Distribution of multidrug-resistant bacterial infections in diabetic foot ulcers and risk factors for drug resistance: a retrospective analysis

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Abstract

Objective：To investigate the distribution, drug resistance and risk factors of multi-drug resistant bacterias（MDROs） in patients with Type 2 diabetic foot ulcers（DFU）.

Method：The clinical data, foot secretions, pathogenic microorganisms and drug sensitivity tests of 147 patients with type 2 diabetes admitted to our department from January 2018 to December 2021 were analyzed. Patients were divided into two groups according to whether they had been infected with MDROs or not. 71 cases were infected with MDROs as the case group, and the remaining 76 cases were the control group. Chi-square test and t-test were used to analyze the results of MDROs infection and DFU, and logistic multivariate regression was used to evaluate the risk factors of MDROs infection.

Results：A total of 71 strains were isolated from the MDROs-positive group, with the top three being Staphylococcus aureus (46.48%), Escherichia coli (22.53%), and Pseudomonas aeruginosa (18.31%), respectively.Logistic multifactorial regression analysis showed that history of previous antimicrobial exposure, neuroischemic wound, Wagner grade 3-5 , and combined osteomyelitis were associated with Type 2 diabetic foot infection MDROs (P < 0.05).

Conclusion：Previous history of antimicrobial exposure, neuroischemic wounds, Wagner grade 3-5, and combined osteomyelitis are independent risk factors for MDROs, which can identify the risk factors for MDROs at an early stage and help to identify people at high risk of MDROs infection and take relevant comprehensive treatment in time to slow down the development of the disease.

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Results：A total of 71 strains were isolated from the MDROs-positive group, with the top three being Staphylococcus aureus (46.48%), Escherichia coli (22.53%), and Pseudomonas aeruginosa (18.31%), respectively.Logistic multifactorial regression analysis showed that history of previous antimicrobial exposure, neuroischemic wound, Wagner grade 3-5 , and combined osteomyelitis were associated with Type 2 diabetic foot infection MDROs ($P < 0.05$).

Conclusion：Previous history of antimicrobial exposure, neuroischemic wounds, Wagner grade 3-5, and combined osteomyelitis are independent risk factors for MDROs, which can identify the risk factors for MDROs at an early stage and help to identify people at high risk of MDROs infection and take relevant comprehensive treatment in time to slow down the development of the disease.

Keywords: Diabetic foot,multidrug-resistant bacteria,infection, risk-factors

27

Background

29   Diabetic foot ulcer (DFU) is a common complication of Type 2 diabetes, and approximately

30   10%-25% of people with diabetes will develop DFU over the course of their lifetime(Zubair &

31   Ahmad, 2019).DFU can cause serious health problems, diminish patients' quality of life, and

32   increase the incidence of infections among diabetics, imposing a significant social, psychological,

33   and economic burden on patients and the health care system(Raspovic & Wukich, 2014; Armstrong

34   et al., 2017).The greatest barrier to DFU is increased vulnerability to several possible

35   pathogens, which can result in significant effects such as infection, gangrene, osteomyelitis,

36   amputation, and even death.(Hitam et al., 2019).

37   DFU infections are primarily microbial infections, and many of the complications of DFU

38   are caused by bacterial infections(Hawkins et al., 2022); thus, DFU can be reduced through early

39   and appropriate intervention, as well as glycemic control. Early detection of specific pathogens

40   and their bacterial susceptibility drug sensitivity results allow for early antibiotic treatment.

41   Furthermore, because the susceptibility of different bacteria to the same drug varies and bacterial

42   resistance shows different trends depending on the time of drug administration and geographic

43   area, the clinic must still adjust the drug regimen and prevent antibiotic misuse through drug

44   sensitivity identification.

45   Multidrug-resistant organisms (MDROs) are common pathogens in patients with DFU

46   infection(Kandemir et al., 2007; Adeyemo et al., 2021),The situation of MDROs has deteriorated

47   in recent years as a result of excessive use of clinical antibiotics, and the problem of multidrug-

48   resistant bacteria in DFU patients infected with pathogens is particularly serious. As a result, the

49   correct and reasonable application of antibiotics is the key to improve the cure rate of diabetic

50   foot infection, reduce the incidence of adverse reactions and reduce the occurrence of bacterial

51   resistance. Due to the rising occurrence of MDROs and the importance of early and effective

52   antimicrobial therapy, current national guidelines recommend the use of broad-spectrum

53   antibiotics as an empirical treatment in patients with moderate to severe DFU(Lipsky et al.,

54   2012).Given that the risk of MDROs infection is increasing year after year, combined with the

55   complex and variable strain resistance, the infection is difficult to control, treatment costs are

56   high, the amputation rate and mortality rate are increasing, reducing treatment effectiveness and

57   quality of life in DFU patients.In order to reduce the occurrence of infections caused by drug-

58   resistant bacteria and improve patient prognosis, numerous studies have reported risk factors for

59   infections in MDROs in patients with DFU(Noor et al., 2017; Saltoglu et al., 2018; Datta et

60   al., 2019; Pessoa et al., 2020; Matta-Gutierrez et al., 2021; Liu et al., 2022).In recent years,

61   with the increase of studies related to MDROs infection in DFU patients, more and more

62   attention has been paid to the related risk factors, but due to the interference of relevant factors

63   such as sample size, study population, and different geographical areas, the conclusions reached

64   are inconsistent and sometimes even contradictory, leading to a decrease in the strength and

65   credibility of the study(Dai et al., 2020). The aim of this study was to pool and analyze the

66   traumatic bacterial cultures of DFU patients in our hospital in recent years and the antimicrobial

67   susceptibility drugs of these bacterial isolates in order to understand the relationship between

68   MDROs infections and DFU patients in our region. An attempt was made to identify risk factors

69   associated with MDROs infections in DFU patients in our region for early treatment with

70   appropriate antibiotics.

71   **Data and methods**

72   **Data**

73   A total of 147 patients with Type 2 diabetic foot were selected from the Diabetic Foot

74   Treatment Center of Fuyang People's Hospital from January 2018 to December 2021 with

75   complete clinical cases and follow-up data, including 93 males and 54 females, aged

76   62.62±11.71 years.Diabetes course 12.13±6.90 years; All cases met the criteria of the

77   International Diabetic Foot Task Force and the relevant diagnosis of diabetic foot of the

78   American Society of Infectious Diseases. The diagnostic criteria for diabetic foot infections were

79   the 2012 Special Guidelines of the International   Diabetic Foot Working Group on the

80   treatment of diabetic foot infections(Lipsky et al., 2012).

81   The Wagner grading scale was used to grade the diabetic foot in this study: 0: risk factors

82   for the development of foot ulcers but no current ulcers Grade 1:superficial foot ulcers without

83   signs of infection, penetrating the superficial or total skin layer; grade 2:ulcers deep to the

84   ligaments, tendons, joint capsule, or deep fascia, without abscess or osteomyelitis; grade 3:ulcers

85   deep to the ligaments, tendons, joint capsule, or deep fascia, with abscess, osteomyelitis, or

86   sepsis; Grade 4: ischemic gangrene (toe, heel, or forefoot dorsum) usually combined with

87   neuropathy; Grade 5: total foot gangrene(Monteiro-Soares et al., 2020).

88   Inclusion criteria: (1) Clinically confirmed Type 2 diabetic foot ulcer; (2) Complete clinical

89   cases and follow-up data;(3)Patients with positive bacterial culture. Exclusion criteria: (1)

90   patients with type 1 diabetes mellitus; (2) Foot ulcers caused by other diseases were excluded

91   from the study, such as vasculitis, varicose ulcers, or those wounds caused by specific infections

92   or tumors. (3) Patients taking glucocorticoids for a long time; (4) Incomplete clinical data.

93   **Grouping mode**

94   Patients with MDROs infection were divided to the MDROs infection group based on

95   bacterial culture and drug sensitivity results, whereas the rest of the patients were assigned to the

96   NMDROs infection group. MDROs was defined as acquired non-susceptibility to at least one

97   agent in three or more antimicrobial categories(Magiorakos et al., 2012). If drug-resistant

98   bacteria coexisted with sensitive bacteria in the same patient, the patient was classified as having

99   MDROs.

100   **Index of observations**

101   Clinical data of the patient were collected, including gender, age, blood pressure, diabetes

102   course, glycosylated hemoglobin at admission, cholesterol, triglycerides, inflammatory indicators,

103   ankle-brachial index(ABI), previous antibiotic exposure history, amputation, osteomyelitis,

104   diabetes-related complications, Wagner's grade, and hospitalization of the same ulcer surface > 2

105   times/year. Enter and build database. The two groups were respectively compared to see whether

106   there was statistical significance in the differences of various indicators.

107   **Isolation and identification of specimens**

108   Specimen collection was done after the patient was admitted to the hospital and prior to the

109   administration of antimicrobial drugs. The surrounding skin was disinfected with iodophor

110   before collecting specimens, and the ulcer foci were rinsed with sterile saline. Tissues from

111   infected wounds were collected in sterile test tubes with sterilised cotton swabs at the ulcer's base

112   and sent for analysis within 1 hour. The VITEK 2 Compcact fully automated microbiological

113   analysis system from bioMérieux, France, was used for bacterial identification, and the reagents

114   were Gram-negative and Gram-positive bacteria from bioMérieux's bacterial identification card.

115   The drug sensitivity test results were evaluated using the American Clinical Laboratory

116   Standardisation Institute's (CLSI) standards.

117   **Ethical approval**

118   This clinical study was reviewed and approved by the Ethics Committee of Fuyang People's

119   Hospital (project number :([2022.182]).

120   **Statistical methods**

121   SPSS 25.0 software was used for statistical analysis of the data. Count data were expressed

122   as cases or percentages, and two independent data t-test was used for comparison of two samples;

123   chi-square test was used for comparison of sample rates; univariate analysis with statistical

124   significance was included in multifactor analysis, and unconditional logistic regression model

125   was used for multifactor analysis, and risk factors with $P < 0.05$ in multivariate analysis were

126   independent risk factors. $p < 0.05$ indicated that the comparison of two groups of data had

127   Statistical significance.

128   # Results

129   **Comparison of the general conditions of the two groups of patients**

130   A total of 147 DFU patients meeting the inclusion criteria were collected between the two

131   groups.   There were no statistically significant differences between the two groups in gender,

132   age, duration of diabetes, glycosylated haemoglobin (HbA1c (%)) ,Erythrocyte Sedimentation

133   Rate（ESR）,C-reactive protein (CRP), Procalcitonin(PCT), ABI were not statistically

134   significant ($P > 0.05$). See Table 1.

Pathogenic bacteria distribution in DFU patients

A total of 154 strains of pathogenic bacteria were isolated from 147 DFU patients, and 7 patients were cultured with 2 strains of bacteria in the same culture. Among the 154 pathogenic bacteria, the number of gram-positive bacteria (G+) was 89, accounting for 57.79%, and the number of gram-negative bacteria (G-) was 65, accounting for 42.21%. According to the bacterial culture results of DFU patients, the number of G- cases was significantly lower than that of G+, which was different from the results of previous studies, which may be related to regional differences.(Liu et al., 2022; Wu et al., 2018), and the G- bacteria were dominated by Pseudomonas aeruginosa (13.00%) and Escherichia coli (14.29%), while the G+ bacteria were dominated by Staphylococcus aureus (27.92%).See Table 2 and figure 1.

The detection rate and location of positive MDROs in DFU patients' secretions.

A total of 71 MDROs (48.30%)were isolated in this study, with 33 (46.48%) of Gram-positive bacteria dominated by S. aureus, followed by 2 (2.82%) of S. epidermidis, and 16 (22.53%) of Gram-negative bacteria dominated by Escherichia coli, followed by 13 (18.31%) of Pseudomonas aeruginosa , Klebsiella pneumoniae pneumoniae subspecies 5(7.04%), Citrobacter burgdorferi 1(1.41%), and Acinetobacter baumannii 1 (1.41%).See Table 3 and figure 2.

Resistance of main MDROs to antibiotics

In MDROs, S. aureus was resistant to clindamycin (96.97%), erythromycin (96.97%) and penicillin (96.97%), but S. aureus was sensitive to furantoin, quinuputin-dafoputin, vancomycin and cefoxitin. Pseudomonas aeruginosa were mainly resistant to ciprofloxacin (100%), levofloxacin (76.92%) and ceftazidine (76.92%), but Pseudomonas aeruginosa were sensitive to cefoxitin, linezolid, moxifloxacin, β-lactamase, quinuputin-dafodine, rifampicin, tegacycline and vancomycin. Escherichia coli was mainly sensitive to cotrimoxazole (93.75%), cefuroxime (75%), cefuroxime axetil (75%) and levofloxacin (75%). Escherichia coli was sensitive to tetracycline, tegacycline and vancomycin. The sensitivity rate to vancomycin in MDROs was 100%.See Table 4.

Results of a univariate analysis of wound infection in patients with diabetic foot.

162   In the univariate analysis of risk factors for the occurrence of MDROs infection, nine

163   possible risk factors were analyzed univariately, of which five factors, including history of

164   previous antimicrobial exposure, hospitalization for the same infected wound >2 times/year,

165   neuroischemic wound, Wagner classification, and combined osteomyelitis, constituted multiple

166   drug resistance risk factors. See Table 5

167   **Multifactorial analysis of risk factors for the occurrence of MDROs infection.**

168   Multifactorial logistic regression analysis revealed that the occurrence of MDROs in DFU

169   patients was associated with previous antimicrobial exposure, duration of exposure,

170   neuroischemic wounds, and osteomyelitis; it was not associated with more than 2

171   hospitalizations/year for the same infected wound. See Table 6.

172   **Discussion**

173   Today, Type 2 diabetes is a worldwide epidemic affecting about 400 million people, or

174   approximately 10 of the world's population(Li et al., 2018), and DFU is a common and serious

175   complication in people with Type 2 diabetes, with DFU occurring in about 6.3% (5.4% -7.3%) of

176   people with Type 2 diabetes(Zhang et al., 2017), with a prevalence of more than 15% in some

177   developed countries (USA)(Menke et al., 2015; Nelson et al., 2018).DFU is one of the most

178   significant and expensive complications in Type 2 diabetics.It is predicted that the incidence of

179   DFU in diabetic foot patients will increase year by year and even reach 50%(Hurlow et al.,

180   2018).   MDROs is a common pathogen in DFU, and MDROs can lead to DFU aggravation,

181   while improper treatment of DUF can easily cause MDROs, thus forming a vicious cycle. In

182   recent years, with the abuse and misuse of antibiotics, bacterial resistance has become more and

183   more serious, especially the problem of Type 2 diabetic foot infection caused by MDROs.   The

184   correct and reasonable application of antibiotics is the key to improve the efficacy of diabetic

185   foot infection, reduce the incidence of adverse reactions and reduce the occurrence of bacterial

186   resistance.

187   In the present study, G+ were predominantly Staphylococcus aureus (46.48%) and G-

188   bacteria were predominantly Escherichia coli (22.53%) and Pseudomonas aeruginosa (18.31%)

189   in the MDROs of DFU inpatients, which is the same as the recent data reported nationally and

190   internationally(Du F et al., 2022; Atlaw et al., 2022).

191   In this study, the number of G+ was slightly higher than that of G-(G+89 strains, G-65

192   strains), but some studies showed that the proportion of G- in the bacterial culture of DFU

193   patients gradually increased(Ma et al., 2021), which may be related to the widespread use of

194   broad-spectrum antibacterial drugs, particularly third-generation cephalosporins, in recent years,

195   because the antibacterial spectrum of third-generation cephalosporins primarily targets G-.It has

196   been shown that G- infections are positively associated with amputation and negatively

197   associated with DFU healing(de Vries et al., 2014). Therefore, special attention should be paid

198   to infections caused by G- in patients with DFU.Furthermore, Logistics analysis revealed that

199   previous antimicrobial exposure, neuroischemic wounds, Wagner grade 3-5, and combined

200   osteomyelitis were the most important independent risk factors for MDROs infections. This

201   study shows that the history of antibacterial drug exposure is a risk factor for multiple drug

202   resistance. Repeated use of multiple antimicrobials for a long time can easily induce mutation of

203   drug resistance genes, and drug resistance genes can form a complex of multi-drug resistance

204   genes through the transfer of drug resistance gene elements, resulting in the emergence of multi-

205   drug resistance. The function of the defense mechanism of the autoimmune immune system of

206   diabetic patients is weakened compared with that of normal people, so diabetic patients are prone

207   to concurrent infection, which is not easy to control. In clinical practice, broad-spectrum

208   antibiotics are often used to control infection, and long-term application of broad-spectrum

209   antibiotics is likely to cause bacterial imbalance and increase drug resistance (Xia et al., 2021),

210   which will not only prolong the treatment time, but also prolong the treatment time. It will also

211   limit the use of multiple antibiotics, greatly increasing the difficulty of treatment, and have to use

212   higher levels of antibiotics to treat infections, and over time, the formation of a vicious cycle.

213   ERTUGRUL et al.(Ertugrul et al., 2012) found that a history of antibiotic exposure within 30

214   days was associated with a four-fold increase in MDROs infection. Therefore, in clinical work,

215   antibiotics should be used rationally and the importance of standardized diagnosis and treatment

216   should be emphasized to patients to reduce the increase of the risk of drug resistance caused by

217   improper drug use. Studies have shown that the incidence of infection in hospitalized patients

218   with Type 2 diabetic foot is between 9.68% and 11.25%(Zhou et al., 2021).

219   This study also shows that the frequency of hospitalization for the same infected wound is

220   also a risk factor for MDROs, suggesting that MDROs are more likely to develop infection in

221   hospital. For patients with the same ulcer surface repeatedly hospitalized, due to repeated

222   infection, wound debridement and other operations, the possibility of cross-infection of ulcers

223   will be increased. After antibacterial treatment, some drug-resistant bacteria may occur on the

224   same ulcer surface, and cross-infection will promote the growth of drug-resistant bacteria.

225   Studies have confirmed that the incidence of hospital-associated MDROs infection can reach

226   67%, and compared with community-associated MDROs infection, hospital-associated MDROs

227   infection is more adverse to patient prognosis and treatment outcomes (Wang et al., 2010). A

228   history of antimicrobial exposure increases the risk of exposure to MDROs, which can cause

229   iatrogenic infections when nursing or touching patients. This suggests that in addition to rational

230   use of antibiotics, aseptic operation, hand hygiene and other links should be strictly controlled to

231   reduce cross infection between different patients.

232   Some studies have found that nerve defect wound is a risk factor for MDROs infection,

233   which is consistent with the results of this survey(Laakso et al., 2017; Datta et al., 2019;

234   Lazaro-Martinez et al., 2022). Amin et al. found that DFU patients with nerve ischemic wounds

235   had a 7-fold increased risk of MDROs infection

236   (Amin & Doupis, 2016).Neuroischemic wounds, in contrast to ordinary wounds, are frequently

237   characterised by vascular (including microvascular and macrovascular) circulation disorders and

238   neuropathy(Khanolkar et al., 2008), and blood perfusion at the ulcer site is obstructed, making it

239   difficult for antimicrobial drugs to reach the lesion site, resulting in a decrease in the

240   concentration of local antimicrobial drugs and a consequent weakening of the antimicrobial

241   effect, easily inducing the generation of drug-resistant bacteria.Furthermore, ischemic nerve

242   wounds frequently have reduced leukocyte phagocytosis function and abnormal expression of

243 cytokines and inflammatory factors, increasing the difficulty of wound healing and increasing

244 the chance of wound repeated infection(Zhang et al., 2014), so that patients for the same wound

245 repeated visits, followed by longer and higher intensity of antibacterial drugs, so that in the past,

246 It also comes at the cost of increasing the number of drug-resistant bacteria.

247   The Wagner grade was also discovered to be a risk factor for MDROs in this investigation.

248 Studies have shown that the higher the Wagner grade, the more severe the degree of tissue

249 destruction, infection, and ischemia of patients is, and the probability of pathogenic bacteria

250 spreading deep is increased (Xie et al., 2017), making bacteria removal difficult and prolonging

251 treatment time. Exposing the wound to the multidrug-resistant bacteria-prone milieu of the

252 hospital increases the likelihood of MDROs infection in patients (McComb, 2023). Simultaneously,

253 the bacterial composition of the wounds of patients with mixed infections was complicated,

254 which increased the synergistic action and lethality of the bacteria and boosted the level of

255 medication resistance.

256   Concurrent osteomyelitis has recently been identified as an independent risk factor for

257 MDROs infection.(Feng et al., 2013; Garcia et al., 2020; Yan et al., 2022).The results of the

258 present study also showed that osteomyelitis can increase the risk of MDROs infection.Patients

259 with osteomyelitis are more difficult to treat clinically because bacteria are usually able to invade

260 the reticular structure of the bone cell space and evade debridement and antibiotic action(Ji et

261 al., 2014; de Mesy et al., 2018; Masters et al., 2019). In addition, these bacterial colonies can

262 form abscesses in the skin, which act as a physical barrier and prevent immune cells from

263 entering and killing the bacteria, allowing them to survive for a long time, thus inducing MDROs

264 infection. At present, long-term conservative antimicrobial therapy is still the main treatment for

265 osteomyelitis, which induces MDROs. Therefore, when DFU patients are accompanied by

266 osteomyelitis, the use of antibiotics should be appropriately reduced, and the use of bacteria-

267 sensitive antibiotics can avoid the occurrence of MDROs(Lipsky & Uckay, 2021).

268 **Conclusion**

269   To summarise,Previous antibiotic exposure,nerve ischemia wound, Wagner grade, and

270   osteomyelitis were the most relevant independent risk variables for MDROs infection in this

271   investigation. As a result, medical staff should pay attention to key risk factors when patients are

272   admitted, which can assist us to identify high-risk groups of MDROs early and implement

273   appropriate treatment measures as soon as possible, reducing the occurrence of MDROs

274   infection. Furthermore, DFU can infect one or more diseases and generate a significant number

275   of MDROs. Because drug resistance is increasing year after year, it is critical to perform

276   bacterial biological analysis and drug sensitivity testing before utilising antibacterial medications.

Limitations

278   Although our study contributed to the identification of medicines that should be taken

279   frequently following bacterial infection in DFU patients in our location, it has several drawbacks.

280   Firstly, the study's sample was drawn from a tertiary care institution, and the sample size was

281   tiny. is not a complete representation of all Chinese DFU sufferers;Secondly, because the

282   collection time node of patients' wound secretions and relevant clinical data is the day of

283   admission, it is impossible to determine whether patients were infected with MDROs prior to

284   admission, so it is unclear whether some factors are the cause of MDROs infection or the

285   outcome caused by MDROs infection. Furthermore, cross-sectional studies lack the power to

286   demonstrate causality between factors, hence prospective cohort studies are required for

287   additional evidence.

Author contributions

289   Huihui Guo and Qiwei Song have the same contribution.

290   Junjie Li and Tao Ning are co-corresponding authors.

291   Huihui Guo is responsible for writing the thesis; Huihui Guo and Qiwei Song are responsible for

292   the main operation; Tao Ning puts forward the research idea of this chapter; Siwei Mei and

293   Zhengqiang Xue is responsible for collecting and processing data; Junjie Li put forward a lot of

294   suggestions for the later article modification and the places to be improved.

Conflict of interest

There is no conflict of interest.

Consent for publication

The author(s) read and approved the final manuscript.

Availability of data and materials

All the data were from Fuyang People's Hospital, and the data were true and legally liable.

Data availability

321   Data are available. All data used in the study have been uploaded.

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464

Table 1(on next page)

Comparison of general clinical data between the two groups of patients.

Comparison of general clinical data between the two groups of patients.

1 **Table 1**

2 Comparison of general clinical data between the two groups of patients.

Index		MDROs Group （n=71）	NMDROs Group(n=76)	Statistics	P Value
Gender	Male	42	51	χ^2=0.793	0.373
	Female	29	25		
Age		64.60±11.25	62.00±11.45	t=1.354	0.181
Hospital stays (days)		12.42±7.35	11.68±6.21	t=0.757	0.452
HbA1c（%）		8.83±1.96	8.52±1.64	t=1.038	0.303
Systolic pressure		144.87±19.54	143.55±18.81	t=0.378	0.706
Diastolic pressure		83.4±10.77	82.31±12.93	t=0.578	0.565
Cholesterol(mmol/L)		4.62±1.26	4.22±1.59	t=1.642	0.105
TG(mmol/L)		1.40±0.59	1.34±0.71	t=0.585	0.561
ESR(mm/h)		65.04±24.75	60.12±28.62	t=1.250	0.215
CRP(mg/L)		40.34±17.76	36.65±22.20	t=1.191	0.238
PCT(pg/ml)		260.20±48.53	245.62±44.63	t=1.862	0.067
ABI		0.75±0.28	0.82±0.29	t=1.834	0.071

3 Abbreviations:

4 HbA1c:Hemoglobin A1c;CHO:Cholestero;TG ;Triglyceride;TG:Triglyceride;ESR:Erythrocyte Sedimentation

5 Rate;CRP:C-reactive protein, PCT:Procalcitonin;ABI:Ankle-Brachial Index.

6 *P < 0.05 indicated statistically significant difference.

7

Table 2(on next page)

Distribution of pathogenic bacteria in patients with DFU.

Distribution of pathogenic bacteria in patients with DFU.

1 **Table 2**

2 Distribution of pathogenic bacteria in patients with DFU.

3

Bacteria	MDROs Group(n=71)	NMDROs Group(n=76)	Total	Percentage （%）
Gram-positive bacteria				
Staphylococcus aureus	33	10	43	27.92
Other Staphylococcus	2	6	8	5.19
Enterococcus	0	8	8	5.19
Streptococcus	0	11	11	7.14
Others	0	19	19	12.33
Gram-negative bacteria				
Pseudomonas aeruginosa	13	7	20	13.00
Klebsiella pneumoniae	5	5	10	6.50
E. coli	16	6	22	14.29
Enterobacteriaceae	0	3	3	1.95
Aspergillus singularis	0	6	6	3.89
Others	2	2	4	2.60
Total	71	83	154	100

Table 3(on next page)

Distribution characteristics of MDROs

Distribution characteristics of MDROs

1 **Table 3**

2

Distribution characteristics of MDROs		
Bacteria	Frequency	Percentage（%）
Staphylococcus aureus	33	46.48
E. coli	16	22.53
Pseudomonas aeruginosa	13	18.31
Klebsiella pneumoniae subspecies	5	7.04
Staphylococcus epidermidis	2	2.82
Citrobacter brucei	1	1.41
Acinetobacter baumannii	1	1.41
Total	71	100

3

Table 4(on next page)

Drug resistance rate of main MDROs to antibiotics in patients with DFU and positive secretion.

Drug resistance rate of main MDROs to antibiotics in patients with DFU and positive secretion.

1   **Table 4**

2   Drug resistance rate of main MDROs to antibiotics in patients with DFU and positive secretion.

Antibacterial drugs	Staphylococcus aureus（n=33）		Pseudomonas aeruginosa（n=13）		E. coli（n=16）	
	Frequency	Percentage（%）	Frequency	Percentage（%）	Frequency	Percentage（%）
Ciprofloxacin	8	24.24	13	100	1	6.25
Clindamycin	32	96.97	3	23.08	-	-
Erythromycin	32	96.97	3	23.08	-	-
Cefoxitin	2	6.06	0	0	6	37.50
Inducible clindamycin resistance	22	66.67	3	23.08	-	-
Linezolid	1	3.03	0	0	-	-
Levofloxacin	8	24.24	10	76.92	12	75
Moxifloxacin	1	3.03	0	0	-	-
Furantoin	0	0	6	46.15	1	6.25
Benzocillin	31	93.94	3	23.08	-	-
β-lactamase	1	3.03	0	0	-	-
Penicillin	32	96.97	3	23.08	-	-
Quinupristin-Dafopristin	0	0	0	0	-	-
Rifampin	1	3.03	0	0	-	-
Cotrimoxazole	7	21.21	1	7.69	15	93.75
Tetracycline	13	39.39	3	23.08	0	0
Tigecycline	1	3.03	0	0	0	0
Vancomycin	0	0	0	0	-	-
Ceftazidime	-	-	10	76.92	11	68.75
Ceftriaxone	-	-	6	46.15	17	106.25
Cefuroxime	-	-	-	-	12	75
Cefepime	-	-	1	7.69	9	56.25
Cefoxitin	0	0	-	-	1	6.25
Imipenem	-	-	1	7.69	0	0
Cefoperazone / Sulbactam	-	-	0	0	2	12.50
Piperacillin-tazobactam	-	-	1	7.69	1	6.25
Amoxicillin-rod acid	-	-	-	-	6	37.50
Amikacin	-	-	-	-	2	12.50
Ampicillin	-	-	6	46.15	6	37.50
Aminotransol	-	-	-	-	5	31.25
Cefotetan	-	-	5	38.46	0	0
Cefazolin	-	-	6	46.15	6	37.50

Tobramycin	-	-	0	0	6	37.50
Ampicillin-Sulbactam	-	-	6	46.15	6	37.50
Polymyxin E	-	-	0	0	-	-
Meropenem	-	-	0	0	-	-
Ticarcillin-rod acid	-	-	4	30.77	-	-

3   Note: "-" means not measured.

4

Table 5(on next page)

Univariate analysis of risk factors for the infection of MDROs.

1 **Table 5**.

2   Univariate analysis of risk factors for the infection of MDROs.

3

Exposure factor	MDROs Group (n=71)		NMDRO Group (n=83)		OR-value	95% CI	P-value
	+	-	+	-			
Previous antimicrobial exposure	63	8	35	41	8.944	(2.349,34.049)	0.001
Combined osteomyelitis	51	20	14	62	4.140	(1.219,14.064)	0.023
Concomitant neuropathy	60	11	55	21	0.297	(0.078,1.122)	0.073
Concomitant retinopathy	20	51	21	55	2.141	(0.612,7.484)	0.233
Complicated nephropathy	32	41	31	45	0.468	(0.135,1.623)	0.232
The same infected wound >2 times per year	19	52	18	58	0,143	(0.030,0.682)	0.015
Whether to amputate toe/limb	16	55	10	66	2.746	(0.642,11.744)	0.173
Wanger grade 3-5	50	21	27	49	0.157	(0.030,0.808)	0.027
Ischemic nerve wound	48	23	25	51	36.790	(8.386,161.395)	0.000

Table 6(on next page)

Multivariate Logistic regression analysis for the infection of MDROs.

Multivariate Logistic regression analysis for the infection of MDROs.

1 **Table 6**

2 <div align="center">Multivariate Logistic regression analysis for the infection of MDROs.</div>

Selected variable	β	SE	Wald	P-value	OR(95% CI)
Previous antimicrobial exposure	1.925	0.606	10.085	0.001	6.853(2.090,22.477)
Combined osteomyelitis	1.294	0.577	5.030	0.025	3.649(1.177,11.311)
Wanger grade 3-5	1.708	0.777	4.833	0.028	0.181(0.040,0.831)
Ischemic nerve wound	3.074	0.659	21.762	0.000	21.629(5.945,78.697)
The same infected wound >2 times per year	1.288	0.681	3.579	0.059	0.276(0.073,1.047)

3

4

Figure 1

Figuer1 Distribution of pathogenic bacteria in DFU patients

A:Bacterial distribution;B:G+ bacterial distribution;C:G- bacterial distribution.
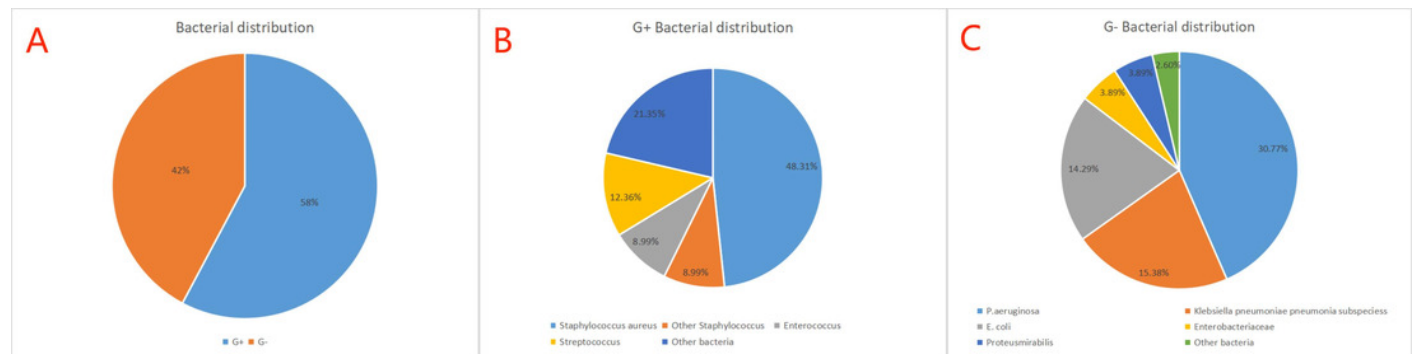
Figure 2

Figuer2 Bacteria distribution of MDROS.

Bacteria distribution of MDROS.