

# Risk Factors for Multidrug-Resistant Organisms Infection in Diabetic Foot Ulcer

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**Objective:** The aim of this study is to analyze the microbiological characteristics of diabetic foot ulcer (DFU) and drug resistance of multidrug-resistant organisms (MDROs) and to reveal the potential risk factors for MDROs. This provides a basis for early empiric antibiotic treatment.

**Methods:** This study included 348 patients with diabetic foot ulcer in Chu Hsien-I Memorial Hospital & Metabolic Disease Hospital of Tianjin Medical University between May 2020 and November 2021. A total of 475 strains of bacteria were cultured, among which 240 strains were multidrug-resistant bacteria, accounting for 51%. Binary logistic regression was used to analyze risk factors. First, univariate analysis was used to calculate the *p* value of variables, and then multivariate analysis was conducted for variables with *p* < 0.1 to analyze independent risk factors. Risk factors with *p* < 0.05 in multivariable analysis were considered as independent risk factors. The strength of the association was represented by odds ratio and 95% confidence interval.

**Results:** Univariable logistic regression analysis demonstrated that previous hospitalization, previous antibiotic therapy, ulcer size >4cm<sup>2</sup>, surgical therapy, D-dimer, and CRP were associated with MDRO infection in patients with DFU. Multivariate logistic regression analysis demonstrated that previous hospitalization (OR = 1.91; 95% CI = 1.11–3.28; *p* = 0.02), ulcer size >4cm<sup>2</sup> (OR = 1.68; 95% CI = 1.03–2.76; *p* = 0.04), surgical therapy (OR = 2.14; 95% CI = 1.03–4.47; *p* = 0.04), and CRP (OR = 1.01; 95% CI = 1.00–1.01; *p* = 0.03) were independent risk factors for MDROs infection in diabetic foot patients. Drug resistance analysis may indicate that the proportion and drug resistance rate of *Acinetobacter baumannii* in Tianjin, China, have changed.

**Conclusion:** Previous hospitalization, ulcer size >4cm<sup>2</sup>, surgical therapy and CRP were independent risk factors for MDROs infection in diabetic foot patients. Identifying these risk factors can help us identify the high-risk patients of diabetic foot with MDRO infection early. More attention to high-risk patients and more aggressive isolation precautions may reduce the incidence of MDRO infection in diabetic foot patients.

**Keywords:** diabetic foot ulcer, multidrug-resistant organisms, infection, risk factors, logistic regression analysis

## Introduction

Diabetic foot ulcer (DFU) is one of the most serious complications of diabetes.<sup>1</sup> Epidemiological investigation found that the global prevalence of DFU is 6.3%,<sup>2</sup> and what is more troublesome is that DFU also has a high recurrence rate.<sup>3</sup> Cohort studies have shown that DFU have a high mortality rate in both developed and developing countries, with a 5-year mortality rate of up to 42%.<sup>4–7</sup> With high morbidity and mortality, DFU has been the main cause of nontraumatic lower-limb amputations.<sup>8,9</sup> We have developed a model for predicting the risk of early DFU, which may potentially guide early intervention.<sup>10</sup> Hyperglycemia impair immune cells activity in eliminating pathogens,<sup>11,12</sup> while severe infection can cause stress hyperglycemia.<sup>13</sup> The interaction of the two ways has resulted in a rapid development of diabetic foot infection (DFI) and sometimes a necrotizing abscess can be developed in just 6 days.<sup>14</sup> Early empiric antibiotic treatment is necessary due to the long culture time of microorganisms and the lack of basic microbiology laboratories. But

Multidrug-resistant organisms (MDROs) infection is easy to make antibiotic treatment failure, increasing the difficulty of diabetic foot treatment.

In recent years, MDRO infection in patients with DFU has received a lot of attention. Although there is insufficient evidence that MDRO delay wound healing,<sup>15</sup> some studies have shown that MDRO significantly increase the rate of recurrence and amputation in patients with DFU.<sup>16,17</sup> There are significant differences in the prevalence of MDROs in different regions,<sup>18–21</sup> and there are few reports on the prevalence of MDROs in DFU in North China. The aim of this study is to analyze the microbiological characteristics of DFU and drug resistance of MDROs, and to reveal the potential risk factors for MDROs. This provides a basis for early empiric antibiotic treatment.

## Patients and Methods

This study included 348 patients with diabetic foot ulcer in Chu Hsien-I Memorial Hospital & Metabolic Disease Hospital of Tianjin Medical University between May 2020 and November 2021. A total of 475 strains of bacteria were cultured, among which 240 strains were multidrug-resistant bacteria, accounting for 51%.

All patients were graded according to the University of Texas Wound Classification System after admission and grade 0 patients were excluded. Identify diabetic foot ulcer infection according to IWGDF/IDSA recommendations.<sup>22,23</sup> Previous hospitalization was defined as hospital admissions for diabetic foot within 12 months. Previous antibiotic therapy was defined as the use of antibiotics within 30 days. Osteomyelitis was determined by X-ray and sterile forceps exploration. Ischemia was defined by an ankle brachial index <0.9, lower extremities CT angiography was performed when necessary. Peripheral neuropathy was defined as the absence of perception of the Semmes–Weinstein monofilament 5.07/10 g at 2 of 10 standardized plantar sites on either foot or vibration sense <5/8 grade of a 128-Hz tuning fork, neuroelectrophysiological examination was performed when necessary. Diabetic kidney disease (DKD) was determined by glomerular filtration rate (GFR) below 60 mL/min/1.73m<sup>2</sup> or urinary albumin/creatinine ratio (ACR) above 30 mg/g for more than three months. Diabetic retinopathy (DR) was determined by dilated fundus examination that reveals microaneurysms or more serious lesions. Surgical therapy includes both minor and major amputations. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured with a standard ambulatory blood pressure monitor, and the mean value of 24-hour ambulatory blood pressure was obtained. All the laboratory results, including HbA1c, blood lipid and C-reactive protein (CRP), were taken from the first inspection after admission.

On admission, the skin around the wound was cleaned with povidone iodine solution. After careful irrigation of the wound with normal saline, remove necrotic tissue as needed. Irrigate the wound again, press a sterile cotton swab firmly into the wound and rotate to collect deep secretions. After 30 minutes, the swabs were transported to the microbiology laboratory in a sterile container. The specimens were inoculated and cultured, and the strains were identified by VIETK mass spectrometry (bioMérieux, Marcy l'Etoile, France), and drug sensitivity test was conducted by VITEK 2-Compact system (bioMérieux, Marcy l'Etoile, France). Sensitivity tests were performed using the disc diffusion method to determine sensitivity, according to the guidelines of Clinical and Laboratory Standards Institute (CLSI). MDROs were defined according to an international expert proposal set by the European Centre for Disease Prevention and Control (ECDC) and the Centers for Disease Control and Prevention (CDC).<sup>24</sup> The ECDC criteria define MDRO as acquired non-susceptibility to at least one agent in three or more antimicrobial categories.

## Treatment

After admission, all the patients were given insulin therapy, and insulin dose is adjusted according to blood glucose levels throughout the day. Empiric antibiotic treatment depended on DFI duration, previous antibiotic treatment and severity of infection. Antibiotics sensitive to gram-positive bacteria were mainly used for mild and moderate DFI patients with short DFI duration and no recent antibiotic treatment. Broad-spectrum antibiotic was mainly used for severe DFI patients. Therapy was adjusted according to the antibiotic susceptibility results and the clinical response. Infected wound care is once a day. Patients with deep abscess were treated with timely debridement and drainage with sterile gauze, and enclosed negative pressure drainage was used when necessary. The surgical treatment was adopted for the patients whose condition worsened with conservative treatment.

The patients received tertiary care at Chu Hsien-I Memorial Hospital & Metabolic Disease Hospital of Tianjin Medical University. Tianjin is located in the north temperate zone in the middle latitude east coast of Eurasia continent, a warm temperate zone semi-humid monsoon climate. Tianjin straddles the Haihe River, which is the largest river in North China.

## Statistical Analysis

According to normality, quantitative variables were expressed as mean  $\pm$  standard deviation and quartile, respectively, and Mann–Whitney *U*-test was used. Qualitative variables were expressed as percentages and Pearson's chi-squared test was used. Binary logistic regression was used to analyze risk factors. First, univariate analysis was used to calculate the *p* value of variables, and then multivariate analysis was conducted for variables with *p* < 0.1 to analysis independent risk factors. Risk factors with *p* < 0.05 in multivariable analysis were considered as independent risk factors. The strength of the association was represented by odds ratio (OR) and 95% confidence interval (CI). All statistical analyses were performed using SPSS 25.0 software. *p* < 0.05 was considered significant (Table 1).

## Results

There was no statistical difference in Age, Sex, Diabetes duration, Ulcer duration, Osteomyelitis, Retinopathy, DKD, SBP, DBP, Fibrinogen, HbA1c, TG, TC and LDL-C of baseline data between the two groups. Logistic regression analysis demonstrated that Previous hospitalization (OR = 2.52; 95% CI = 1.63–3.91; *p* < 0.01), previous antibiotic therapy (OR = 2.39; 95% CI = 1.41–4.05; *p* < 0.01), ulcer size > 4cm<sup>2</sup> (OR = 2.62; 95% CI = 1.69–4.07; *p* < 0.01), Surgical therapy (OR = 3.39; 95% CI = 1.72–6.65; *p* < 0.01), D-Dimer (OR = 1.20; 95% CI = 1.01–1.42; *p* = 0.04), CRP (OR = 1.01; 95% CI = 1.00–1.01; *p* < 0.01) were associated with MDRO infection in patients with DFU. Four independent risk factors were found after adjusting for potential confounders, were Previous hospitalization (OR = 1.91; 95% CI = 1.11–3.28; *p* = 0.02), ulcer size > 4cm<sup>2</sup> (OR = 1.68; 95% CI = 1.03–2.76; *p* = 0.04), Surgical therapy (OR = 2.14; 95% CI = 1.03–4.47; *p* = 0.04), CRP (OR = 1.01; 95% CI = 1.00–1.01; *p* = 0.03) (Table 2).

A total of 475 strains of bacteria were cultured, including 240 strains of MDRO, accounting for 51%. Among them, there were 50 strains of *Staphylococcus aureus* with MDRO rate of 42%, 49 strains of *Pseudomonas aeruginosa* with MDRO rate of 24%, 47 strains of *Acinetobacter baumannii* with MDRO rate of 70%, 47 strains of *Klebsiella pneumoniae* with MDRO rate of 24%, 44 strains of *Streptococcus* spp. with MDRO rate of 45%, and 23 strains of *Staphylococcus epidermidis* with MDRO rate of 91% (Table 3).

In the analysis of multidrug-resistant bacteria, we found that 71.4% of *Staphylococcus aureus* were sensitive to oxacillin or ceftazidime. All *Staphylococcus aureus* were resistant to penicillin, but sensitive to vancomycin and quinupristin/dalfopristin. Most *Staphylococcus epidermidis* defined as multi-resistant because of combined fluoroquinolones or tetracycline resistance in addition to erythromycin and clindamycin resistance. *Pseudomonas aeruginosa* kept high resistance to several antibiotics, but higher sensitivity to aminoglycoside antibiotics. *Acinetobacter baumannii* was resistant to most antibiotics, only sulfamethoxazole and polymyxin had higher sensitivity. *Escherichia coli* had higher drug resistance rates to fluoroquinolones, tetracycline and first and second-generation cephalosporins, and higher sensitivity to ceftazidime, cefepime, penicillins +  $\beta$ -lactamase inhibitors and carbapenems (Table 4).

## Discussion

The top MDRO in this study were *Acinetobacter baumannii*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus* spp. and *Escherichia coli*, while the top MDRO in a study of our hospital in 2012 were *Staphylococcus aureus*, *Enterobacter* spp, *Pseudomonas aeruginosa* and *Staphylococcus epidermidis*.<sup>25</sup> This indicated that the detection rate of multidrug-resistant *Acinetobacter baumannii* in our hospital increased significantly. Since all bacteria were collected on admission, hospital acquired infection was almost impossible due to this hospitalization. The increase of *Acinetobacter baumannii* may indicate that the proportion and drug resistance rate of *Acinetobacter baumannii* in Tianjin, China, have changed.

Early empiric antibiotic treatment is necessary for patients at high risk of MDRO infection. Early detection of suspected *Pseudomonas aeruginosa* infection (green staining of toes clearance or wound dressing), early empiric use of

**Table 1** Baseline Data of Patients with Diabetic Foot Ulcer

Characteristics	Total (N=348)	MDRM+ (N=202)	MDRM- (N=146)	p-value
Age (years)	63.99±11.40	63.74±11.97	64.34±10.59	0.63
Sex [n (%)]				0.35
Male	250 (71.8)	149 (73.8)	101 (69.2)	
Female	98 (28.2)	53 (26.2)	45 (30.8)	
Previous hospitalization [n (%)]				<0.01
Yes	177 (50.9)	122 (60.4)	55 (37.7)	
No	171 (49.1)	80 (39.6)	91 (62.3)	
Previous antibiotic therapy [n (%)]				0.01
Yes	275 (79)	172 (85.1)	103 (70.5)	
No	73 (21)	30 (14.9)	43 (29.5)	
Diabetes duration (years)	15.0 (9.3,21)	15.0 (10.0,20.0)	15.0 (8.0,23.3)	0.72
Ulcer duration (weeks)	8.0 (3.0,16.0)	8.0 (3.0,16.0)	8.0 (2.0,16.0)	0.91
Ulcer size>4cm <sup>2</sup> [n (%)]				<0.01
Yes	186 (53.4)	128 (63.4)	58 (39.7)	
No	162 (46.6)	74 (36.6)	88 (60.3)	
Osteomyelitis [n (%)]				0.32
Yes	246 (70.7)	147 (72.8)	99 (67.8)	
No	102 (29.3)	55 (27.2)	47 (32.2)	
Retinopathy [n (%)]				0.37
Yes	179 (51.4)	108 (53.5)	71 (48.6)	
No	169 (48.6)	94 (46.5)	75 (51.4)	
DKD [n (%)]				0.11
Yes	182 (52.3)	113 (55.9)	69 (47.3)	
No	166 (47.7)	89 (44.1)	77 (52.7)	
Surgical therapy [n (%)]				<0.01
Yes	59 (17.0)	47 (23.3)	12 (8.2)	
No	289 (83.0)	155 (76.7)	134 (91.8)	
SBP (mmHg)	137.51±19.58	137.61±20.19	137.38±18.77	0.91
DBP (mmHg)	77.01±12.16	76.82±11.94	77.28±12.49	0.73
Fibrinogen (g/L)	5.28±1.88	5.41±1.97	5.10±1.75	0.12
D-Dimer (mg/L)	0.78 (0.47,1.34)	0.85 (0.49,1.47)	0.67 (0.44,1.09)	<0.01
HbA1c (%)	8.58±2.03	8.59±1.91	8.56±2.18	0.88
TG (mmol/L)	1.35±0.74	1.38±0.77	1.32±0.69	0.47
TC (mmol/L)	4.28±1.30	4.23±1.28	4.35±1.33	0.38
LDL-C (mmol/L)	2.98±1.00	2.96±0.98	3.02±1.03	0.62
CRP (mg/L)	24.59 (0.50,73.07)	30.61 (6.33,81.04)	18.6 (3.61,49.82)	<0.01

tobramycin, ceftazidime, cefepime, imipenem, rather than ertapenem, amoxicillin/clavulanic acid, ceftriaxone, is recommended when secretion culture is not returned. Early detection of suspected *Staphylococcus aureus* infection (local suppurative infection, cellulitis), early empiric use of levofloxacin, quinupristin/dalfopristin, rather than penicillin, erythromycin, clindamycin, is recommended when secretion culture is not returned. Tobramycin, piperacillin/tazobactam, imipenem, ceftazidime and cefepime can be used to treat other suspected gram-negative bacterial infections, and antibiotics can be adjusted after the results of secretion culture and antibiotic treatment.

This study identified previous hospitalization as an independent risk factor for MDRO infection. Hospital-acquired infection is one of the most common causes of MDRO infection, which leads to a high mortality.<sup>26,27</sup> The occurrence of hospital acquired infection is mainly due to the poor environment of the ward and the inadequate implementation of isolation measures for patients infected with MDRO. In order to avoid MDRO infection caused by hospitalization, we should strictly observe and implement the isolation measures for patients with MDRO infection, and discharge patients in

**Table 2** Logistic Regression Analysis of MDRO Infection in DFU Patients

Characteristics	Univariable Analysis			Multivariable Analysis		
	OR	95% CI	p-value	OR	95% CI	p-value
Age	1.00	0.98–1.01	0.63			
Male gender	0.80	0.50–1.29	0.35			
Previous hospitalization	2.52	1.63–3.91	<0.01	1.91	1.11–3.28	0.02
Previous antibiotic therapy	2.39	1.41–4.05	<0.01	1.17	0.63–2.20	0.62
Diabetes duration	1.00	0.98–1.02	0.98			
Ulcer duration	1.00	0.99–1.00	0.58			
Ulcer size>4cm <sup>2</sup>	2.62	1.69–4.07	<0.01	1.68	1.03–2.76	0.04
Osteomyelitis	1.27	0.80–2.02	0.32			
Retinopathy	1.21	0.79–1.86	0.37			
DKD	0.71	0.46–1.08	0.11			
Surgical therapy	3.39	1.72–6.65	<0.01	2.14	1.03–4.47	0.04
SBP	1.00	0.99–1.01	0.91			
DBP	1.00	0.98–1.02	0.73			
Fibrinogen	1.10	0.98–1.23	0.12			
D-Dimer	1.20	1.01–1.42	0.04	1.09	0.92–1.28	0.32
HbA1c	1.01	0.91–1.12	0.88			
TG	1.12	0.83–1.50	0.47			
TC	0.93	0.79–1.09	0.38			
LDL-C	0.95	0.77–1.17	0.62			
CRP	1.01	1.00–1.01	<0.01	1.01	1.00–1.01	0.03

**Table 3** Bacterial Distribution and Drug Resistance Rate

Bacteria	MDRO+	MDRO-	Resistant Rates
Gram positive			
<i>Staphylococcus</i> spp.			
<i>Staphylococcus aureus</i>	21	29	0.42
<i>Staphylococcus epidermidis</i>	21	2	0.91
Other <i>Staphylococcus</i> spp.	8	3	0.73
<i>Streptococcus</i> spp.	20	24	0.45
<i>Enterococcus</i> spp.	18	3	0.86
Gram negative			
<i>Escherichia coli</i>	20	6	0.77
<i>Enterobacter cloacae</i>	8	17	0.32
<i>Morganella morganii</i>	5	8	0.38
<i>Proteus</i> spp.	14	13	0.52
<i>Serratia marcescens</i>	5	13	0.28
<i>Klebsiella pneumoniae</i>	16	31	0.34
<i>Pseudomonas aeruginosa</i>	12	37	0.24
<i>Stenotrophomonas maltophilia</i>	5		
<i>Acinetobacter baumannii</i>	33	14	0.70
Others	34	35	0.49
Total	240	235	0.51

stable condition as soon as possible and follow-up in the clinic to reduce the length of stay and the risk of hospital acquired infection.

Ulcer size >4cm<sup>2</sup> is also an independent risk factor for MDRO infection. The decreased immune function of diabetic patients provides conditions for the propagation of opportunistic pathogen, and larger ulcer area means more exposure to

**Table 4** Resistance Rate of Common MDRO to Commonly Used Antibiotics

Antibiotic	<i>Staphylococcus aureus</i>		<i>Pseudomonas aeruginosa</i>		<i>Acinetobacter baumannii</i>		<i>Escherichia coli</i>		<i>Klebsiella pneumoniae</i>		<i>Enterococcus spp.</i>	
	Strains	Resistance Rates (%)	Strains	Resistance Rates (%)	Strains	Resistance Rates (%)	Strains	Resistance Rates (%)	Strains	Resistance Rates (%)	Strains	Resistance Rates (%)
Oxacillin or ceftazidime	6	28.6										
Levofloxacin	9	42.9	5	41.7	30	90.9	18	90.0	16	100.0	7	38.9
Moxifloxacin	8	38.1					12	60.0	12	75.0		
Penicillin	21	100.0									1	0.1
Vancomycin	0	0.0									0	0.0
Gentamicin	12	57.1	2	16.7			9	45.0	9	56.3	9	50.0
Tobramycin			0	0.0	23	69.7	9	45.0	8	50.0		
Erythromycin	16	76.2									18	100.0
Clindamycin	16	76.2									18	100.0
Quinupristin/ Dalfopristin	0	0.0									17	94.4
Amoxicillin/ Clavulanic acid			12	100.0	33	100.0	6	30.0	9	56.3		
Piperacillin/ Tazobactam			6	50.0	28	84.8	3	15.0	8	50.0		
Meropenem			4	33.3	30	90.9	1	5.0	0	0.0		
Imipenem			3	25.0	29	87.9	1	5.0	1	0.1		
Ertapenem			12	100.0			1	5.0	0	0.0		
Cefazolin			12	100.0			20	100.0	16	100.0		
Cefuroxim			12	100.0	33	100.0	15	75.0	15	93.8		
Ceftriaxone			12	100.0			13	65.0	9	56.3		
Ceftazidime			4	33.3	28	84.4	5	25.0	3	18.8		
Cefepime			3	25.0	28	84.4	4	20.0	1	0.1		
Tetracycline	3	14.3	12	100.0	26	78.8	15	75.0	14	87.5	17	94.4
Aztreonam					33	100.0	6	30.0	5	31.3		
Sulfamethoxazole	13	61.9	12	100.0	12	36.4	11	55.0	11	68.8		
Polymyxin					0	0.0						

pathogen. Studies have shown that ulcer size is important for the prognosis of diabetic foot.<sup>28,29</sup> This suggests that more attention should be paid to patients with larger ulcers.

Surgical therapy is an independent risk factor for MDRO infection. Surgical therapy can result in changes in the biomechanics of the foot, and the ways in which surgical therapy increase the risk of multidrug-resistant infections remain to be explored. Some studies have shown that diabetic foot patients have a higher mortality rate after amputation.<sup>30–32</sup> Amputation should be the last option, which can be devastating for patients with DFU. Timely vascular reconstruction and standardized debridement can effectively prevent amputation.

C-reactive protein is a marker for infection and inflammation, and its levels increase during bacterial infection.<sup>33</sup> Our study showed that CRP is an independent risk factor for MDRO infection. The higher the CRP level, the greater the risk of MDRO infection. C-reactive protein is also an independent and strong predictor of cardiovascular diseases.<sup>34</sup>

This study has some limitations. Specimens were obtained using cotton swabs instead of tissue and bone, but none of the specimens was obtained as superficial swabs. Some studies have shown there is a high concordance rate between swab and deep tissue cultures.<sup>35,36</sup> More than 95% of patients were diagnosed with different degrees of diabetic peripheral vascular disease and peripheral neuropathy, so these two factors were not included in the study. Despite the above limitations, our study found certain risk factors for DFUs infected with MDROs.

In conclusion, previous hospitalization, ulcer size  $>4\text{cm}^2$ , surgical therapy and CRP were independent risk factors for MDROs infection in diabetic foot patients. Identifying these risk factors can help us identify the high-risk patients of diabetic foot with MDRO infection early. More attention to high-risk patients and more aggressive isolation precautions may reduce the incidence of MDRO infection in diabetic foot patients.

## Ethics Statement

This study was approved by the Institutional Review Board of Tianjin Medical University Chu Hsien-I Memorial Hospital. This study is a retrospective non-interventional study, which does not interfere with routine diagnosis and treatment, does not affect any medical rights of patients, and does not increase the risk of patients. Consent was waived because most of the patients could not be found and the research project did not involve personal privacy or commercial interests.

In order to fully protect personal privacy, the names of the included patients were coded, and the medical records were stored in the special computer of the Department of Diabetic Foot, Chu Hsien-I Memorial Hospital of Tianjin Medical University, for researchers' access only.

We declare that this study is in accordance with the Helsinki Declaration and the information of all patients included in the study was confidential.

## Author Contributions

These authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

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