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Title: Multi-Drug Resistant Organism Predicts Ulcer Recurrence following Surgical Management of Diabetic Foot Osteomyelitis

Running Title: Multi-Drug Resistant Organism Predicts Ulcer Recurrence

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Multi-Drug Resistant Organism Predicts Ulcer Recurrence following Surgical Management of Diabetic Foot Osteomyelitis

Abstract:

Diabetic foot ulcers commonly precede diabetic foot osteomyelitis 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 one-year diabetic foot outcomes (re-ulceration, amputation, 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 one-year outcomes. Patients with osteomyelitis managed surgically were younger and exhibited more painful peripheral neuropathy than outpatients with diabetes alone (both $p < 0.0001$**)**. 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 modeling ($p <0.001$) and importance rankings. This is the first study to use prediction modeling to identify a relationship between multidrug resistant organisms and diabetic foot ulcer recurrence following diabetic foot osteomyelitis.

Key Words: Diabetic foot osteomyelitis, multi-drug resistant organisms, ulcer recurrence, diabetic foot ulcer, amputation

Key Messages:

- The paper examines the relationship between proximal margin culture organism and outcomes following surgery for diabetic foot osteomyelitis

- We analyzed a cohort of 223 patients who underwent surgery to manage diabetic foot osteomyelitis using univariate, multivariate, and random forests to predict outcomes

- Recurrence of diabetic foot ulcer is predicted by presence of multidrug resistant organism on proximal bone cultures

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). Multi-drug resistant organisms (MDROs) are often present in DFU: about one-third of patients with a history of previous hospitalization 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 DFI reaches 56% and approximately 30% of cultures are resistant to recommended treatment(3). Evidence suggest that

MDROs in DFU leads 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 organism 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.

Materials and Methods

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 Center Institutional Review Board.

Pre-operative diagnosis of DFO was established by clinical signs/symptoms of infection (erythema, warmth, purulent drainage, 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 standardized manner, histopathology results were recorded at the surgical margin from the resected bone (i.e. dirty margin) in binary fashion as either 'viable' or 'non-viable' to denote the presence of necrotic bone. Next, the margin proximal to the amputation site (i.e. 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 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 on 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).

Study variables

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

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 chi-squared tests for categorical variables. Using classification and regression tree (CART) permutations, a random forest plot was used to identify microbiologic predictors of one-year outcomes. Data were analyzed using SAS software for Windows, version 9.4, and R packages "rpart" and "randomForest". All p-values are 2 sided, and findings were considered statistically significant at $p < .05$.

Results

Demographics

A total of 223 patients with DFO who subsequently underwent ablative surgery were included in the study. When compared to 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 v. 65.7 years, $p < 0.001$) and more frequently reported painful paresthesia associated with diabetic

peripheral neuropathy (DPN,95% v 73%; p<0.001). 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 neuroischemic etiologies 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%.

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 *Staphylococcus 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.

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 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. 13 patients (5.8%) died within the follow-up time; no death was directly related to DFU. 138 patients (72.3%) only had recurrent DFU, but not amputation or death. During the follow-up time, 94 (49.2%) patients did not experience recurrent DFU, amputation, or death.

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 ($p<0.001$). Specifically, MRSA ($p<0.035$) 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 ($p=0.01$). Specifically, *P. aeruginosa* ($p<0.01$), *E. coli* ($p<0.01$), *E. faecium (p<0.05)*, and *E. faecalis* ($p<0.05$) 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 modeling.

In a multivariate analysis of laboratory values in patients with recurrent DFU, Westergren sedimentation rate (ESR, Log(OR) 0.00943, p = 0.0479), high immature granulocyte count (0.7943, p=0.0078), and low lymphocyte counts (-0.0369, p=0.0225) 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 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.

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 longevity of disease status, but were younger ($p<0.0001$) and had more severe painful DPN ($p<0.0001$) compared to our historic comparison group. The vast majority of our patients developed osteomyelitis from contiguous

chronic neuropathic or neuroischemic 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 previous 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 outcome including re-ulceration, amputation, or death. They also did not demonstrate significance in random forest modeling. However, their relationship to outcome is not defined by the parameters of this study as sample size is too small. Further investigation is needed to understand their role in DFO microbiome using molecular techniques such as 16s rRNA and qPCR.

The overall rate of MDROs in DFO patients was 13.9%, which is comparable to some centers 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 one year. The MDRO which reached statistical significance as a risk factor for DFU recurrence within the one-year follow-up was MRSA, present in 5.8% (n= 13). Through the use of advanced prediction modeling 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 to control skin(24) and antibiotic use destabilizes 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 (MSC)(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, 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.

Recurrent rate of DFU within one-year following amputation was 44.5% and is similar to reported literature for DFU recurrence of approximately 40% at one-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, hemoglobin 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 center. Antibiotics were often administered prior to obtaining bone cultures intraoperatively, though 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 one 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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Table 1: Diabetic Patient Characteristics within Podiatry (n= 459).

Patients with diabetic foot osteomyelitis were younger and experienced more painful peripheral neuropathy as compared to a historical comparator group without either diabetic foot ulcer or osteomyelitis.

	Diabetic without DFU (n= 236)	**Diabetic with DFO (n=223)**	**p-value**
Sex – n (% male)	164 (69.5)	176 (78.9)	p = 0.08
Race – n (% white)	204 (86.4)	194 (87)	p = 0.06
BMI ± Std Dev (kg/m^2)	30.7 ± 9.9	33.3 ± 5.1	p = 0.54
Age ± Std Dev (years)	65.7 ± 14.8	57.3 ± 10.1	**p <0.0001**
CKD – n (%)	64 (27)	26 (22)	p = 0.29
CAD – n (%)	85 (36)	36 (31)	p = 0.34
DPN – n (%)	172 (73)	112 (95)	**p < 0.0001**
Retinopathy n (%)	28 (11.9)	33 (14.7)	p = 0.39
Duration of DM ± Std Dev (years)	14.7 ± 13.4	13.3± 8.8	p = 0.27

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%)

Table 3. Summary of Outcomes	
Outcome	**Count (%)**
Recurent DFU by 3 Months	70/191 (36.6%)
Ever Ulcer by 6 Months	82/191 (42.9%)
Ever Ulcer by 12 Months	85/191 (44.5%)
Re-amputation by 3 months	12/222 (5.4%)
Ever Amputation by 6 months	35/222 (15.8%)
Ever Amputation by 12 months	41/222 (18.5%)
Death or recurrent DFU or re-amputation by 12 months	97/191 (50.8%)
Death or amputation by 12 months	53 / 222 (23.9%)
Death by 12 months	13/223 (5.8%)
Ordered combined outcome	
No ulcer, amputation, or death	94/191 (49.2%)
Ulcer but no amputation no death by 12 months	44/191 (23%)

Amputation but no death by 12 months	40/191 (20.9%)

Table 4. Ulcer, Amputation, or Death by 12 months

Microorganism	No	Yes	Chi-sq p-value	Fisher's exact p-value
MSSA	35/94 (37.2%)	29/97 (29.9%)	0.28	
CoNS	21/94 (22.3%)	13/97 (13.4%)	0.11	
E. faecalis	10/94 (10.6%)	17/97 (17.5%)	0.17	
E. faecium	5/94 (5.3%)	11/97 (11.3%)	0.13	
S. agalactiae	10/94 (10.6%)	14/97 (14.4%)	0.43	
Achromobacter sp.	0/94f (0%)	2/97 (2.1%)		0.50
Citrobacter sp.	2/94 (2.1%)	1/97 (1%)		0.62

E. coli	1/94 (1.1%)	7/97 (7.2%)		0.065
Klebsiella sp.	2/94 (2.1%)	1/97 (1%)		0.62
Serratia sp.	0/94 (0%)	3/97 (3.1%)		0.25
Other sp. (counts no less than 1)	15/94 (16%)	18/97 (18.6%)		0.70
MDRO	3/94 (3.2%)	20/97 (20.6%)		**0.00022**
MRSA	1/94 (1.1%)	8/97 (8.2%)		**0.035**
VRE	0/94 (0%)	1/97(1%)		1.00
Pseudomonas aeruginosa	3/94(3.2%)	10/97(10.3%)		0.082
Acinetobacter baumanii	1/94 (1.1%)	2/97(2.1%)		1.00
Microbiologic Growth	70/92 (76.1%)	78/92 (84.8%)	0.14	
Polymicrobial Culture	31/94 (33%)	43/97 (44.3%)	0.11	

Figure 1: Boxplots of Laboratory Values in DFO Cohort. Boxplots for western sedimentation rate (ESR) and lymphocyte count is provided below. The range of values for patients with DFO undergoing surgery is wide. Lymphocyte count has similar findings.

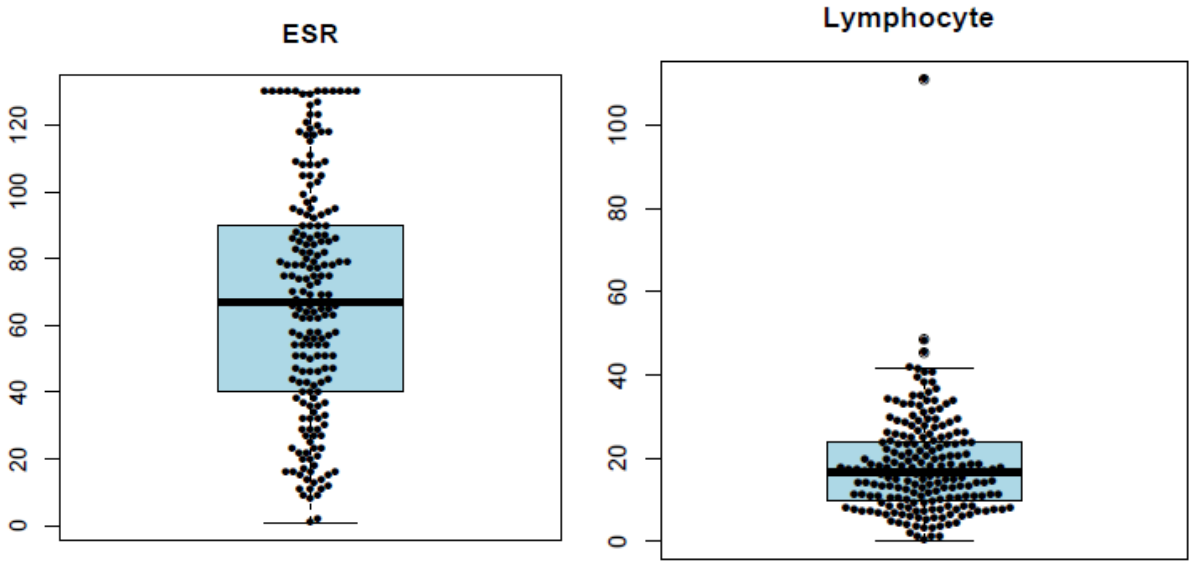
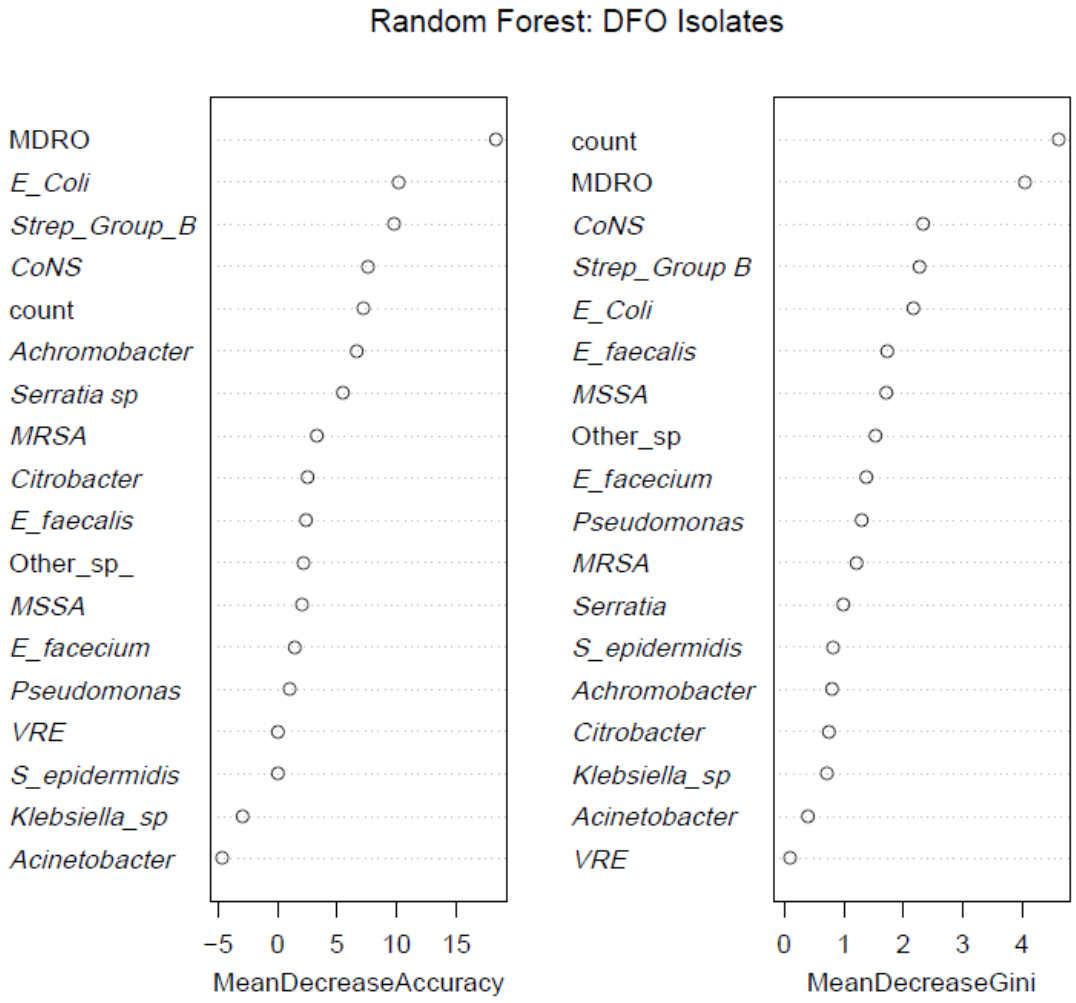


Figure 2: Random Forest for DFO isolates. The figure indicates that removal of MDRO-DFO presence from classification and regression tree (CART) analysis leads to misclassification for prediction of variable of interest. For our cohort, presence of MDRO demonstrated most significant contribution to mean decrease accuracy and a mean decrease in Gini, and demonstrates MDRO presence best predicts DFU recurrence.



Key Messages:

- The paper examines the relationship between proximal margin culture organism and outcomes following surgery for diabetic foot osteomyelitis

- We analyzed a cohort of 223 patients who underwent surgery to manage diabetic foot osteomyelitis using univariate, multivariate, and random forests to predict outcomes

- Recurrence of diabetic foot ulcer is predicted by presence of multidrug resistant organism on proximal bone cultures