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# Influence of multidrug resistant organisms on the outcome of diabetic foot infection

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ABSTRACT

*Objectives:* We described the clinical outcomes of the diabetic patients who had foot infections with multidrug resistant organisms.
*Methods:* We included the patients with diabetic foot infections (DFI) from 19 centers, between May 2011 and December 2015. Infection was defined according to IDSA DFI guidelines. Patients with severe infection, complicated moderate infection were hospitalized. The patients were followed-up for 6 months after discharge.
*Results:* In total, 791 patients with DFI were included, 531(67%) were male, median age was 62 (19–90). Severe infection was diagnosed in 85 (11%) patients. Osteomyelitis was diagnosed in 291(36.8%) patients. 536 microorganisms were isolated, the most common microorganisms were *S. aureus* (20%), *P. aeruginosa* (19%) and *E. coli* (12%). Methicillin resistance (MR) rate among *Staphylococcus aureus* isolates was 31%. Multidrug resistant bacteria were detected in 21% of *P. aeruginosa* isolates. ESBL (+) Gram negative bacteria (GNB) was detected in 38% of *E. coli* and Klebsiella isolates. Sixty three patients (8%) were re-hospitalized. Of the 791 patiens, 127 (16%) had major amputation, and 24 (3%) patients died. In multivariate analysis, significant predictors for fatality were; dialysis (OR: 8.3, CI: 1.82–38.15, p = 0.006),

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isolation of Klebsiella spp. (OR:7.7, CI: 1.24–47.96, p = 0.028), and chronic heart failure (OR: 3, CI: 1.01–9.04, p = 0.05). MR Staphylococcus was detected in 21% of the rehospitalized patients, as the most common microorganism ($p < 0.001$).

*Conclusion:* Among rehospitalized patients, methicillin resistant *Staphylococcus* infections was detected as the most common agent, and *Klebsiella* spp. infections were found to be significantly associated with fatality.



## Introduction

Diabetic foot infections (DFI) cause significant health problems, reduce the patients' quality of life, cause lower limb amputation, increase morbidity (Raspovic and Wukich, 2014; Crouzet et al., 2011), and increase the cost of health services (Prompers et al., 2008; Eckman et al., 1995). DFI frequently require hospitalization of patients, and could lead to death. Lavery et al. reported that the risk of hospitalization among the patients with DFI was 56 times and the risk of amputation was 155 times higher than non-diabetics (Lavery et al., 2006).

The most common microorganisms isolated from patients with DFI were reported as *Staphylococcus aureus*, *Pseudomonas aeruginosa, Escherichia coli, Streptococcus* spp., *Enterococcus* spp., *Proteus mirabilis* and anaerobes (Lipsky et al., 2004). Detection of the etiologic agent has a crucial role in effective treatment, avoiding amputation (Karchmer and Gibbons, 1994) and also prevention of dissemination of the infection. In recent years, few guidelines regarding the management of DFI were published (Lavery et al., 2007; Pinzur et al., 2005; Lipsky et al., 2016; Lipsky et al., 2012). These guidelines helped to improve the management of diabetic foot infections; however, they may not cover the epidemiologic differences and details regarding antibiotic resistance (Crouzet et al., 2011; Saltoglu et al., 2015a). In this multicenter observational study, we aimed to describe the epidemiological characteristics, resistant organisms, and their impact on the outcomes of patients with DFI.

## Methods

The study was performed by the DFI Study Group of the Turkish Society of Clinical Microbiology and Infectious Diseases (KLIMIK), patients with DFI from 19 centers were included between May 2011 and December 2015. Diabetic foot infection was diagnosed by a trained infectious diseases physician, and DFI severity score was grouped as mild, moderate or severe following the guidelines of the Infectious Diseases Society of America (IDSA) (11). Specimens were obtained using wound curettage after debridement, needle aspiration of purulent material, or tissue biyopsy and/or bone biopsy. Swabbing of the wound was not allowed in order to avoid contamination. Standart Clinical Laboratory methods were used for identification of the microorganism. Multidrug resistance (MDR) was defined as the resistance to 3 ≥ different antimicrobial classes, except Stapyhlococcus infections. All patients with severe infection, and selected patients with a moderate infection with complicating features were hospitalized. Each patient was followed-up, and re-hospitalization or treatment failure were recorded. The Ethical Committee of Istanbul University, Cerrahpasa Medical Faculty approved the study (3 May 2011,G-08).

### *Statistical analysis*

For comparison of continuous variables, non-parametric Kruskal-Wallis test, and for categorical variables, chi square test was performed. Multivariate analysis was performed for the predictors of the fatality. The significant independent variables in univariate analysis were included to the multivariate analysis. Statistical significance was set as $p < 0.05$, and STATA (version 11, USA) was used.

## Results

We included 791 patients, 531 (67,1%) were male, median age was 62 (19–90) years. In total 536 microorganisms were isolated, and 282 were monomicrobial (52%). The case fatality rate was significantly higher among the patients with polymicrobial infections (13% vs 2.3%). A total of 412 (52%) patients had moderate skin soft tissue infection (SSTI), and 85 (11%) patients had severe SST infection according to the IDSA DFI clasification. Osteomyelitis was diagnosed in 291 (37%) patients. In 344 (43.5%) patients, erythrocyte sedimentation rate was >70 mm/h, in 371 patients (47%) CRP level was greater than 20 fold, in 208 (26%) patients leukocyte count was >10.000/mm$^3$ (Table 1). The majority of the patients in this study were hospitalized (92.5%). The median day of hospitalization was 21 (3–170), and the median follow up time after discharge of the patients was 60 days.

A total of 536 microorganisms were isolated from 791 patients, in 282 of them, infection was monomicrobial. Gram negative

**Table 1**
Characteristics of the patients with DFI.

| Patients (N = 791) | n (%) |
|---|---|
| Demographic | |
| Male gender | 531 (67) |
| Mean age (SD; min-max) | 62 (11; 19–90) |
| Median year of diabetes (Interquartiles) | 15 (10–20) |
| Insulin use | 606 (77) |
| History | |
| Hypertension | 462 (58) |
| Renal failure | 229 (29) |
| Coronary artery disease | 196 (25) |
| Retinopathy | 174 (22) |
| Amputation | 177 (22) |
| Vascular surgery | 117 (15) |
| Dialysis | 75 (9) |
| Previously hospitalization with DFI (in 3 months) | 442 (56) |
| Previously DFI (in 3 months) | 362 (46) |
| Previously antibiotic use against DFI (in 1 month) | 414 (52) |
| Clinical and laboratory findings | |
| HbA1c level | 8,9 |
| CRP (median, IQR) | 16 (6–71) |
| ESR (median, IQR) | 74 (50–98) |
| Leukocyte (median, IQR) | 10,000 (8,000–10,000) |
| IDSA Infection- moderate | 412 (52) |
| IDSA Infection -severe | 85 (11) |
| Osteomyelitis | 291 (37) |
| Hospitalization days (median, IQR) | 21 (14–30) |
| Outcome | |
| Re-hospitalization within 1 month | 63 (8) |
| Major amputation | 127 (16) |
| Fatality | 24 (3) |

*DFI, diabetic foot infection.

bacteria (GNB) were isolated in 301 (56,1%) cultures. The most common isolated microorganisms were *S. aureus* (20%), *P. aeruginosa* (19%) and *E. coli* (12%) (Figure 1). Methicillin resistance rate among *Staphylococcus aureus* isolates was 31%, and it was 79% among coagulase negative *Staphylococcus*. Fourteen out of 33 (42%) were isolated on initial hospitalization. Multidrug resistant (MDR) *P. aeruginosa* was detected in 21/99 (21%) isolates. ESBL producing GNB were detected in 32 (38%) isolates of *E. coli* (27/65) and *Klebsiella pneumonia* (5/19) (Figure 1). Rehospitalization within one month among the patients with known bacteriologic agents is shown Table 2.

Sixty three patients (8%) were rehospitalized due to DFI after discharge from the hospital. MRS including MRSA was detected in 21% of the rehospitalized patients, as the most common microorganism ($p < 0.001$). Of the 791 patiens, 127/791 (16%) had major amputation, and 24 patients (3%) died. In multivariate analysis, significant predictors for overall mortality were dialysis (OR: 8.3, CI: 1.82–38.15, $p = 0.006$), isolation of Klebsiella spp. (OR:7,7, CI: 1.24–47.96, $p = 0.028$) and chronic heart failure (OR: 3, CI: 1.01–9.04, $p = 0.05$) (Table 3). Area under the receiver operating curve was 80%.

**Table 2**
Rehospitalization within one month among the patients with known bacteriologic agents.

| | Rehospitalization n = 38 | P | Fatality n = 24 | p |
|---|---|---|---|---|
| *S. aureus* (n = 107) | 12 (11) | 0.445 | 0.445 | 0.303 |
| MRS (n = 67) | 14 (21) | <**0.001** | **0.344** | 0.338 |
| *Enterococcus* spp. (n = 64) | 8 (13) | 0.303 | 0.303 | 0.749 |
| *E.coli* (n = 65) | 5 (8) | 0.578 | 0.578 | 0.338 |
| *P.aeruginosa* (n = 99) | 11 (11) | 0.541 | 0.541 | 0.547 |
| *Klebsiella* spp. (n = 19) | 3 (16) | 0.343 | 0.343 | 0.139 |
| ESBL(+) GNB (n = 32) | 4 (11) | 0.553 | 0.553 | 0.108 |

## Discussion

In recent years, the emergence of antibiotic resistant pathogens has made it increasingly difficult to select appropriate empirical antibiotics for the treatment of DFI (Lipsky, 2016). We performed this multi-center observational study including 10 University Hospitals and 9 training and research hospitals in Turkey with a high rate of antibiotic resistance. Although a large number of studies have been conducted to explore the risk factors implicated in the emergence of MDR microorganisms, very few of them have evaluated the influence of such strains on the clinical course or outcome of DFI. In this study, we described the antibiotic resistance and its impact on prognosis.

The most common microorganisms were *S. aureus*, *P. aeruginosa* and *E. coli*. MRSA rate was 31%, and Pseudomonas, MDR rate was 21%, 38% of the isolates were ESBL (+) *E. coli* and *Klebsiella* spp. Among GNB, *Pseudomonas* spp. was predominant and accounted for 33% of the isolated bacteria. Gram positive cocci was reported as the most common pathogenic agent from USA and Europe (Lipsky, 2007; Lipsky et al., 2014; Dang et al., 2003; Aragon-Sanchez et al., 2008), whereas GNB were the most frequently reported pathogenic agents reported from Asian studies (Ramakant et al., 2011), including the studies from Turkey with a similar spectrum bacterial etiology (Saltoglu et al., 2010; Ertugrul et al., 2012; Hatipoglu et al., 2014; Saltoglu et al., 2015b).

In this study, 56% of the patients were hospitalised because of diabetic foot infection within the last three months, while antibiotic use within the last month was 52% and osteomyelitis occurred in 37% of the cases. The risk factors for MDR microorganism in DFI were reported to be prior antibiotic use and duration of antibiotics, prior hospitalisation or prior hospitalisation due to same wound, duration of hospitalisation, and presence of osteomyelitis (Ji et al., 2014; Hartemann-Heurtier et al., 2004; Richard et al., 2008; Kandemir et al., 2007).

In our study, MRSA growth was associated with an increase in rehospitalisation rate but it is to be noted that there was no impact on fatality. While there are conflicting results regarding whether MRSA worsens clinical outcome more than other causative agents of DFI, it is almost unanimously agreed that there is an increase in treatment failure, increase in the time required for ulcer healing and rate of amputations as a result of MRSA infections (Tentolouris et al., 1999; Vardakas et al., 2008).

Uçkay et al. reviewed 48 DFI studies in the literature. They reported further treatment for DFI with MRSA (Zenelaj et al., 2014).

Interestingly, our study revealed a remarkably higher rate of MRSA incidence as compared to the rates reported earlier in

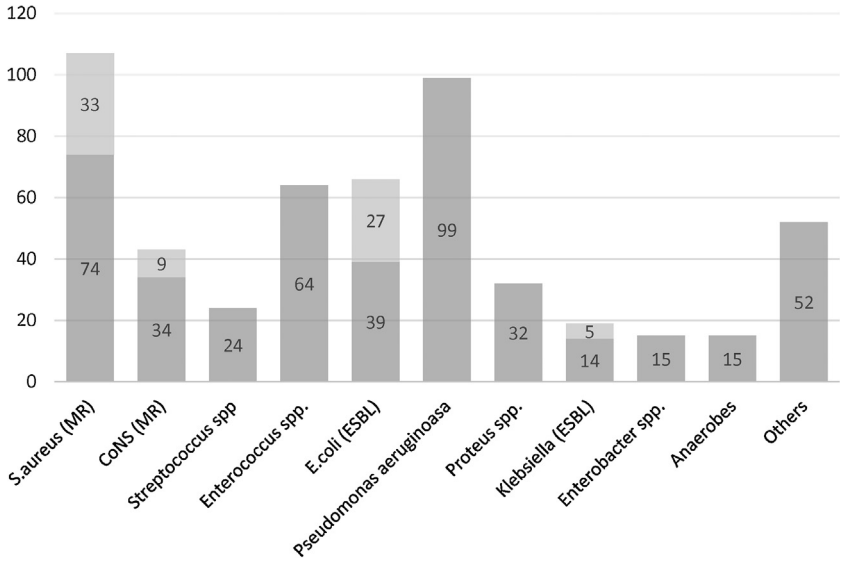


**Figure 1.** Microorganisms isolated from patients with diabetic foot infection. The proportion of methicillin resistant isolates among Staphylococcus spp., and proportion of ESBL producing isolates among Psedumonas aeruginosa.

**Table 3**
Predictors of fatality among the patients with diabetic foot infections.

| | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | OR | CI | P | OR | CI | p |
| Age | 1.01 | 0.98–1.05 | 0.323 | 0.98 | 0.93–1.04 | 0.627 |
| Male gender | 0.97 | 0.41–2.31 | 0.961 | 1.09 | 0.33–3.54 | 0.88 |
| Renal failure | 5.2 | 2.19–12.33 | <**0.001** | 1.01 | 0.21–4.73 | 0.981 |
| Chronic heart disease | 4.5 | 1.96–10.3 | <**0.001** | **3** | 1.01–9.04 | **0.05** |
| Dialysis | 9.2 | 4–21.5 | <**0.001** | **8.3** | 1.82–38.15 | **0.006** |
| Osteomyelitis | 2 | 0.91–4.7 | 0.079 | 1.2 | 0.39–3.78 | 0.727 |
| Methicillin resistant *Staphylococcus* | 1.8 | 0.54–5.61 | 0.344 | 2 | 0.54–8.72 | 0.267 |
| *Pseudomonas aureus* | 1.4 | 0.47–4.11 | 0.549 | 1.7 | 0.51–5.79 | 0.374 |
| *Klebsiella pneumoniae* | 3 | 0.64–14.58 | 0.159 | **7.7** | 1.24–47.96 | **0.028** |
| *Escherichia coli* | 1.8 | 0.54–5.61 | 0.344 | 1.8 | 0.49–6.86 | 0.367 |

similar studies (Ertugrul et al., 2012; Hatipoglu et al., 2014; Saltoglu et al., 2015b). As MRSA rates are known to vary between the centres, there is an urgent need for continuous surveillance and precautions in order to prevent cross contamination.

The rates of ESBL producing microorganisms have been rising steadily over the last few years. In our study, ESBL was detected in a total of 38% of *E. coli* and *Klebsiella* specimens that were isolated from patient samples. In recent years, in the etiology of DFI, VRE, MDR *Pseudomonas*, ESBL-producing *E. coli* and *Klebsiella* as well as MRSA were reported to be increased (Guillameta and Kollef, 2016; Ambrosch et al., 2011).

*Pseudomonas* spp. was the second most commonly isolated pathogens in our study and a certain percentage of the isolated specimens were found to be MDR. These strains are generally known to be a part of the polymicrobial etiology of long-term infections. However, the rate of their incidence is also increasing in the case of monomicrobial complicated infections (Guillameta and Kollef, 2016; Ambrosch et al., 2011).

Studies of outcomes of DFIs caused by multi-resistant pathogens compared with other organisms have produced conflicting results, with some finding no worse outcomes (Dang et al., 2003; Byren et al., 2009), while others have (Gadepalli et al., 2006).

In our multivariate analysis, it was revealed that, apart from known risk factors such as dialysis and heart failure, the presence of *Klebsiella* was also significantly associated with mortality. Tascini et al. have reported that the rectal colonisation of KPC producing *Klebsiella* spp. was a significant risk factor in the case of mortality amongst patients presenting with DFI (Tascini et al., 2015).

Sixty three patients (8%) were rehospitalized due to DFI after discharge from the hospital. MRS was detected in 21% of the rehospitalized patients, as the most common microorganism ($p < 0.001$). *Klebsiella* spp. was identified as one of the risk factors for mortality. Active surveillance regarding prevalence of MDR microorganisms is very crucial for the effective management of DFI as well as choice of effective empirical treatment.

One of the strengths of our study was being a multi-centre observational study with a large number of cases including those that presented with complications. The authors from these centers were highly qualified physicians, who were active members of the study group on diabetic foot infections of the Society. Limitations of the study were lack of obtaining anaerobic cultures in some of the centers and issues related to obtaining bone biopsies. Another limitation was being a retrospective study.

In conclusion, among rehospitalized patients, methicillin resistant *Staphylococcus* infection was detected as the most common agent, and Klebsiella spp. infections were found to be significantly associated with fatality. Chronic heart diseases and the need for dialysis increase the risk of fatality.

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## Ethical approval

The Ethical Committee of Istanbul University, Cerrahpasa Medical Faculty approved the study (3 May 2011,G-08).

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The authors declare that they have noconflict of interest.

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