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MAJOR ARTICLE

The Impact of Multidrug-Resistant Organisms on Outcomes in Patients With Diabetic Foot Infections

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Background. Multidrug-resistant organisms (MDROs) are important diabetic foot infection (DFI) pathogens. This study evaluated the impact of DFIs associated with MDRO pathogens (DFI-MDRO) on clinical outcomes.

Methods. Adults admitted to Detroit Medical Center from January 2012 to December 2015 with culture-positive DFI were included. Associations between outcomes and DFI-MDRO (evaluated as a single group that included methicillin-resistant *Staphylococcus aureus* [MRSA], vancomycin-resistant enterococci, *Enterobacteriaceae* resistant to third-generation cephalosporin [3GCR-EC], *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*) were analyzed. Outcomes included above- and below-knee lower extremity amputation (LEA), readmissions, and mortality within a year after DFI. A propensity score predicting the likelihood of having DFI-MDRO was computed by comparing patients with DFI-MDRO with patients with DFI with non-MDRO pathogens (DFI-non-MDRO). Using conditional logistic regression, DFI-MDRO was analyzed as an independent variable after patients in the MDRO and non-MDRO groups were matched by propensity score.

Results. Six hundred forty-eight patients were included, with a mean age ± SD of 58.4 ± 13.7. Most patients in the cohort presented with chronic infection (75%). DFI-MDRO occurred in greater than one-half of the cohort (n = 364, 56%), and MRSA was the most common MDRO (n = 224, 62% of the DFI-MDRO group). In propensity-matched analyses, DFI-MDRO was not associated with 1-year LEA or readmissions, but was associated with recurrent DFI episodes (odds ratio, 2.1; 95% confidence interval, 1.38–3.21).

Conclusions. DFI-MDRO was associated with a 2-fold increased risk of recurrent DFI compared with patients with DFI-non-MDRO.

Keywords. diabetic foot infection; multidrug-resistant organisms.

Among patients with diabetes, 10%–25% will develop diabetic foot ulcer (DFU) throughout their lives [1]. Sixty percent of DFUs may become infected, leading to a diabetic foot infection (DFI) [2]. Diabetic foot complications are the leading cause of hospitalization among patients with diabetes and are associated with an increased risk of lower limb amputation [2]. Other consequences of DFI include impaired mobility, impaired quality of life, and depression [3, 4]. In addition to the associated morbidity, DFI substantially increases health care costs, comprising up to 30% of the excess medical costs of patients with diabetes [3].

Multidrug-resistant organisms (MDROs) are common pathogens in DFI patients [5], due in part to frequent health care exposures and repeated courses of antibiotic treatment. The growing prevalence of MDROs associated with DFI limits antibiotic choices and sometimes leads to suboptimal therapy [6–8]. Due to this increased MDRO prevalence and the importance of early effective antimicrobial therapy, current national guidelines recommend the empiric use of broad-spectrum antibiotics in patients who have moderate to severe DFI [6].

Although some data suggest that infections due to MDROs result in worse outcomes more frequently than susceptible isolates [7, 9, 10], evidence pertaining to the impact of MDROs on DFI is conflicting. In several studies, DFI due to MRSA has been associated with poor ulcer healing [11], treatment failure [7], readmission to the hospital [12], and increased mortality [13], and MDROs have been associated with poor glycemic control [8]. However, in other studies of DFI, MDROs were not associated with worse clinical outcomes [14, 15]. In addition, the association between DFIs due to MDROs and lower extremity

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amputation (LEA) remains unclear. The objective of this study was to evaluate the impact of DFI associated with MDROs on clinical outcomes, including recurrent DFI, hospital readmission, and LEA.

METHODS

Study Setting and Cohort Description

The cohort included all adult patients with DFI who were admitted to the Detroit Medical Center (DMC; a metropolitan health system including 4 acute care hospitals and 1 rehabilitation center) between January 2012 and December 2015 with positive cultures from diabetic foot lesions. Potential DFI cases were identified based on having an International Classification of Diseases, 9th revision (ICD-9), code for diabetes mellitus and for skin and soft tissue infection (SSTI) and/or osteomyelitis (ICD-9 codes that were used were 249, 250, 680–686, 730). Subsequently admission and discharge notes, as well as podiatry and infectious diseases consult notes, were reviewed, and actual DFI diagnosis was confirmed by documented signs and symptoms of infection (erythema, warmth, pus drainage, and/or fetid odor). Patients were excluded from the study if any of the following were met: (1) infection status of the ulcer could not be determined from chart review or infection was ruled out by care providers, (2) the SSTI was not related to the foot, (3) infection following a fracture and/or a surgical site infection was present, (4) cultures grew organisms that were considered to be contaminants (eg, coagulase-negative *Staphylococcus* spp. and/or *Corynebacterium* spp. that grew from only a single set of cultures, or grew only in a nonsterile culture) [6, 16]. The institutional review boards of Wayne State University and the DMC approved this study for waiver of informed consent.

Definitions

The date of DFI diagnosis was defined as the day of the first positive culture for a DFI episode. An index episode was defined as the first DFI episode over the study period associated with a multidrug-resistant organism (DFI-MDRO), and if a subject had no DFI episode with an MDRO during the entire study period, then the first DFI episode during the study period was considered to be the index episode (DFI-non-MDRO). Subjects contributed only 1 unique index episode to the cohort. All DFI episodes for all subjects were captured throughout the study period both before and after the index episode.

For the purposes of these analyses MDROs included methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), *Enterobacteriaceae*-resistant third-generation cephalosporins (3GCR-EC) and/or carbapenem, and all antimicrobial susceptibility phenotypes of *Pseudomonas aeruginosa, Acinetobacter baumannii*, and *Stenotrophomonas maltophilia*.

Outcome Definitions

Recurrent DFIs were defined as a DFI episode that occurred during the time period spanning from 14 days after the index episode until 1 year later. Lower extremity amputation (LEA) included below-knee amputation or above-knee amputation that occurred during admission for the index episode or within 1 year of follow-up. In addition, less extensive amputations ("other amputations") were captured during index admission and the 1-year follow-up period. Readmission was defined as any admission within 1 year of the index episode. Mortality was captured within 1 year of an index episode. Length of stay for the index admission was calculated from the day of DFI diagnosis to the day of discharge.

Study Variables

Data pertaining to demographics, source of admission (home, long-term care facilities [LTCFs], transfer from another hospital), hospitalization within the past 90 days, comorbidities including the Charlson comorbidity index, insurance type, admission unit, and severity of sepsis at time of index DFI episode diagnosis [17] (determined using the most extreme values of the Systemic Inflammatory Response Syndrome Score within 2 days of DFI diagnosis) were collected. Intensive care unit (ICU) admission and mechanical ventilation and acute hemodialysis status were captured within 7 days after the date of the DFI diagnosis. Variables associated with diabetes status that were collected included highest HbA1C value within 3 months before the DFI episode, presence of diabetes-related end-organ damage, and ankle-brachial index (ABI) values when available. The depth of involvement of DFI was determined based on providers' documentation and radiology and pathology findings and was classified as superficial, deep tissue, or bone involvement. Definitive therapy was defined as the antimicrobial treatment given following release of microbiology results, including susceptibility testing. Duration of antibiotic treatment was categorized into "inpatient duration of therapy" and "total duration of therapy." The latter included inpatient administration as well as outpatient treatment, which was determined according to discharge notes and prescriptions. Antimicrobial treatment information in the 3 months before DFI diagnosis was also abstracted from the medical record.

Surgical interventions were recorded for all DFI episodes, including bedside debridement, operating room (OR) debridement, and amputations (including LEA and less extensive amputations).

Microbiology

Microbiology data for each patient included cultures obtained from DFI lesions and were classified as swab cultures obtained at the bedside, tissue cultures obtained at the bedside, swab cultures obtained in the OR, tissue cultures obtained in the OR, and bone cultures obtained in the OR. For a given episode, all

cultures from the DFI lesion that were obtained within a period of 14 days after the index episode date were considered to be part of the index DFI episode. A polymicrobial episode was defined as an episode during which more than 1 pathogen was recovered.

Data Analysis

Participant characteristics among the cohort and prevalence of MDROs were calculated using means and SDs, as well as medians with interquartile range (IQRs) where appropriate.

Baseline characteristics of subjects with DFI-MDRO were compared with subjects with DFI-non-MDRO using the Fisher exact test. Similarly, subjects with a specific MDRO were compared with subjects without that specific MDRO (eg, subjects with DFI associated with *P. aeruginosa* [DFI-PA] were compared with subjects without PA [DFI-non-PA]).

A multivariable model predicting DFI-MDRO was developed and is described elsewhere [18]. In brief, variables with a *P* value of <.2 in the bivariable analysis were included in a candidate logistic regression model. Backwards stepwise regression was performed to identify independent predictors for DFI-MDRO. Variables predicting DFI-MDRO were then used to compute a propensity score [18]. The independent association between DFI-MDRO and each outcome was determined by conditional logistic regression models with frequency-matching by strata of propensity score between DFI-MDRO and DFI-non-MDRO.

Similar analytic methodology was used to identify the impact of each individual MDRO on outcomes. For example, a propensity score for having DFI associated with PA (DFI-PA) was computed by comparing subjects with DFI-PA with subjects who had DFI without PA (DFI-non-PA), and propensity-matched conditional logistic regression was conducted for each outcome.

All *P* values were 2-sided.

RESULTS

Between 2012 and 2015, 1210 subjects with possible DFI were screened. Five hundred sixty-two patients were excluded for 1 or more of the following reasons: absence of positive cultures, skin and soft tissue infection located in an area other than the foot, documentation of noninfected diabetic foot ulcer, or isolation of coagulase-negative *Staphylococci* or *Corynobacterium* spp. from a single nonsterile culture.

Six hundred forty-eight unique subjects were determined to have DFI and were included in the study cohort (Table 1). The mean age was 58.4 ± 13.7, 64% were male, and 73% were African American. The median Charlson comorbidity index (IQR) was

Table 1. Description of the Cohort and Outcomes of Patients With DFI-MDRO Compared With Patients With DFI-Non-MDRO

	DFI-MDRO (n = 364)	DFI-Non-MDRO (n = 284)	Crude OR (95% CI)[a]	Adjusted OR (95% CI)
Demography and comorbid conditions				
Age, mean ± SD, y	59.2 ± 13.8	57.4 ± 13.6	*P* = .09	
Gender (female), No. (%)	135 (37.1)	96 (33.8)	*P* = .41	
Bedridden status, No. (%)	74 (21.1)	36 (13.2)	1.32 (0.81–2.16)	
Recent hospitalization, No. (%)	141 (38.7)	56 (19.7)	1.53 (0.99–2.38)	
LTCF residence, No. (%)	40 (11.0)	18 (6.3)	1.48 (0.74–2.95)	
Charlson comorbidity index, median (IQR)	5 (3 to 7)	4 (3 to 6)	*P* < .001	
CKD, No. (%)	118 (32.4)	65 (22.9)	1.48 (1.00–2.18)	
Retinopathy, No. (%)	68 (18.7)	49 (17.3)	1.10 (0.73–1.656)	
Neuropathy, No. (%)	308 (84.6)	227 (79.9)	1.38 (0.92–2.07)	
PVD, No. (%)	270 (74.2)	172 (60.6)	1.45 (1.00–2.09)	
ABI (n = 231), median (IQR)	0.99 (0.69 to 1.20)	0.99 (0.67 to 1.17)	*P* = .36	
HbA1C (n = 531), mean ± SD	8.8 ± 2.5	9.4 ± 2.8	*P* = .01	
Management				
Inpatient duration of treatment, median (IQR)	9 (6 to 15)	8 (5 to 13)	*P* = .06	
Total duration of treatment, median (IQR)	20 (13 to 42)	16 (11 to 34)	*P* = .002	
Outcomes (within 1 y)				
Recurrent DFI, No. (%)	90 (24.7)	35 (12.3)	2.34 (1.53–3.58)	2.1 (1.38–3.21)
LEA, No. (%)	59 (16.2)	29 (10.2)	1.70 (1.06–2.73)	1.25 (0.74–2.13)
Less extensive amputation, No. (%)	170 (46.7)	145 (51.1)	0.84 (0.62–1.15)	0.79 (0.96–1.35)
Length of stay, median (IQR), d	9 (6 to 13)	7 (5 to 11)	*P* < .001	
Readmissions, No. (%)	234 (64.3)	157 (55.3)	1.46 (1.06–2.0)	1.13 (0.80–1.61)
Mortality, No. (%)	23 (7.6)	13 (5.6)	1.38 (0.68–2.78)	0.95 (0.43–2.09)

Abbreviations: ABI, ankle-brachial index; CI, confidence interval; CKD, chronic kidney disease; HbA1C, hemoglobin A1C; LEA, lower extremity amputation; LTCF, long-term care facility; MDRO, multidrug-resistant organism; OR, odds ratio; PVD, peripheral vascular disorder.

[a]For continuous variables, *P* values are presented instead of odds ratios (ie, age, Charlson score, ABI, HbA1C, length of stay, duration of treatment).

5 (3 to 6), and 83% had peripheral neuropathy. Twenty-five percent of the patients presented with either sepsis or septic shock. The majority of patients (63%) had bone involvement with their infection.

Three hundred sixty-four patients (56%) had DFI with at least 1 MDRO (DFI-MDRO). The most common MDRO was MRSA (n = 224 patients, 62% of patients who had DFI-MDRO), followed by *P. aeruginosa* (n = 94, 26%), 3GCR-EC (n = 51, 14%), and VRE (n = 52, 14%). Most cultures (n = 457, 72%) were polymicrobial and were obtained in the OR (70%), including bone biopsies. One hundred sixty-four subjects had anaerobic organisms recovered from their DFI. Ninety patients (13.9%) had DFI with more than 1 MDRO, and 20 (3.1%) had DFI with 3 or more MDROs (18 had 3 MDROs, and 2 had 4 MDROs). The most common MDROs recovered from polymicrobial cultures were *P. aeruginosa* (n = 56) and MRSA (n = 26).

In bivariable analysis, patients who had DFI-MDRO had higher prevalence of comorbid conditions were more likely to be admitted from long-term care facilities, to be bedridden, and to have a history of recent hospitalization compared with patients with DFI-non-MDRO (Table 1). In addition, patients with DFI-MDRO had a higher frequency of prior use of an antibiotic within the previous 3 months compared with patients with DFI-non-MDRO (168, 46.2%, vs 71, 25%; $P < .001$).

Management

The median duration of inpatient antibiotic treatment (IQR) was 9 (6 to 14) days, and the median duration of total antibiotic treatment (IQR) was 18 (12 to 40) days. Patients with DFI-MDRO were treated with longer antibiotic durations than patients with DFI-non-MDRO (median of total duration [IQR], 20 [13 to 42] days and 16 [11 to 34] days, respectively; $P = .002$). Overall, 546 subjects (85%) received treatment that was considered to be active against all of the pathogens associated with DFI, and the median time between the day of DFI diagnosis and receiving active therapy (IQR) was 0 (−1 to 1) days. Among subjects who had DFI-MDRO, 22% (n = 79) received definitive therapy that was not active against all pathogens, compared with 8% (n = 23) of DFI-non-MDRO subjects ($P < .001$). Among patients with DFI-VRE, VRE was not treated in 44% of cases (n = 23/52); among patients with DFI-PA, *P. aeruginosa* was not treated in 11% of cases (n = 10/94); and among patients with DFI-3GCR-EC, the resistant *Enterobacteriaceae* were not treated in 16% of cases (n = 9/51).

Overall, surgical debridement was performed in 89.1% of the patients (574), and 323 (49%) had an amputation during their admission.

Description of Outcomes in the Cohort

One hundred twenty-five patients (19.3%) had recurrent DFI episodes within 1 year of the index episode (Table 1). Eighty-eight (14%) underwent lower limb amputation, 391 (60%) were readmitted, and 36 (7%) patients died within 1 year.

Outcomes Among Patients With DFI-MDRO vs Non-MDRO

In bivariable analyses, patients with DFI-MDRO were more likely to have recurrent DFI (Operating room [OpR], 2.34; 95% confidence interval [CI], 1.53–3.58), LEA occurring within 1 year (OR, 1.7; 95% CI, 1.06–2.7), readmission within 1 year (OR, 1.46; 95% CI, 1.06–2.0), and longer duration of hospitalization during index admission (median duration [IQR], 9 [6 to 13] days compared with 7 [5 to 11] days) compared with DFI-non-MDRO ($P < .001$) (Table 1). There was no difference in frequency of less extensive amputations or in all-cause mortality between the groups. A propensity score for DFI-MDRO included the following predictors for DFI-MDRO: admission from an LTCF, prior hospitalization within the last 90 days, chronic kidney disease, bedridden status, peripheral vascular disease, prior debridement within the last year, use of any antibiotic within the last 3 months, and prior diabetic foot ulcer with an MDRO. When controlling for differences between the 2 groups in a propensity-matched model (n = 583) (Supplementary Table 1), DFI-MDRO was an independent predictor for recurrent DFI (OR, 2.02; 95% CI, 1.27–3.22), but not for LEA or any other outcomes.

Outcomes Among Patients With DFI-PA

In bivariate analysis, patients with DFI-PA (as compared with patients without DFI-PA) had significantly higher risk for higher risk for LEA occurring within 1 year (OR, 2.09; 95% CI, 1.21–3.62) (Table 2). The duration of hospitalization was longer for patients with DFI-PA compared with DFI-non-PA (median duration [IQR], 10 [6 to 15] days compared with 8 [5 to 12] days; $P = .009$). The propensity score for DFI-PA included chronic kidney disease, peripheral vascular disease, admission from an LTCF, prior hospitalization within the last 90 days, bedridden status, prior diabetic foot ulcer with PA, and prior use of cefepime or fluoroquinolones within the past 3 months. However, in a propensity score–matched model (n = 480) (Supplementary Table 2), DFI-PA was not associated with any of the outcomes.

Outcomes Among Patient With DFI-VRE

DFI-VRE was associated with a higher prevalence of recurrent DFI (OR, 2.19; 95% CI, 1.19–4.06) and LEA within 1 year (OR, 2.05; 95% CI, 1.03–4.09) (Table 2). The propensity score for DFI-VRE included chronic kidney disease, peripheral vascular disease, prior diabetic foot ulcer with VRE, prior hospitalization within the past 90 days, prior debridement, and prior use of vancomycin within the past 3 months. In a propensity-matched analysis (n = 437) (Supplementary Table 4), DFI-VRE was associated with a >2-fold increased risk of having recurrent DFI

Table 2. Outcomes of DFI With Individual MDRO (Within 1 Year)

	Entire Cohort	PA (n = 94)	Non-PA (n = 554)	OR[a] (95% CI)	Adjusted HR (95% CI)	3GCR-EC (n = 51)	Non-3GCR-EC (n = 597)	OR[a] (95% CI)	Adjusted HR (95% CI)	VRE (n = 52)	Non-VRE (n = 596)	OR[a] (95% CI)	Adjusted HR (95% CI)	DFI-MRSA (n = 224)	DFI-Non-MRSA (n = 424)	OR[a] (95% CI)	Adjusted HR (95% CI)
Recurrent DFI	125 (19.3)	24 (25.5)	101 (18.3)	1.54 (0.92–2.56)	1.55 (0.88–2.74)	14 (27.5)	111 (18.6)	1.66 (0.87–3.17)	2.95 (1.25–6.98)	17 (32.7)	108 (18.1)	2.19 (1.19–4.06)	2.57 (1.29–5.12)	53 (23.7)	72 (17.0)	1.52 (1.02–2.26)	1.47 (0.99–2.18)
LEA, No. (%)	88 (13.6)	21 (22.3)	67 (12.1)	2.09 (1.21–3.62)	1.59 (0.88–2.89)	17 (33.3)	71 (11.9)	3.70 (1.97–6.97)	2.28 (0.93–5.62)	12 (23.1)	76 (12.8)	2.05 (1.03–4.09)	1.50 (0.72–3.09)	28 (12.5)	60 (14.2)	0.87 (0.54–1.40)	0.84 (0.52–1.35)
Less extensive amputation, No. (%)	315 (48.6)	42 (44.7)	273 (49.3)	0.83 (0.54–1.29)	1.09 (0.66–1.79)	19 (37.3)	296 (49.6)	0.60 (0.33–1.09)	1.11 (0.48–2.53)	25 (40.1)	290 (48.7)	0.98 (0.55–1.72)	1.10 (0.59–2.05)	105 (46.9)	210 (49.5)	0.89 (0.65–1.24)	0.92 (0.67–1.28)
Readmissions, No. (%)	391 (60.3)	63 (67.0)	328 (59.2)	1.40 (0.88–2.22)	1.04 (0.62–1.74)	32 (62.8)	359 (60.1)	1.11 (0.62–2.01)	1.34 (0.54–3.31)	38 (73.1)	353 (59.2)	1.87 (0.99–3.52)	1.42 (0.70–2.86)	138 (61.6)	253 (59.7)	1.08 (0.78–1.51)	1.10 (0.78–1.53)
Length of stay, median (IQR), d	8 (5 to 12)	10 (6 to 15)	8 (5 to 12)	0.009	4.5 (−3 to 12.7)	11 (7 to 18)	8 (5 to 12)	*P* < .001	6.6 (−5.3 to 20.2)	7.5 (5 to 13.5)	8 (5 to 12)	*P* = .98	−1.7 (−10.6 to 8)	8 (6 to 12)	8 (5 to 12)	*P* = .06	5.5 (0.3 to 11)
Mortality (n = 535), No. (%)	36 (6.7)	7 (8.3)	29 (6.4)	1.32 (0.56–3.12)	0.65 (0.25–1.73)	8 (19.1)	28 (5.7)	3.90 (1.65–9.21)	1.02 (0.22–4.72)	4 (9.1)	32 (6.5)	1.43 (0.48–4.25)	1.01 (0.32–3.17)	9 (5)	27 (7.7)	0.63 (0.29–1.36)	0.63 (0.29–1.36)

Abbreviations: 3GCR-EC, third-generation resistant *Enterobacteriaceae*; CI, confidence interval; DFI, diabetic foot infection; LEA, lower extremity amputation; LOS, length of stay; MDRO, multidrug-resistant organism; MRSA, methicillin-resistant *Staphylococcal aureus*; OR, odds ratio; PA, *Pseudomonas aeruginosa*; VRE, vancomycin-resistant *Enterococcus*.

[a]For continuous variables, *P* values are presented instead of odds ratios (ie, age, Charlson score, ankle-brachial index, hemoglobin A1C, length of stay, duration of treatment).

(OR, 2.57; 95% CI, 1.29–5.12) but was not associated with other outcomes.

Outcomes Among Patients With DFI-3GCR-EC

Patients who had DFI-3GCR-EC had higher risk of LEA occurring within 1 year (OR, 3.23; 95% CI, 1.66–6.28) and had longer duration of hospitalization (median duration [IQR], 11 [7 to 18] days) compared with patients who had DFI-non-3GCR-EC (median duration [IQR], 8 [5 to 12] days; $P < .001$) (Table 2). In addition, the mortality rate was higher in the DFI-3GCR-EC group (n = 8/51, 19%, vs n = 28/597, 5.7%; OR, 3.9; 95% CI, 1.65–9.21). The propensity score for DFI-3GCR-EC included peripheral vascular disease, congestive heart failure, dementia, admission from an LTCF, bedridden status, prior diabetic foot ulcer with 3GCR-EC, prior hospitalization within the past 90 days, prior use of third-generation cephalosporin, and receipt of cefepime or a beta-lactam/beta-lactamase inhibitor within the past 3 months. In propensity-matched analyses (n = 438) (Supplementary Table 3), DFI-3GCR-EC was associated with recurrent DFI within 1 year (OR, 2.12; 95% CI, 1.00–4.51), but not with other outcomes.

Outcomes Among Patients With DFI-MRSA

In bivariable analysis, patients with DFI-MRSA were at higher risk for recurrent DFI within 1 year compared with patients with DFI-non-MRSA (OR, 1.52; 95% CI, 1.02–2.26) (Table 2). The propensity score for DFI-MRSA included diabetic neuropathy, dementia, bedridden status, prior diabetic foot ulcer with MRSA, prior debridement, and prior use of beta-lactam within the past 3 months.

In a propensity-matched model (n = 452) (Supplementary Table 5), there was no association between DFI-MRSA and any of the outcomes. However, there was a trend toward significantly higher likelihood of having recurrent DFI within 1 year (OR, 1.47; 95% CI, 0.99–2.18).

DISCUSSION

In this cohort of poorly controlled diabetic patients with DFI and a high degree of comorbidity, almost 60% of the patients had infection involving at least 1 MDR pathogen, and in one-quarter of DFI-MDRO cases, more than 1 MDRO was recovered. MRSA was the most common MDRO recovered, followed by *P. aeruginosa*, VRE, and third-generation cephalosporin-resistant *Enterobacteriaceae*.

Patients who had DFI involving MDRO pathogens had a >2-fold increased risk for having recurrent DFI and a prolonged duration of hospitalization during their index admission, compared with patients who had DFI involving only susceptible pathogens. Similar associations were observed for each individual type of MDRO. Interestingly, although other outcomes, such as LEA, readmission, and mortality, were more prevalent in patients who had DFI-MDRO compared with patients

who had DFI-non-MDRO, none of these outcomes was independently associated with DFI-MDRO in propensity-adjusted analyses. Other studies have reported weak or no association between MDRO and DFI outcomes [14, 19]. To our knowledge, this is the largest study that has evaluated the impact of individual MDROs on LEA.

Several reasons may have explain the lack of an independent association between MDRO and certain outcomes including LEA, readmission, and mortality. First, the majority of the patients in both the DFI-MDRO and DFI-non-MDRO groups had polymicrobial infections, with various combinations of different types of pathogens. Nevertheless, in both of the study groups, the majority of patients received therapy with in vitro activity against all pathogens present (effective therapy) during the index episode. Given that both groups received effective therapy, any expected differences in DFI outcomes related to the presence of MDROs may have been obviated. In instances where therapy did not provide activity against all MDROs present, the most common MDRO not treated was VRE. The role of VRE as a true pathogen, particularly in the setting of polymicrobial infection, is debatable [20]. Second, most of the patients who were treated for DFI had chronic infection (only 25% of patients in the cohort presented with signs and symptoms of sepsis or septic shock). In the setting of chronic infection, factors such as peripheral neuropathy and poor vascular supply may have a greater impact on ulcer healing than the presence of MDROs. Finally, surgical debridement and source control are critical components of the effective management of DFI, and these associations are likely independent of MDRO status.

The frequency of MDROs in this cohort from metro Detroit was extremely high (approaching 60%). This high frequency of MDRO pathogens raises the question of whether, in some settings, empiric antibiotic regimens for DFI should include coverage for MDROs. Although MDROs were not independently associated with some adverse outcomes including readmission, LEA, and mortality, they were associated with recurrent DFI and increased duration of hospitalization. Prospective controlled studies are needed to better understand the role of broad-spectrum empiric antibiotic therapy that provides coverage against MDROs in the management and clinical outcomes of patients with DFI-MDRO.

Supplementary Data

Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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