viable" or "non-viable" to denote the presence of necrotic bone. Next, the margin proximal to the amputation site (ie, clean margin) was copiously lavaged with sterile normal saline at the discretion of the surgeon. Then, after exchanging gloves, the proximal bone was transected using power instrumentation and split for microbiology following the previously described standard of care.[12,13] The samples were sent for microbiologic analysis, including aerobic, anaerobic, fungal, and acid-fast bacilli cultures. Microorganism growth was recorded as a binary result. Organism identification and susceptibility were also noted in all positive cultures.

For this study, the following were defined as MDRO: methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococci* (VRE), *Enterobacteriaceae* resistant to third-generation cephalosporins and/or carbapenems (*Enterobacteriacae*-R), *Acinetobacter baumannii*, and all susceptibility phenotypes of *Pseudomonas aeruginosa*, a definition used by previous studies.[3]

2.2 | Study variables

Demographics and comorbidities of patients with DFO who underwent ablative surgery were obtained from the medical record, then compared with characteristics of a group of diabetic patients without DFU or DFO during the same period. Surgical patients were followed for 1 year after surgery, and primary outcomes of DFU recurrence (defined as healing of the surgical site, followed by DFU on the operative foot), reamputation, and death at 3, 6, and 12 months were obtained.

2.3 | Statistics

Univariate and multivariate analyses of the primary outcome were performed. Association between MDROs on bone culture and clinical outcomes were evaluated using Student's *t*-testing for continuous variables and χ^2 tests for categorical variables. Using classification and regression tree (CART) permutations, a random forest plot was used to identify microbiologic predictors of 1-year outcomes. Data were analysed using SAS software for Windows, version 9.4, and R packages "rpart" and "randomForest". All *P*-values are two-sided, and findings were considered statistically significant at $P < .05$.

3 | RESULTS

3.1 | Demographics

A total of 223 patients with DFO who subsequently underwent ablative surgery were included in the study. When compared with a historic control group of patients with DM but no history of DFU or DFO (Table 1), patients who

developed DFO and underwent surgery were younger (57.2 vs 65.7 years, $P < .001$) and more frequently reported painful paraesthesia associated with diabetic peripheral neuropathy (DPN, 95% vs 73%; $P < .001$). Sex, race, body mass index, chronic kidney disease, coronary artery disease, diabetic retinopathy, and duration of DM did not reach statistical significance. In patients with DFO, neuropathic and neuroischaemic aetiologies accounted for 93.7% (79.4% and 14.3%, respectively) of events. 39.5% (n = 88) had a previous history of partial foot amputation. DFO occurred on the right foot 54.3% and on the left foot 44.4%.

3.2 | Histopathology and microbiology

Histopathology of the resected bone (dirty margin) revealed viable margins in 71.3% (n = 159) samples. Proximal (clean margin) bone cultures were positive for any microbiologic growth in 79.2% (n = 216) of patients; 39% (n = 87) of cultures were polymicrobial (Table 2**)**. The most commonly cultured organisms included methicillin-sensitive *S. aureus* (MSSA, n = 69; 30.9%), coagulase-negative *Staphylococci* (CoNS, n = 36; 16.1%), *Streptococcus agalactiae* (n = 29; 13%), *Enterococcus faecalis* (n = 30, 13.5%), and *Enterococcus faecium* (n = 16; 7.2%). MDROs were found in 13.9% of cultures (n = 31). The diversity of cultured organisms was high with 43 cultures (19.3%) positive for an organism other than those listed in Table 2.

3.3 | Outcomes

Of the 223 patients, 191 (85.7%) had defined primary outcomes at 1 year (Table 3). There were 32 patients (14.3%) who had incomplete or missing data with respect to the primary outcomes and were excluded from this analysis.

Of the 191 patients, 36.6% (n = 70), 42.9% (n = 82), and 44.5% (n = 85) developed recurrent DFU by 3, 6, and 12 months, respectively. Re-amputation rates were 5.4% (n = 12), 15.8% (n = 35), 18.5% (n = 41) at the same time points. Thirteen patients (5.8%) died within the follow-up time; no death was directly related to DFU. One hundred and thirty-eight patients (72.3%) only had recurrent DFU, but not amputation

TABLE 2 Microorganism in the study population

Microorganism	Count (%)
Any growth	171/216 (79.2%)
Polymicrobial growth	87/223 (39%)
Non-MDRO	
MSSA	69/223 (30.9%)
CoNS	36/223 (16.1%)
E. faecalis	30/223 (13.5%)
E. faecium	16/223 (7.2%)
S. agalactiae	29/223 (13%)
Achromobacter sp.	2/223 (0.9%)
Citrobacter sp.*	3/223 (1.3%)
*E. coli**	9/223 (4%)
Klebsiella sp.*	6/223 (2.7%)
Serratia sp.	3/223 (1.3%)
Other sp. (counts of 1)	43/223 (19.3%)
MDRO	31/223 (13.9%)

Abbreviation: MDRO, multidrug-resistant organism.

TABLE 1 Diabetic patient characteristics within podiatry (n = 459)

	Diabetic without DFU (n = 236)	Diabetic with DFO (n = 223)	*P*-value
Sex—n (% male)	164 (69.5)	176 (78.9)	.08
Race—n (% white)	204 (86.4)	194 (87)	.06
BMI ± SD (kg/m^2)	30.7 ± 9.9	33.3 ± 5.1	.54
Age ± SD (y)	65.7 ± 14.8	57.3 ± 10.1	**<.0001**
CKD—n (%)	64 (27)	26 (22)	.29
CAD—n (%)	85 (36)	36 (31)	.34
DPN—n (%)	172 (73)	112 (95)	**<.0001**
Retinopathy n (%)	28 (11.9)	33 (14.7)	.39
Duration of DM ± SD (y)	14.7 ± 13.4	13.3 ± 8.8	.27

Note: Patients with diabetic foot osteomyelitis were younger and experienced more painful peripheral neuropathy as compared with a historical comparator group without either diabetic foot ulcer or osteomyelitis. Bold *p*-values are with statistical significance.

Abbreviations: BMI, body mass index; DFO, diabetic foot osteomyelitis; DFU, diabetic foot ulcers; DM, diabetes mellitus; DPN, diabetic peripheral neuropathy.

TABLE 3 Summary of outcomes

Outcome	Count (%)
Recurrent diabetic foot ulcers (DFU) by 3 mo	70/191 (36.6%)
Ever ulcer by 6 mo	82/191 (42.9%)
Ever ulcer by 12 mo	85/191 (44.5%)
Re-amputation by 3 mo	12/222 (5.4%)
Ever amputation by 6 mo	35/222 (15.8%)
Ever amputation by 12 mo	41/222 (18.5%)
Death or recurrent DFU or re-amputation by 12 mo	97/191 (50.8%)
Death or amputation by 12 mo	53 / 222 (23.9%)
Death by 12 mo	13/223 (5.8%)
Ordered combined outcome	
No ulcer, amputation, or death	94/191 (49.2%)
Ulcer but no amputation no death by 12 mo	44/191 (23%)
Amputation but no death by 12 mo	40/191 (20.9%)

or death. During the follow-up time, 94 (49.2%) patients did not experience recurrent DFU, amputation, or death.

3.4 | Risk factors for poor outcome by 1 year

In the univariate analyses, histopathology results were not significantly associated with outcome, but the presence of an MDRO was significantly associated with the composite outcome of recurrent DFU, amputation, or death at 1 year ($P < .001$). Specifically, MRSA ($P < .035$) was significantly associated with re-ulceration while VRE, *P. aeruginosa*, and *A. baumanii* were not. No resistant *Enterobacteriaceae* were identified in this cohort (Table 4).

For the composite outcome of re-amputation or death at 1 year, the presence of any organism growth on proximal margins was associated with an increased risk ($P = .01$). Specifically, *P. aeruginosa* ($P < .01$), *Escherichia coli* ($P < .01$), *E. faecium* ($P < .05$), and *E. faecalis* ($P < .05$) were associated with amputation or death at 12 months. No single microorganism or class (polymicrobial, sensitive, or resistant) was a predictor of death in univariate modelling.

TABLE 4 Ulcer, amputation, or death by 12 months

Microorganism	No	Yes	χ^2 *P*-value	Fisher's exact *P*-value
MSSA	35/94 (37.2%)	29/97 (29.9%)	.28	
CoNS	21/94 (22.3%)	13/97 (13.4%)	.11	
E. faecalis	10/94 (10.6%)	17/97 (17.5%)	.17	
E. faecium	5/94 (5.3%)	11/97 (11.3%)	.13	
S. agalactiae	10/94 (10.6%)	14/97 (14.4%)	.43	
Achromobacter sp.	0/94f (0%)	2/97 (2.1%)		.50
Citrobacter sp.	2/94 (2.1%)	1/97 (1%)		.62
E. coli	1/94 (1.1%)	7/97 (7.2%)		.065
Klebsiella sp.	2/94 (2.1%)	1/97 (1%)		.62
Serratia sp.	0/94 (0%)	3/97 (3.1%)		.25
Other sp. (counts no less than 1)	15/94 (16%)	18/97 (18.6%)		.70
MDRO	3/94 (3.2%)	20/97 (20.6%)		**.00022**
MRSA	1/94 (1.1%)	8/97 (8.2%)		**.035**
VRE	0/94 (0%)	1/97 (1%)		1.00
Pseudomonas aeruginosa	3/94 (3.2%)	10/97 (10.3%)		.082
Acinetobacter baumanii	1/94 (1.1%)	2/97 (2.1%)		1.00
Microbiologic growth	70/92 (76.1%)	78/92 (84.8%)	.14	
Polymicrobial culture	31/94 (33%)	43/97 (44.3%)	.11	

Abbreviations: MDRO, multidrug-resistant organism; MRSA, methicillin-sensitive *S. aureus*; VRE, vancomycin-resistant *Enterococci*. Bold *p*-values are with statistical significance.

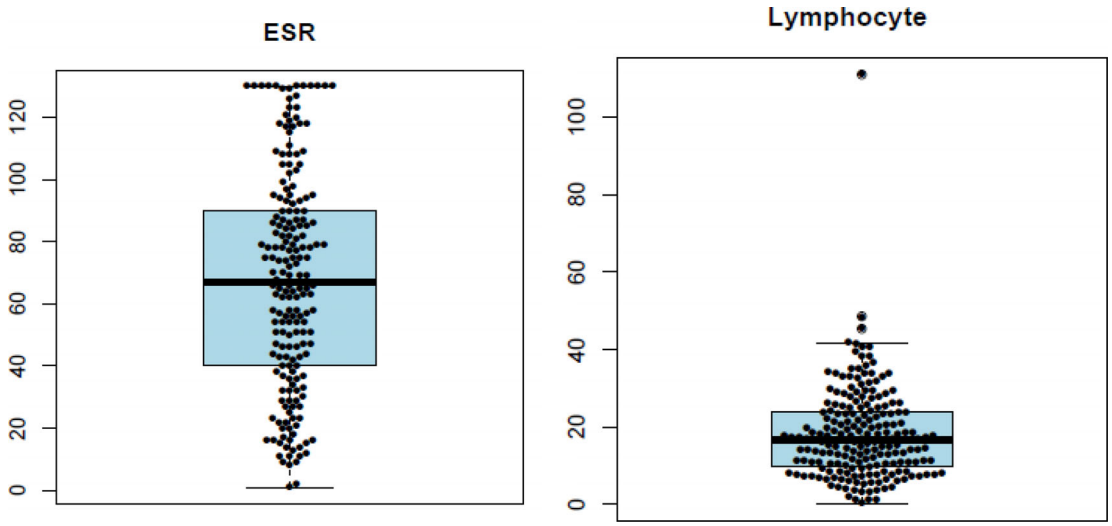

FIGURE 1 Boxplots of laboratory values in DFO cohort. Boxplots for western sedimentation rate (ESR) and lymphocyte count are provided below. The range of values for patients with DFO undergoing surgery is wide. Lymphocyte count has similar findings. DFO, diabetic foot osteomyelitis

In a multivariate analysis of laboratory values in patients with recurrent DFU, Westergren sedimentation rate (ESR, Log[OR] 0.00943, $P = .0479$), high immature granulocyte count (0.7943, $P = .0078$), and low lymphocyte counts (−0.0369, $P = .0225$) were found to be significant (Figure 1). Statistical testing did not reveal a deviation from non-linearity for these identified risk factors.

Both CART analysis and a random forest analysis for predicting DFU recurrence by 12-months using organisms isolated from proximal bone culture were carried out to explore potential predictors for DFU recurrence. Importance ranking based on a mean decrease in Gini Index in the random forest model is shown in Figure 2. Results from both analyses suggest the presence of MDROs on proximal bone culture contributed most significantly to DFU recurrence.

4 | DISCUSSION

Recent public health evidence suggests lower extremity amputations are on the rise after nearly two decades of decline[14] in the United States. Our cohort did not differ significantly in terms of end-stage diabetes complications (CKD and retinopathy), nor the longevity of disease status, but were younger ($P < .0001$) and had more severe painful DPN ($P < .0001$) compared with our historic comparison group. The vast majority of our patients developed osteomyelitis from contiguous chronic neuropathic or neuroischaemic foot ulcers (93.7%), which is consistent with the literature.[15]

DFO microbial diversity was broad, and proximal bone cultures were polymicrobial in 39% of patients.[16] The organisms most commonly cultured were reflective of soft tissue infections and included MSSA, *S. agalactiae*, *E. faecalis*, *E. faecium*, and CoNS.[1,17-21] Our results were in line with the previously reported literature for conventional culture techniques.[17,19,20,22]

In addition, 19.3% of cultured organisms were different from all other cultures. These varied organisms, however, were not predictive of negative outcomes, including re-ulceration, amputation, or death. They also did not demonstrate significance in random forest modelling. However, their relationship to outcome is not defined by the parameters of this study, as the sample size is too small. Further investigation is needed to understand their role in the DFO microbiome using molecular techniques, such as 16 seconds rRNA and qPCR.

The overall rate of MDROs in DFO patients was 13.9%, which is comparable to some centres and less than others.[3] Consistent with published data, MRSA was the most common MDRO.[23] Patients with MDRO-DFO were more likely to have a negative outcome, including recurrent DFU, re-amputation, or death by 1 year. The MDRO, which reached statistical significance as a risk factor for DFU recurrence within the 1-year follow-up was MRSA, present in 5.8% (n = 13). Through the use of advanced prediction modelling using random forest plots, MDROs significantly predicted in DFU recurrence, something not previously described in the literature.

It is not clear at this time why these patients had higher rates of re-ulceration, and whether the presence of an MDRO changed the course of disease for a patient. One explanation may be the reduction in skin barrier function due to causative organisms. At baseline, diabetic pedal skin has reduced diversity compared with control

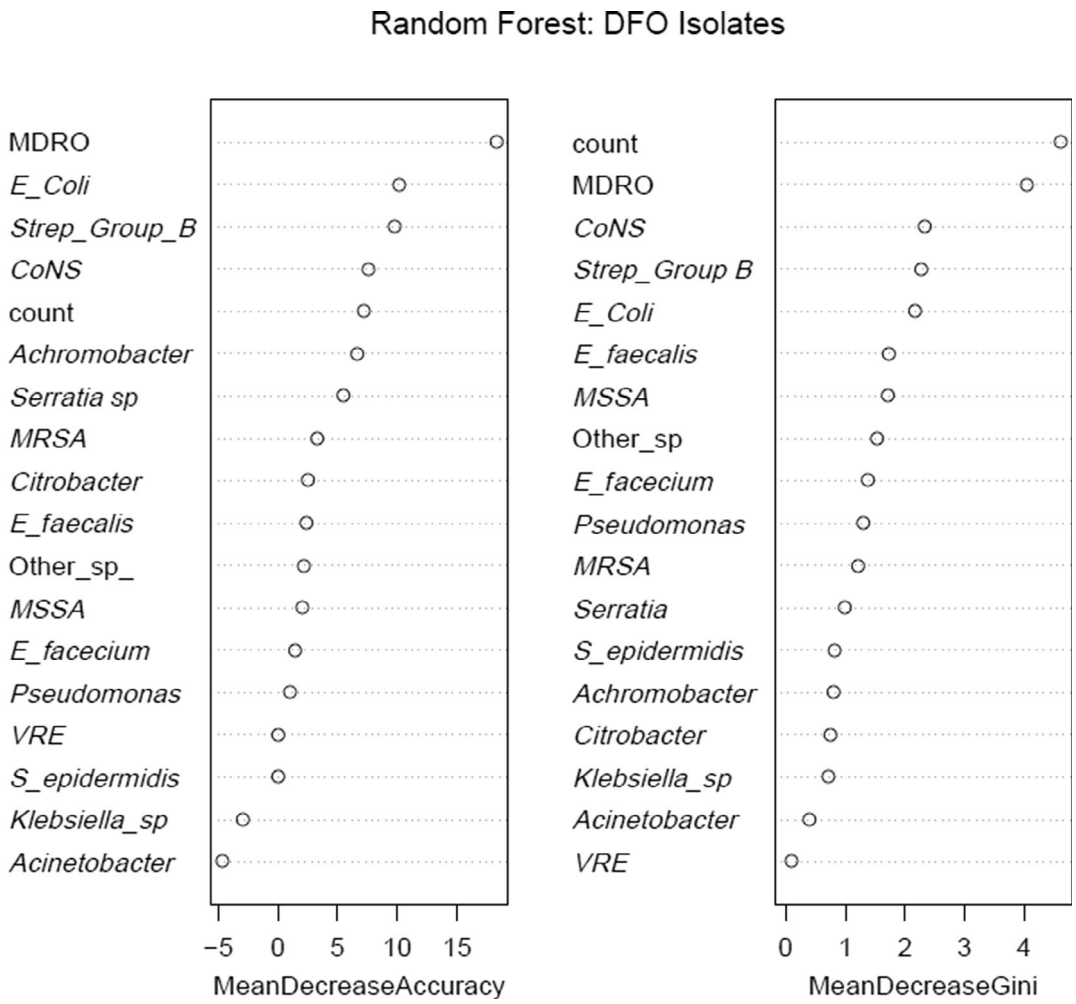

FIGURE 2 Random forest for DFO isolates. The figure indicates that removal of MDRO-DFO presence from classification and regression tree (CART) analysis leads to misclassification for prediction of the variable of interest. For our cohort, the presence of MDRO demonstrated the most significant contribution to mean decrease accuracy and a mean decrease in Gini, and demonstrates MDRO presence best predicts DFU recurrence. DFO, diabetic foot osteomyelitis; MDRO, multidrug-resistant organism

skin,[24] and antibiotic use destabilises the pedal microbiome.[25] More specifically, exposure to *S. aureus* and *P. aeruginosa* biofilms diminishes the migration ability of cells and hinder multi-lineage differentiation of mesenchymal stromal cells.[26] MRSA and *P. aeruginosa* were found to be related to poor outcomes in our cohort. Cumulatively, the prolonged exposure of pedal skin to resistant organisms necessitates prolonged antibiotic therapy and may lead to decreased tissue (skin) strength and place patients at risk for additional breakdown.

Another explanation may be that patients are self-contaminating their wounds as unknowing carriers of MDROs on their hands.[27] As a result, treatment for the MDRO with the appropriate antibiotic was not identified earlier, initiated late, or was more difficult to tolerate, leading to the poor outcome. In addition, the presence of MDROs on initial culture also suggests more frequent exposure to the health care system, and these patients may be more medically frail at baseline and, therefore, more likely to have recurrent DFU.

The recurrent rate of DFU within 1-year following amputation was 44.5% and is similar to reported literature for DFU recurrence of approximately 40% at 1-year.[8] As this cohort was comprised exclusively of DFO patients, this may account for the modestly elevated recurrence rates.

Multivariate testing revealed several laboratory factors associated with DFU recurrence: ESR, lymphocyte count, and immature granulocyte count. While statistical significance in multivariate analysis was achieved, the strength of the relationship was weak. More traditional factors predictive of healing, including albumin, creatinine, C-reactive protein, haemoglobin A1c, and white blood cell count did not reach significance. Our evidence suggests laboratory testing is not predictive of long-term outcomes in this patient cohort.

This study has limitations. First, this was an observational study and performed at a single centre. Antibiotics were often administered prior to obtaining bone cultures intraoperatively, although a recent meta-analysis suggests this does not significantly affect culture yields when one excludes vertebral osteomyelitis.[28] Second, our study did not have an active control group. Third, we had incomplete outcome data in 32 patients, which was attributable to differing documentation strategies.

In conclusion, MDRO-DFO is related to higher rates of recurrent DFU at 1 year in a large observational cohort with strong longitudinal follow-up. Our findings strongly support the need for more aggressive DFO management in individuals who have MDRO-DFO to avoid these events. Further work is needed to more rapidly identify MDR infection in patients with DFO in order to potentially reduce negative outcomes.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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