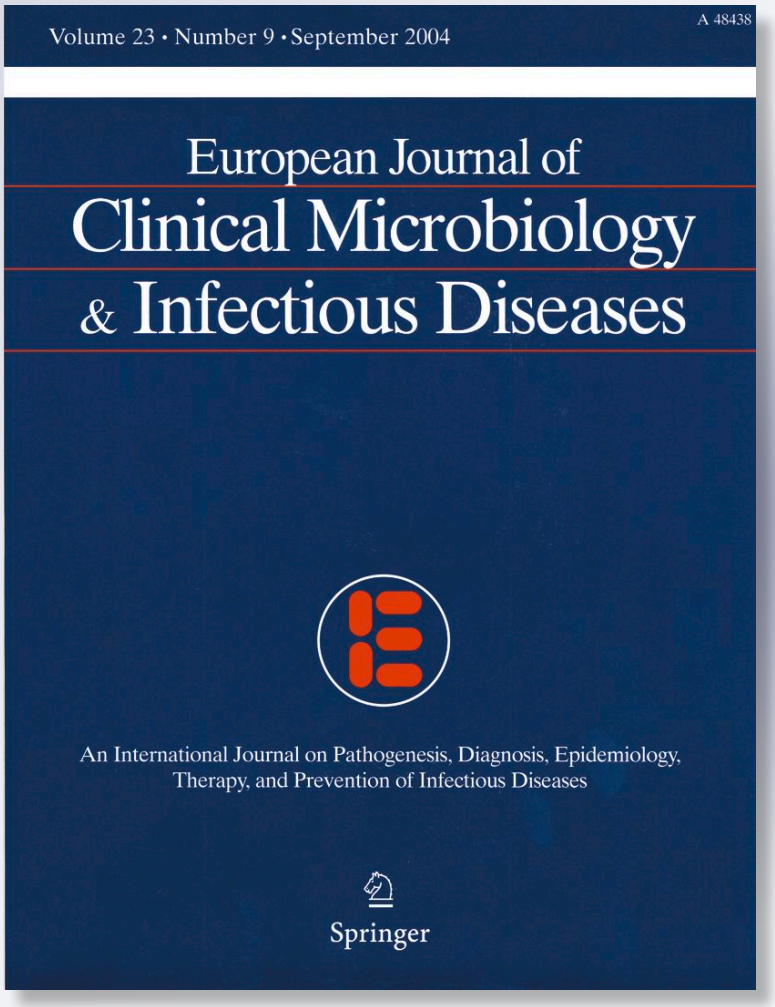
A prospective, multi-center study: factors related to the management of diabetic foot infections

B. M. Ertugrul, O. Oncul, N. Tulek, A. Willke, S. Sacar, O. G. Tunccan, E. Yilmaz, O. Kaya, B. Ozturk, O. Turhan, N. Yapar, M. Ture & F. Akin

European Journal of Clinical Microbiology & Infectious Diseases

ISSN 0934-9723

Eur J Clin Microbiol Infect Dis
DOI 10.1007/s10096-012-1574-1



Springer

Eur J Clin Microbiol Infect Dis
DOI 10.1007/s10096-012-1574-1

ARTICLE

A prospective, multi-center study: factors related to the management of diabetic foot infections

B. M. Ertugrul · O. Oncul · N. Tulek · A. Willke · S. Sacar · O. G. Tunccan · E. Yilmaz · O. Kaya · B. Ozturk · O. Turhan · N. Yapar · M. Ture · F. Akin

Received: 22 September 2011 / Accepted: 28 January 2012

Abstract The Turkish Association of Clinical Microbiology and Infectious Diseases, Diabetic Foot Infections Working Group conducted a prospective study to determine the factors affecting the outcomes of diabetic foot infections. A total of 96 patients were enrolled in the study. Microbiological assessment was performed in 86 patients. A total of 115 causative bacteria were isolated from 71 patients. The most frequently isolated bacterial species was *Pseudomonas aeruginosa* (*n*=21, 18.3%). Among cases with bacterial growth, 37 patients (43%) were infected with 38 (33%) antibiotic-resistant bacteria. The mean (±SD) antibiotics cost was 2,220.42 (±994.59) USD in cases infected with resistant bacteria, while it was 1,206.60 (±1,160.6) USD in patients infected with susceptible bacteria ($p<0.001$). According to the logistic regression analysis, the risk factors related to the growth of resistant bacteria were previous amputation ($p=0.018$, OR=7.229) and

B. M. Ertugrul (✉) · B. Ozturk
School of Medicine, Department of Infectious Diseases and Clinical Microbiology, University of Adnan Menderes, 09100 Aydin, Turkey
e-mail: bertugrul@adu.edu.tr

O. Oncul
Department of Infectious Diseases and Clinical Microbiology, Gulhane Military Medical Academy Haydarpasa Training Hospital, Istanbul, Turkey

N. Tulek
Department of Infectious Diseases and Clinical Microbiology, Ankara Training and Research Hospital, Ankara, Turkey

A. Willke
School of Medicine, Department of Infectious Diseases and Clinical Microbiology, University of Kocaeli, Kocaeli, Turkey

S. Sacar
School of Medicine, Department of Infectious Diseases and Clinical Microbiology, University of Pamukkale, Denizli, Turkey

O. G. Tunccan
School of Medicine, Department of Infectious Diseases and Clinical Microbiology, University of Gazi, Ankara, Turkey

E. Yilmaz
School of Medicine, Department of Infectious Diseases and Clinical Microbiology, University of Bursa, Bursa, Turkey

O. Kaya
School of Medicine, Department of Infectious Diseases and Clinical Microbiology, University of Suleyman Demirel, Isparta, Turkey

O. Turhan
School of Medicine, Department of Infectious Diseases and Clinical Microbiology, University of Akdeniz, Antalya, Turkey

N. Yapar
School of Medicine, Department of Infectious Diseases and Clinical Microbiology, University of Dokuz Eylul, Izmir, Turkey

M. Ture
School of Medicine, Department of Biostatistics, University of Adnan Menderes, Aydin, Turkey

F. Akin
School of Medicine, Department of Endocrinology and Metabolism, University of Pamukkale, Denizli, Turkey

Published online: 22 February 2012

antibiotics administration within the last 30 days (p=0.032, OR=3.796); that related to the development of osteomyelitis was wound size >4.5 cm^2 (p=0.041, OR=2.8); and that related to the failure of the treatment was the growth of resistant bacteria (p=0.016, OR=5.333). Diabetic foot osteomyelitis is usually a chronic infection and requires surgical therapy. Amputation is the accepted form of treatment for osteomyelitis. Limited limb-saving surgery and prolonged antibiotic therapy directed toward the definitive causative bacteria are most appropriate. This may decrease limb loss through amputations. As a result the infections caused by resistant bacteria may lead to a high cost of antibiotherapy, prolonged hospitalization duration, and failure of the treatment.

Introduction

Foot ulcers in diabetic patients are associated with increasing morbidity and are the commonest cause of prolonged outpatient care. In patients with foot ulcer history in the past, developing superficial and/or bone infection, causative agents, antibiotic cost, the therapy success, amputation rates are affected by multiple factors. It is very important for clinicians to know which clinical and laboratory findings at admission are associated with poor outcome in patients with diabetic foot ulcers [1]. This information could help to predict which patients are at highest risk of diabetic foot infections, thereby helping to plan optimally targeted preventative strategies. The clinician treating a patient with a diabetic foot infection must immediately address several issues [2, 3]. Key among these are how broad-spectrum the antibiotic regimen should be and by what route it should be administered, when to request urgent surgical or other specialty consultations, and whether or not hospitalization is required. These decisions will affect the cost of care, the likelihood of adverse events and presumably the clinical outcomes. The most important factor affecting these decisions is the clinical severity of the infection [2, 3]. Unfortunately, clinicians currently have little evidence-based guidance for identifying which patients have a severe diabetic foot infection or which clinical findings are associated with a poor outcome [3].

The Turkish Association of Clinical Microbiology and Infectious Diseases, Diabetic Foot Infections Working Group conducted a prospective study to determine the factors affecting the outcomes of diabetic foot infections and to develop a management program.

Materials and methods

The present study was performed by the Turkish Association of Clinical Microbiology and Infectious Diseases, Diabetic Foot Infections Working Group between 1 March 2010 and 1 March 2011. A total of 10 medical centers were included in this prospective study. Patients were screened for risk factors known to be associated with lower extremity complications (e.g., age, gender, duration of diabetes, previous hospitalization, previous amputation, previous foot infections, previous osteomyelitis, peripheral neuropathy, peripheral vascular disease, antibiotics administration within the last 30 days, wound depth, ulcer localizations). The data of enrolled subjects were recorded on patient follow-up forms. Resistant bacteria, osteomyelitis, duration of hospitalization, amputation, cost-effectiveness of prescribed antibiotics; factors related to the treatment in diabetic foot infections were analyzed. Infection was diagnosed clinically by a trained physician according to International Working Group on the Diabetic Foot (IWGDF) criteria, Perfusion, Extent, Depth, Infection, Sensation (PEDIS) classification [4].

Patients with newly diagnosed diabetic foot pathology, recurrent infection after being totally cured, and history of amputation below the metatarsus were enrolled in the study.

On admission, specimens for culture were obtained following cleansing and the debridement of the wound by swabbing the ulcer base, curettage, needle aspiration or biopsy, depending on the wound depth. The following criteria should be met for the resistant bacteria: methicillin-resistant staphylococcus, betalactam-resistant enterococcus, extended spectrum betalactamase (ESBL), and/or induced betalactamase (IBL)-produced Gram-negative bacteria and resistant bacteria against two or more antibiotics (quinolone and aminoglycoside, betalactam and quinolone, etc.). All centers involved in the study prescribed the antibiotics and determined the duration of the therapy themselves without any intervention.

The diagnosis of osteomyelitis was based on the positivity of any of the following tests; bone biopsy, X-ray, MRI, scintigraphy or the probe-to-bone test. The following criteria should be met for the diagnosis of neuropathy: positive monofilament test result, or neuropathy diagnosed by a neurologist. Body mass index (Quetelet index) was calculated as the weight in kilograms divided by the square of the height. Glycemic control was evaluated with HbA1c. The following criteria should be met for the diagnosis of hypertension: current antihypertensive medication or blood pressure higher than 90/140 mmHg on admission or prescription of antihypertensive medication by a cardiologist on admission to the hospital.

In this study, proportional comparisons for categorical variables were done using the Chi-squared test. Prior to univariate analysis, the Kolmogorov–Smirnov test was used to determine the normal distribution of constant variables. We performed Student's t test for variables with a normal distribution and nonparametric Mann–Whitney U test for variables without a normal distribution. The factors affecting

the development of osteomyelitis, the growth of resistant bacteria, amputation rate, and the failure of the therapy were evaluated by univariate and multivariate logistic regression analyses. For the determination of risk factors affecting the duration of hospitalization, Chi-squared automatic interaction detector (CHAID) analysis was used. The statistical significance was set at a p value of <0.05.

Results

A total of 96 patients were enrolled in the study. Of these, 73 (76%) were male. The mean±SD age was 60.32± 12.96 years, the mean±SD diabetes duration was 15.1± 9.4 years, the median duration of the diabetic foot infection was 29 days, the mean±SD hospitalization duration was 23.8±14.9 days, the mean±SD follow-up period was 33.2± 20.2 days, the mean antibiotics cost was 1,650 USD. Seventy-eight patients were evaluated for osteomyelitis and of these, 48 (61.5%) were diagnosed as osteomyelitis. The demographic characteristics of the patients are shown in Table 1.

Microbiological assessment was performed in 86 patients. A total of 115 causative bacteria were isolated from 71 patients. The cultures remained sterile in 15 patients. The most frequently isolated bacteria were *Pseudomonas aeruginosa* (n=21, 18.3). The others were *Streptococcus* spp. (n=17, 14.8%) and *Staphylococcus aureus* (n=16, 13.9%) respectively (Table 2). Among cases with bacterial growth, 37 patients (43%) were infected with 38 (33%) resistant bacteria. The mean (±SD) antibiotics cost was 2,220.42 (±994.59) USD in cases infected with resistant bacteria while it was 1,206.60 (±1,160.6) USD in cases infected with susceptible bacteria (p<0.001; Fig. 1). The antibiotic costs of infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) and the other multi-drug-resistant bacteria (median=1,889.16 USD and 2,001.66 USD respectively) were higher than the infections caused by susceptible bacteria and the difference was statistically significant (p=0.038 and p<0.001 respectively). There was no significant difference between the antibiotic cost of infections caused by MRSA and those caused by the other multi-drug resistant bacteria (p=0.582)

The most important factor determining the duration of hospitalization was the diagnosis of osteomyelitis (Fig. 2). The mean hospitalization duration was 29.25 days in patients with osteomyelitis while it was 17.7 days in those without osteomyelitis (p<0.001). The most important factor determining the duration of hospitalization in cases without osteomyelitis was the type of surgical procedure. In patients without amputation or other surgical intervention (mean hospitalization stay 11.35 days), the mean hospitalization duration was longer in than the patients who underwent soft tissue debridement (mean hospitalization stay 20.92 days; p< 0.001). The duration of hospitalization due to osteomyelitis

Table 1 Demographic and clinical characteristics of the study subjects

	n (%)
Age mean (±SD) (years)	60.32 ±12.96
Gender (male)	73 (76)
Duration of diabetes (year) median (25–75%)	15 (10 – 20)
Hypertension	54 (56.2)
Smoking	46 (47.9)
Duration of diabetic foot infection (days) median (25–75%)	29 (15–60)
HbA1c median (25–75%)	8 (7—9.5)
Body mass index mean (±SD)	27.97±4.7
Previous hospitalization history	62 (64.6)
Previous foot infection	45 (46.9)
Previous osteomyelitis	20 (20.8)
Previous debridement (soft tissue)	26 (27.1)
Previous amputation	20 (20.8)
Previous vascular surgery	7 (7.3)
Renal failure	9 (9.3)
Antibiotics administration within the last 30 days	75 (78.1)
Peripheral vascular disease	
Grade 1	64 (66.7)
Grade 2	20 (20.8)
Grade 3	12 (12.5)
Wound depth (n=76)	
Grade 1	21(27.6)
Grade 2	48 (63.2)
Grade 3	7 (9.2)
Neuropathy	59 (61.5)
Ulcer localizations (n=76)	
Thumb	14 (18.4)
Other fingers	20 (26.3)
Metatarsal	7 (9.2)
Plantar foot	10 (13.2)
Heel	11 (14.5)
Two or more regions	14 (18.4)
Infection	
Grade 1	1 (1)
Grade 2	39 (40.6)
Grade 3	52 (54.2)
Grade 4	4 (4.2)
Wound size (cm^2) median (25–75%)	5 (2.75–10)
Leukocyte count/mm^3 median (25– 75%)	9,640 (7,290–12,500)
Erythrocyte sedimentation rate mean (±SD)	70±37
C-reactive protein (mg/dL) median (25–75%)	9.3 (2.05–45)
Osteomyelitis (n=78)	48 (61.5)
Resistant bacteria (n=86)	37 (43)
Amputation	23 (24)
Duration of hospitalization mean (±SD) (days)	23.8±14.9
Outcome	
Cured	78 (81.3)
Recurrent infection	10 (10.3)
Need for recurrent surgical treatment	4 (4.2)
Exitus	4 (4.2)

Table 2 Microorganisms isolated from foot infections

Causative bacteria	*n* (%)
Gram-positive aerobic cocci	55 (47.8)
Staphylococcus aureus	16 (13.9)
Methicillin-resistant	8
Multidrug-resistant	2
Coagulase-negative staphylococcus	8 (6.9)
Methicillin-resistant	3
Streptococcus spp.	17 (14.8)
Enterococcus spp.	14 (12.2)
Betalactam-resistant	1
Gram-negative aerobic bacilli	55 (47.8)
Pseudomonas aeruginosa	21(18.4)
IBL[a] positive	8
Escherichia coli	9 (7.8)
ESBL[b] positive	4
Multidrug-resistant	1
Proteus spp.	8 (6.9)
ESBL[b] positive	1
Morganella spp.	8 (6.9)
Multidrug-resistant	3
Klebsiella pneumonia	3 (2.6)
ESBL[b] positive	2
Acinetobacter spp.	3 (2.6)
Multidrug-resistant	3
Enterobacter spp.	3 (2.6)
ESBL[b] positive	2
Other (including anaerobes)	5 (4.4)
Total	115 (100)
Total resistant bacteria	38 (33)

[a] Induced betalactamase

[b] Extended spectrum betalactamase

caused by resistant bacteria was longer than for the susceptible bacteria (~33 days vs. ~23 days, $p=0.025$).

The univariate analysis of the factors affecting the development of osteomyelitis, the growth of resistant bacteria, amputation rate and the failure of the therapy were shown in Table 3. According to the logistic regression analysis, the risk factors related to the growth of resistant bacteria were previous amputation and antibiotic administration within the last 30 days and the risk factor related to the development of osteomyelitis was wound size >4.5 cm^2. The risk factor related to the failure of the treatment was the growth of resistant bacteria (Table 4).

Discussion

The most important aims of diabetic foot infection therapy are patient survival and prevention of limb loss. However, there are few data on which clinical factors present at baseline correlate with the clinical outcome of treatment for these infections [3]. In contrast to the studies in the literature, the etiological role of Gram-positive bacteria, particularly *Staphylococcus aureus* ($n=16$, 13.9%), in this study was relatively small. As a result of this, the rate of MRSA was also low ($n=8$, 7%). One major change in the causative organisms of DFIs in the past 10 years is the increasing frequency of isolation of MRSA [5]. Several studies have found that 30–50% of *S. aureus* isolates from diabetic foot ulcers are methicillin (oxacillin)-resistant [6, 7]. In this study, the most frequently isolated bacteria from diabetic foot infections were *Pseudomonas aeruginosa* (18.4%) and of these, 38% were producing IBL. Lipsky et al. [2] have proposed that Gram-positive bacteria are predominant in acute diabetic foot infections and that chronic infections may involve Gram-negative bacteria and anaerobes. In the present study, 58% of the patients were classified as grades 3 and 4. This result may explain the similar distribution of Gram-positive and Gram-negative isolates. Previous studies performed with similar patient characteristics have also reported increasing frequency of antibiotic-resistant (including extended-spectrum beta-lactamase-producing) Gram-negative organisms, particularly *Pseudomonas* species [8–10].

The present study underlines the high prevalence of resistant bacteria in diabetic foot infection, accounting for 33% of all isolates, which is in accordance with earlier studies [11–13]. Furthermore, recovery of multi-drug resistant isolates in 43% ($n=86$, patients evaluated by microbiological examination) of our patients was a serious concern. In one study of 102 diabetic patients with a foot wound, the significant risk factors for having a multi-drug-resistant diabetic foot pathogen were: previous antibiotic therapy and its duration, frequency of hospitalization for the same wound, duration of hospital stay. and the presence of osteomyelitis[12]. In our study, we found out that amputation history increases the isolation of multi-drug-resistant bacteria 7-fold, while administration of antibiotics within the last 30 days increases this rate 4-fold.

Resistant bacteria infections have been reported to increase hospital stay and cost and, in some cases, to be associated with morbidity or increased death rates [11, 14]. In our study there was a statistically significant difference between the costs of infections with resistant bacteria including MRSA and susceptible bacteria (2,220.42 USD, 1,206.60 USD respectively). Additionally, the difference between the costs of infections caused by resistant bacteria except for MRSA and susceptible bacteria was also statistically significant. Lipsky et al. [15] reported that the cost of infections caused by Gram-negative bacteria including *P. aeruginosa* is higher than that of the infections caused by Gram-positive bacteria including staphylococci. This is due to the costly antibiotic regimens

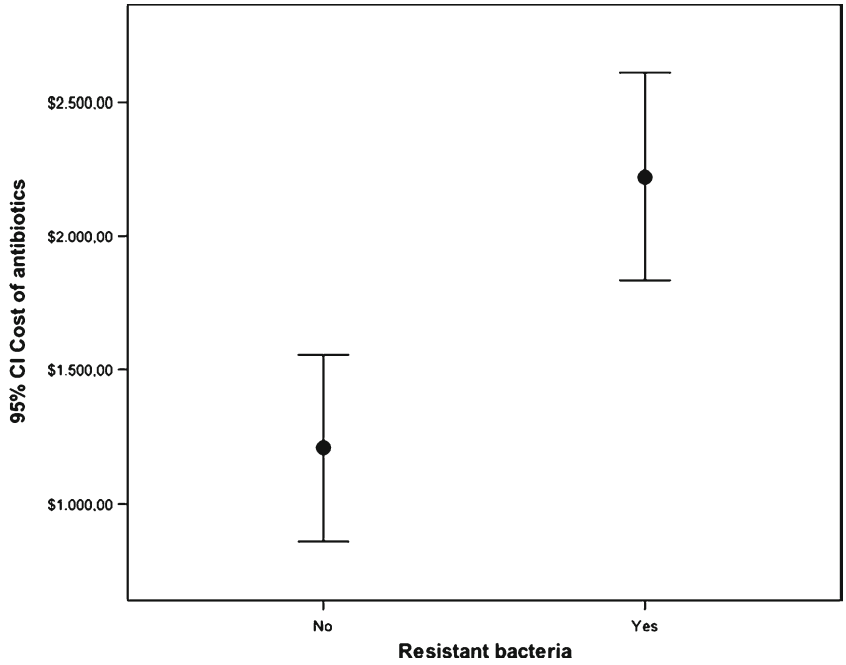


Fig. 1 The cost of antibiotics with resistant bacteria and susceptible bacteria ($p<0.001$)

prescribed for the treatment of infections caused by resistant bacteria.

In our study we found that the growth of resistant bacteria was associated with an approximately 5-fold increased risk of failure of the treatment. Vardakas et al. [14] reported a similar result for only MRSA. On the other hand, do these resistant bacteria lead to invasive infections? In the literature it was reported that MRSA acts more aggressively than methicillin-susceptible *S. aureus* (MSSA). Particularly, community-acquired MRSA infections are associated with a more adverse impact because of the Panton–Valentin leukocidin effect on outcome than community-acquired MSSA infections [16]. Furthermore, diabetic foot ulcer infected by MRSA was associated with a slower healing rate in two retrospective studies [17, 18]. But is this valid for IBL-producing *Pseudomonas* species and ESBL-producing Gram-negative bacteria? The virulence factors of these bacteria should be determined in future studies.

We also found that in patients with osteomyelitis, infections due to resistant bacteria prolong the duration of hospitalization. According to CHAID analysis, the presence of osteomyelitis was the most significant factor affecting the duration of hospitalization. However, the duration of hospitalization due to osteomyelitis caused by resistant bacteria was longer than for the susceptible bacteria (~33 days vs ~23 days). In diabetic foot infections, the treatment has been started empirically. In the case of infection caused by resistant bacteria, narrow spectrum antimicrobial treatment will fail to treat the infection and this may lead to the extension of infection. At this point there is a need for microbiological examination. All these processes may lead to prolonged treatment duration. For these reasons, all risk factors should be considered in order to choose the best empirical antibiotherapy.

In multivariate analysis, we found out that wound size ≥4.5 cm^2 was the only statistically significant factor affecting the development of osteomyelitis. Many papers in the literature report that the wound size ≥2 cm^2 is an important factor in the diagnosis of osteomyelitis [2, 5, 19, 20]. In our study, the statistical analysis of wound size was performed only in patients with osteomyelitis. This may result in a wider wound size than expected.

In our study group, the amputation risk was 7-fold higher in patients with previous foot infection and 6-fold higher in patients with osteomyelitis than in patients without previous infection and without osteomyelitis respectively. Previous studies have identified independent risk factors, including history of foot ulcer, older age, complications of diabetes (nephropathy or retinopathy), neuropathy, poor glycemic control (higher HbA1c), limb ischemia, depth of wounds, and severity of infection, the presence of gangrene (e.g., a higher Wagner grade), and osteomyelitis [1, 21, 22]. It is a fact that all these factors are related to each other. In a neuroischemic foot, the development of severe infection and gangrene is likely. In a foot with severe infection or gangrene, the development of osteomyelitis is inevitable. Diabetic foot osteomyelitis is usually a chronic infection and requires surgical therapy [23]. Most surgeons tend to accept amputation as being the major form of treatment of osteomyelitis. However, the accuracy of this approach in all

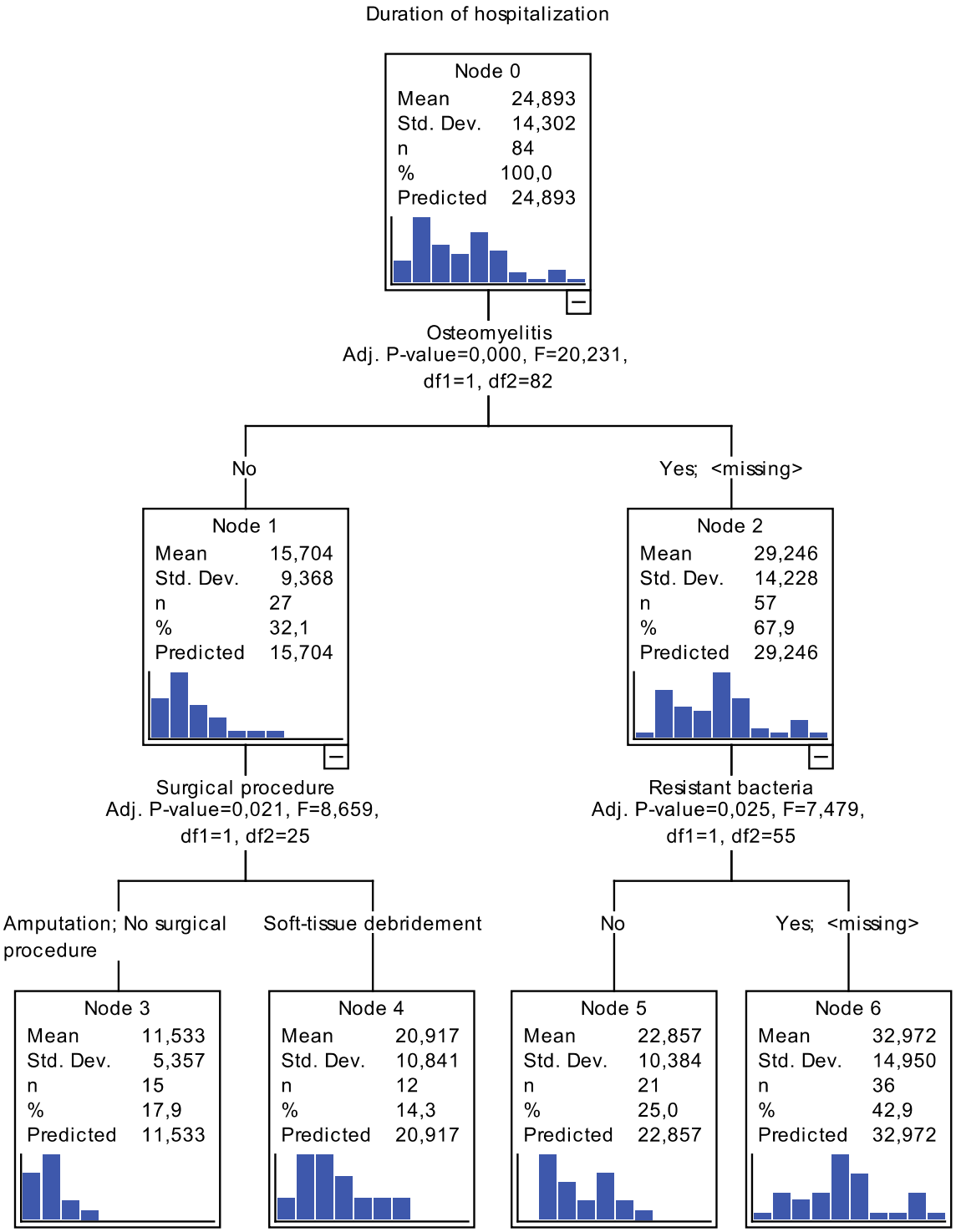


Fig. 2 Chi-squared automatic interaction detector (CHAID) analysis of the factors related to the duration of hospitalization

osteomyelitis cases is controversial. Proper sampling of bone tissue prevents misdiagnosis and determines the definitive causative bacteria, which direct toward the appropriate therapy [24]. Limited limb-saving surgery and prolonged antibiotic therapy directed toward the definitive causative bacteria are the most appropriate approaches. This may decrease significantly limb loss due to major amputations. As a result the infections caused by resistant bacteria may lead to a high cost of antibiotherapy, prolonged hospitalization duration, and failure of the treatment.

Table 3 Univariate analysis of the factors related to the development of osteomyelitis, amputation rates, growth of resistant bacteria, and the outcomes of the treatment

Variables		Parameters		*p*
		Osteomyelitis		
		Yes (%)	No (%)	
N=78		*n*=48	*n*=30	
Previous hospitalization history	Yes (51)	26	25	0.017
	No (27)	22	5	
N=76		*n*=46	*n*=30	
Wound depth				
Grade 1		6	15	<0.001
Grade 2		33	15	
Grade 3		7	0	
N=75		*n*=48	*n*=27	
Duration of diabetic foot infection (days) median (25–75%)		30 (20–63.8)	17.5 (10–32.59)	0.007
Wound size (cm^2) median (25–75%)		7.5 (3.75–15)	3 (2–6.25)	0.003
		Isolation of resistant bacteria		
		Yes (%)	No (%)	
Previous amputation	Yes (17)	14	3	0.014
	No (58)	26	32	
Antibiotics administration within the last 30 days	Yes (40)	33	7	0.031
	No (35)	20	15	
		Amputation		
		Yes (%)	No (%)	
Previous foot infection	Yes (45)	17	28	0.001
	No (49)	5	44	
Previous osteomyelitis	Yes (20)	9	11	0.03
	No (61)	12	49	
Previous amputation	Yes (20)	9	11	0.017
	No (72)	13	59	
Neuropathy	Yes (59)	20	39	0.003
	No (35)	3	32	
Osteomyelitis	Yes (48)	17	31	0.009
	No (30)	3	27	
		Treatment outcome		
		Cured	Failed	
Leukocyte count/mm^3 median (25–75%)		10,006.9 (3,921.4)	12,274.7 (5,204.8)	0.047
N=71		*n*=56 (%)	*n*=15 (%)	
Growth of resistant bacteria	Yes (37)	25 (67.5)	12 (32.5)	0.021
	No (34)	31 (91.4)	3 (8.8)	

Table 4 Logistic regression analysis of independent risk factors for the growth of resistant bacteria, developing osteomyelitis, and the failure of treatment

	Variables	*p*	OR	95% CI
Growth of resistant bacteria	Previous amputation	0.018	7.229	1.410–34.04
	Antibiotic administration within the last 30 days	0.032	3.796	1.123–12.83
Osteomyelitis	Wound size >4.5 cm^2	0.041	2.8	1.044–7.509
Amputation	Previous foot infection	0.005	6.99	1.827–26.743
	Osteomyelitis	0.015	6.173	1.425–26.74
Failure of the treatment	Growth of resistant bacteria	0.016	5.333	1.372–20.735

Acknowledgements We would like to thank Dr. Husrev Diktaş (Gulhane Military Medical Academy Haydarpasa Training Hospital, Department of Infectious Diseases and Clinical Microbiology, Istanbul, Turkey), Dr. Meliha Cagla Sonmezer (Ankara Training and Research Hospital, Department of Infectious Diseases and Clinical Microbiology, Ankara, Turkey), Dr. Esra Ulukaya, (University of Kocaeli, School of Medicine, Department of Infectious Diseases and Clinical Microbiology, Kocaeli, Turkey) for their collaboration in organizing the multicenter study.

Conflict of interest No conflicts of interest.

References

1. Yesil S, Akinci B, Yener S et al (2009) Predictors of amputation in diabetics with foot ulcer: single center experience in a large Turkish cohort. Hormones (Athens) 8:286–295
2. Lipsky BA, Berendt AR, Deery HG et al (2004) Diagnosis and treatment of diabetic foot infections. Clin Infect Dis 39:885–910
3. Lipsky BA, Sheehan P, Armstrong DG, Tice AD, Polis AB, Abramson MA (2007) Clinical predictors of treatment failure for diabetic foot infections: data from a prospective trial. Int Wound J 4:30–38
4. Schaper NC (2004) Diabetic foot ulcer classification system for research purposes: a progress report on criteria for including patients in research studies. Diabetes Metab Res Rev 20 [Suppl 1]:S90–S95
5. Lipsky BA (2009) Diagnosing and treating diabetic foot infections. J Klimik 22:2–13
6. Game FL, Boswell T, Soar C et al (2003) Outcome in diabetic foot ulcers with and without methicillin resistant Staphylococcus aureus (MRSA). Diabet Med 20 [Suppl 2]:30
7. Tentolouris N, Petrikkos G, Vallianou N et al (2006) Prevalence of methicillin-resistant Staphylococcus aureus in infected and uninfected diabetic foot ulcers. Clin Microbiol Infect 12:186–189
8. Ertugrul MB, Baktiroglu S, Salman S et al (2008) Pathogens isolated from deep soft tissue and bone in patients with diabetic foot infections. J Am Podiatr Med Assoc 98:290–295
9. Raja NS (2007) Microbiology of diabetic foot infections in a teaching hospital in Malaysia: a retrospective study of 194 cases. J Microbiol Immunol Infect 40:39–44
10. Saltoglu N, Dalkiran A, Tetiker T et al (2010) Piperacillin/tazobactam versus imipenem/cilastatin for severe diabetic foot infections: a prospective, randomized clinical trial in a university hospital. Clin Microbiol Infect 16:1252–1257
11. Hartemann-Heurtier A, Robert J, Jacqueminet S et al (2004) Diabetic foot ulcer and multidrug-resistant organisms: risk factors and impact. Diabet Med 21:710–715
12. Kandemir O, Akbay E, Sahin E, Milcan A, Gen R (2007) Risk factors for infection of the diabetic foot with multi-antibiotic resistant microorganisms. J Infect 54:439–445
13. Richard JL, Sotto A, Jourdan N et al (2008) Risk factors and healing impact of multidrug-resistant bacteria in diabetic foot ulcers. Diabetes Metab 34:363–369
14. Vardakas KZ, Horianopoulou M, Falagas ME (2008) Factors associated with treatment failure in patients with diabetic foot infections: an analysis of data from randomized controlled trials. Diabetes Res Clin Pract 80:344–351
15. Lipsky BA, Tabak YP, Johannes RS et al (2010) Skin and soft tissue infections in hospitalised patients with diabetes: culture isolates and risk factors associated with mortality, length of stay and cost. Diabetologia 53:914–923
16. Davis SL, Perri MB, Donabedian SM et al (2007) Epidemiology and outcomes of community-associated methicillin-resistant Staphylococcus aureus infection. J Clin Microbiol 45:1705–1711
17. Tentolouris N, Jude EB, Smirnof I, Knowles EA, Boulton AJ (1999) Methicillin-resistant Staphylococcus aureus: an increasing problem in a diabetic foot clinic. Diabet Med 16:767–771
18. Wagner A, Reike H, Angelkort B (2001) Highly resistant pathogens in patients with diabetic foot syndrome with special reference to methicillin-resistant Staphylococcus aureus infections. Dtsch Med Wochenschr 126:1353–1356
19. Ertugrul BM, Savk O, Ozturk B et al (2009) The diagnosis of diabetic foot osteomyelitis: examination findings and laboratory values. Med Sci Monit 15:CR307–CR312
20. Ertugrul MB, Baktiroglu S (2005) Diyabetik Ayak ve Osteomiyeliti. J Klimik 18:8–13 [In Turkish]
21. Aydin K, Isildak M, Karakaya J, Gurlek A (2010) Change in amputation predictors in diabetic foot disease: effect of multidisciplinary approach. Endocrine 38:87–92
22. Nather A, Bee CS, Huak CY et al (2008) Epidemiology of diabetic foot problems and predictive factors for limb loss. J Diabetes Complications 22:77–82
23. Rao N, Ziran BH, Lipsky BA (2011) Treating osteomyelitis: antibiotics and surgery. Plast Reconstr Surg 127 [Suppl 1]:177S–187S
24. Ertugrul MB, Baktiroglu S, Salman S et al (2006) The diagnosis of osteomyelitis of the foot in diabetes: microbiological examination vs. magnetic resonance imaging and labelled leucocyte scanning. Diabet Med 23:649–653