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Infective endocarditis in Turkey: aetiology, clinical features, and analysis of risk factors for mortality in 325 cases

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SUMMARY

Objective: In order to define the current characteristics of infective endocarditis (IE) in Turkey, we evaluated IE cases over a 14-year period in a tertiary referral hospital.
Methods: All adult patients who were hospitalized in our hospital with a diagnosis of IE between 2000 and 2013 were included in the study. Modified Duke criteria were used for diagnosis. The Chi-square test, Student's *t*-test, Mann–Whitney *U*-test, Cox and logistic regression analysis were used for the statistical analysis.
Results: There were 325 IE cases during the study period. The mean age of the patients was 47 years. Causative microorganisms were identified in 253 patients (77.8%) and included staphylococci (36%), streptococci (19%), enterococci (7%), and *Brucella spp* (5%). A streptococcal aetiology was associated with younger age (<40 years) ($p = 0.001$), underlying chronic rheumatic heart disease (CRHD) (odds ratio (OR) 3.89) or a congenital heart defect (OR 4.04), community acquisition (OR 17.93), and native valve (OR 3.68). A staphylococcal aetiology was associated with healthcare acquisition (OR 2.26) or pacemaker lead-associated endocarditis (OR 6.63) and an admission creatinine level of >1.2 mg/dl (OR 2.15). Older age (>50 year) (OR 3.93), patients with perivalvular abscess (OR 9.18), being on dialysis (OR 6.22), and late prosthetic valve endocarditis (OR 3.15) were independent risk factors for enterococcal IE. Independent risk factors for mortality in IE cases were the following: being on dialysis (hazard ratio (HR) 4.13), presence of coronary artery heart disease (HR 2.09), central nervous system emboli (HR 2.33), and congestive heart failure (HR 2.15). Higher haemoglobin (HR 0.87) and platelet (HR 0.996) levels and surgical interventions for IE (HR 0. 33) were found to be protective factors against mortality.
Conclusions: In Turkey, IE occurs in relatively young patients and *Brucella spp* should always be taken into consideration as a cause of this infection. We should first consider streptococci as the causative agents of IE in young patients, those with CRHD or congenital heart valve disease, and cases of community-acquired IE. Staphylococci should be considered first in the case of pacemaker lead IE, when there are high levels of creatinine, and in cases of healthcare-associated IE. Enterococci could be the most probable causative agent of IE particularly in patients aged >50 years, those on dialysis, those with late prosthetic valve IE, and those with a perivalvular abscess. The early diagnosis and treatment of IE before complications develop is crucial because the mortality rate is high among cases with serious complications. The prevention of bacteraemia with the measures available among chronic haemodialysis patients should be a priority because of the higher mortality rate of subsequent IE among this group of patients.

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1. Introduction

Despite its rare occurrence, infective endocarditis (IE) is an important disease because of the difficulties in diagnosis and treatment and the high morbidity and mortality rates. The profile of IE differs between developed and developing countries. In industrialized countries, a decrease in rheumatic heart disease and increase in degenerative heart disease has led to an increase in patient age, frequency of comorbidities, and incidence of *Staphylococcus aureus*, which is acquired mainly from healthcare, and IE still has a high mortality.[1,2] In developing countries, patient age, place of acquisition of the infection, and causative microorganisms may be different because of the ongoing higher rate of chronic rheumatic heart disease (CRHD).

The identification of causative microorganisms is crucial in the management of IE cases. Although the rate of identification of the causative microorganism is reported to be very high in the developed world, it is lower in developing countries.[3–7] Knowledge of the risk factors for specific microorganisms could be beneficial in those cases of IE with an undetermined aetiology. Because IE is a rare disease, case numbers are generally low in studies on IE.[8–12] In this study, we evaluated the aetiology and clinical and laboratory findings of IE cases over a 14-year period at a tertiary referral hospital; we also determined risk factors for *Streptococcus spp*, *Staphylococcus spp*, and *Enterococcus spp* IE. Further, we defined the risk factors for mortality in IE in the population of a tertiary hospital in Turkey.

2. Materials and methods

All adult patients (age >14 years) who were hospitalized in Siyami Ersek Cardiovascular Surgery Hospital with a diagnosis of IE between January 2000 and October 2013 were included in the study. Clinical and laboratory findings of patients were recorded prospectively in the first 5 years and retrospectively thereafter. The following variables were recorded for each patient: age, sex, underlying cardiac predisposition, intravenous drug use (IVDU), comorbid conditions before IE (diabetes mellitus, chronic renal failure, congestive heart failure (CHF), hypertension, chronic obstructive lung disease, being on chronic haemodialysis), admission complaints, physical investigation findings, healthcare or community acquisition, laboratory values (blood sugar, blood urea nitrogen, serum creatinine, C-reactive protein (CRP), alanine aminotransferase (ALT), rheumatoid factor, haemoglobin level, platelet and white blood cell (WBC) counts, erythrocyte sedimentation rate (ESR) at the time of diagnosis), blood culture results, echocardiography findings, results of the Wright agglutination test, antimicrobial treatments, surgical interventions, complications, and mortality.

Modified Duke criteria were used for the diagnosis of IE.[1] All patients who were discharged from the hospital within 6 months before the onset of symptoms were accepted as having hospital-acquired IE.[13]

The identification of *Staphylococcus spp* was performed using standard methods. Methicillin resistance in staphylococci was determined using a disk diffusion test with a 30-μg cefoxitin disk. Identification of streptococci and enterococci, Gram-negative enteric rods, Gram-negative non-fermentative rods, and *Candida spp* were done with API Strep, API 20E, API NE, and API CAUX (bioMérieux, France), respectively, along with standard methods. *Brucella spp* were identified using standard methods (biotyping, sensitivity to dyes, penicillin and streptomycin susceptibility, H_2S production, CO_2 requirement, phage sensitivity) and species-specific antisera. HACEK microorganisms, *Granulicatella elegans*, *Bacillus licheniformis*, and *Kytococcus schroeteri*, were identified using 16S ribosomal RNA analysis. *Bartonella henselae* DNA was determined using a nested PCR. Minimal inhibitory concentrations of penicillin G, gentamicin, ceftriaxone, oxacillin, and vancomycin were determined using the Etest method. Susceptibilities to other antimicrobial agents were determined with the Clinical and Laboratory Standards Institute (CLSI) disk diffusion method. Mortality was defined as in-hospital death.

Statistical analyses were done using SPSS for Windows version 16.0 (SPSS Inc., Chicago, IL, USA). The Chi-square test and Student's *t*-test were used for the univariate analysis of categorical and continuous variables of patient characteristics, respectively. The distribution of continuous variables was investigated with visual (histograms, probability plots) and analytical (Kolmogorov–Smirnov/Shapiro–Wilk tests) methods; variables with a non-normal distribution were compared using the Mann–Whitney *U*-test. Independent risk factors for IE caused by *Streptococcus spp*, *Staphylococcus spp*, and *Enterococcus spp* were determined using multiple logistic regression analysis. Cox regression analysis with backward selection was used to determine independent predictors of mortality. Variables found to be significant ($p < 0.05$) in the univariate analysis were included in the logistic and Cox regression analyses. Among correlated factors with similar effects on survival, only those with clinical significance were included. The proportional hazards assumption and model fit were assessed by means of residual analysis (Schoenfeld and Martingale).

3. Results

A total of 325 adult IE cases occurred between January 2000 and October 2013. One hundred two of 325 patients were recorded prospectively, while 223 were recorded retrospectively at the end of 2013.

Baseline characteristics, predisposing conditions, and clinical and laboratory findings on admission for the 325 endocarditis cases are shown in Tables 1 and 2. According to the modified Duke criteria, 280 (86.2%) patients were classified as having definite IE and 45 (13.8%) as having probable IE. The mean age of patients was 47 years (range 14–90 years) (Table 2). The numbers of patients aged younger than 40, 50, and 65 years were 119 (36.6%), 168 (51.6%), and 277 (85.2%), respectively. Mean patient age did not differ across the years ($p = 0.967$). The mean length of hospital stay was 36.59 ± 22.79 days (range 2–215 days).

3.1. Causative agents of infective endocarditis cases

The causative microorganism was identified in 252 patients, by positive blood culture ($n = 228$), positive heart valve culture ($n = 13$), both blood and heart valve culture ($n = 6$), positive Wright agglutination test ($n = 4$), and blood PCR positivity ($n = 1$). The causative microorganisms are shown in Table 3. Staphylococci were the most frequently isolated microorganisms (36.1%) when all of the IE cases were taken into consideration. The distribution of causative agents is shown by age range in Figure 1. Streptococci were significantly more prevalent in patients aged <40 years ($p = 0.001$), while enterococci were significantly more prevalent in patients aged >50 years ($p = 0.018$). The incidence of *S. aureus*, coagulase-negative staphylococci (CoNS), and *Brucella spp* were not different among IE cases ($p = 0.319$, 0.131, and 0.436, respectively).

Streptococci were the leading cause of IE in patients with a native valve (52/166, 31%) ($p = 0.000$), while staphylococci were the leading cause in patients with an intracardiac prosthesis (58/159, 36%). CoNS, methicillin-resistant *S. aureus* (MRSA), Gram-negative rods, *Enterococcus spp*, and *Candida spp* were isolated more frequently from patients with an intracardiac device than patients with a native valve ($p = 0.011$, 0.038, 0.001, 0.014, and 0.022, respectively).

Table 1
Predisposing conditions, complaints, and clinical and laboratory findings of patients with infective endocarditis

Feature	*n* (%)	Feature	*n* (%)
Predisposing conditions		*Complaints*	
Chronic rheumatic heart disease	110 (33.9)	Fever	276 (84.9)
Prosthetic valve	141 (43.5)	Dyspnoea	131 (40.5)
Pace/ICD*	18 (5.6)	Fatigue	118 (36.4)
Previous infective endocarditis	18 (5.6)	Anorexia and weight loss	33 (10.2)
Bicuspid aortic valve	18 (5.6)	Arthralgia	19 (5.9)
Other congenital heart defects	26 (8.0)	Headache and change in consciousness	15 (4.6)
Structural heart valve disease	12 (3.3)	*Physical investigation and laboratory findings*	
Degenerative heart valve disease	19 (5.9)	Fever	307 (94.4)
Intravenous drug user	3 (0.9)	New murmur	145 (44.8)
Other features		Skin rashes	8 (2.5)
Left-sided endocarditis	284 (87.3)	Roth spot	5 (1.5)
Aortic valve	124 (38.2)	Splenomegaly	55 (16.9)
Mitral valve	124 (38.2)	Peripheral arterial emboli	17 (5.2)
Aortic and mitral valve	36 (11.0)	Central nervous system emboli	52 (16.6)
Right-sided endocarditis	41 (12.7)	Pulmonary emboli	8 (2.5)
Tricuspid valve	21 (6.5)	Splenic abscess	15 (4.6)
Pulmonary valve	2 (0.6)	Congestive heart failure	104 (32.1)
Place of infection acquisition		Vegetation on echocardiography	253 (78.1)
Community-acquired	250 (76.9)	Abscess on echocardiography	48 (14.8)
Healthcare-associated	75 (23.1)	Haematuria	121 (38.6%)
Nosocomial	33 (10.2)	Elevated rheumatoid factor	28 (8.9%)
Non-nosocomial	42 (12.9)	Elevated C-reactive protein level	295 (91)
		Elevated erythrocyte sedimentation rate	276 (85)

* ICD, implantable cardioverter defibrillator.

Streptococci and *Brucella spp* were isolated more frequently from community-acquired endocarditis ($p < 0.000$ and 0.173, respectively), while *S. aureus*, MRSA, Gram-negatives, and *Candida spp* were more frequently associated with healthcare-acquired IE cases ($p = 0.008$, 0.001, 0.000, and 0.044, respectively).

Independent risk factors for staphylococcal, enterococcal, and streptococcal IE are shown in Table 4.

One patient with blood culture-negative IE was positive for *B. henselae* DNA by PCR.

3.2. Antimicrobial susceptibility of causative agents and antimicrobial treatments

All of the streptococci were sensitive to penicillin. All of the enterococci were sensitive to penicillin, gentamicin, and vancomycin, and none of the enterococci showed high-level resistance to gentamicin. The rate of methicillin resistance was 32% (36/117) among Staphylococcus strains isolated from blood cultures of endocarditis cases. The rate of methicillin resistance was 9% (6/65) for *S. aureus* strains and 60% (31/52) for CoNS strains. No methicillin resistance was seen among *S. aureus* strains isolated from community-acquired IE, but the rate of methicillin resistance was 58% (21/36) among CoNS strains isolated from community-acquired IE. In healthcare-associated IE cases, the rate of methicillin resistance was 25% (6/24) for *S. aureus* strains and 63% (10/16) for CoNS strains. The methicillin resistance rate among *S. aureus* strains isolated from healthcare-associated IE cases decreased significantly from 45% to 8% ($p = 0.048$) after the control of MRSA infections began in 2006.

Ampicillin–sulbactam plus gentamicin was the most frequently used antimicrobial combination for the treatment of IE (63 patients), followed by penicillin or ampicillin plus gentamicin (56 patients), cefazolin plus gentamicin (59 patients), vancomycin plus gentamicin (59), ceftriaxone plus gentamicin (10 patients), and daptomycin plus gentamicin (4 patients).

3.3. Univariate analysis of mortality risk factors (Table 2)

Eighty-six of 325 patients died (27.8%) during their hospital stay. The rate of mortality did not differ over the years ($p > 0.05$). In the univariate analysis, risk factors that increased mortality in cases of IE were older age, chronic renal failure, coronary artery disease, diabetes mellitus, being on dialysis, healthcare-associated IE, early prosthetic valve IE, central nervous system (CNS) or peripheral arterial emboli, perivalvular abscess, CHF due to IE, higher WBC count, lower blood thrombocyte count, lower haemoglobin level, higher levels of serum CRP, creatinine, and fasting sugar, higher ESR rate, and *S. aureus* aetiology ($p < 0.05$). Decreased mortality in cases of IE was associated with *Streptococcus spp* aetiology and surgical intervention for the treatment of IE ($p < 0.05$).

3.4. Multivariate analysis of mortality risk factors (Table 2)

In the multivariate analysis, independent risk factors for mortality in cases of IE were found to be the following: being on dialysis (hazard ratio (HR) 4.13), the presence of coronary artery heart disease (HR 2.09), CNS emboli (HR 2.33), and CHF (HR 2.15). Higher haemoglobin (HR 0.87) and platelet (HR 0.996) levels and surgical intervention for IE (HR 0. 25) were found to be protective factors against mortality.

4. Discussion

This study is the largest case series of patients with IE from Turkey to date. Recent studies from the developed world have reported the age of patients with IE to be >60 years.[2,14] Although the median age of patients was reported to be 36 years in the former largest study of IE from Turkey,[8] recent studies of IE in Turkey have found it to be between 45 and 51 years.[9–12] Our finding of a mean age of 47 years is higher than that reported in the study from the 1990s and similar to those reported in the recent studies, but is still lower than the average mean age of patients in the developed world.[1] The major factor contributing to the younger age of patients with IE could be the higher rate of CRHD in Turkey. A recent study investigated the causes of heart valve disease in 1300 cases and concluded that CRHD was the leading cause of heart valve disease – it constituted 46% of the cases in Turkey.[15] Although the rate of CRHD in Turkey among IE cases decreased from 64%[8] in the 1990s to 18–36% in the 2000s,[9–11] it is

Table 2
Baseline characteristics, predisposing conditions, and clinical and laboratory findings of infective endocarditis patients who died and those who survived[a]

Features	Total cohort ($N=325$[b])	Patients who died ($n=234$)	Patients who survived ($n=87$)	Statistical analysis			
				Univariate analysis *p*-Value	Multivariate analysis		
					p-Value	HR	95% CI
Age, years	46.94 ± 17.11	44.54 ± 17.40	54.04 ± 14.37	<0.001			
Sex, male	187	134	53	0.582			
Left-sided IE	284	202	78	0.420			
Aortic valve endocarditis	156	108	48	0.160			
History of previous endocarditis	18	12	6	0.541			
Prosthetic valve endocarditis	141						
Early prosthetic valve endocarditis	52	25	27	<0.001			
Late prosthetic valve endocarditis	89	62	26	0.559			
Chronic renal failure	19	9	10	0.010			
Coronary heart disease	49	27	22	0.002	0.012	2.09	1.17–3.73
Hypertension	46	34	12	0.864			
Diabetes mellitus	31	16	15	0.005			
Congestive heart failure before endocarditis	20	13	7	0.412			
Chronic obstructive lung disease	4	4	0	0.220			
Chronic haemodialysis	11	3	8	0.001	0.001	4.13	1.83–9.30
Healthcare-associated endocarditis	75	45	30	0.005			
Central nervous system emboli	52	23	29	<0.001	0.002	2.33	1.35–4.03
Peripheral arterial emboli	25	14	11	0.049			
Splenic abscess	15	8	7	0.082			
Paravalvular abscess	48	29	19	0.036			
Congestive heart failure	102	55	47	<0.001	0.003	2.15	1.29–3.56
Blood leukocyte count, $\times 10^9$/l	12.02 ± 6.13	10.98 ± 4.67	14.75 ± 8.42	<0.001			
Blood thrombocyte count, $\times 10^9$/l	244.950 ± 111.51	261.920 ± 113.73	198.810 ± 91	<0.001	0.09	0.996	0.994–0.998
Blood haemoglobin level, g/dl	10.57 ± 2.04	10.81 ± 2.15	9.92 ± 1.53	<0.001	0.047	0.87	0.76–0.99
Serum CRP level, mg/l	79.53 ± 68.93	71.32 ± 61.69	101.05 ± 81.53	0.002			
Serum creatinine level, mg/dl	1.33 ± 1.38	1.07 ± 0.78	1.83 ± 0.21	<0.001			
Serum blood sugar level, mg/dl	118.70 ± 46.43	113.70 ± 40.73	131.99 ± 57.24	0.011			
Serum ALT level, U/l	43.94 ± 91.50	38.36 ± 77.15	59.04 ± 120.92	0.096			
ESR, mm/h	63.98 ± 31.01	61.23 ± 30.10	71.24 ± 32.41	0.009			
Vegetation area, cm^2	1.35 ± 1.41	1.23 ± 1.17	1.45 ± 1.65	0.346			
Staphylococcus aureus IE	65	38	25	0.013			
Enterococcus spp IE	21	12	9	0.095			
Viridans Streptococcus IE	63	55	8	0.004			
Cardiac surgery for IE	168	139	29	<0.001	<0.001	0.33	0.19–0.56
Total length of hospital stay, days	36.59 ± 22.79	38.60 ± 17.29	31.65 ± 33.32	<0.001			

HR, hazard ratio; CI, confidence interval; IE, infective endocarditis; CRP, C-reactive protein; ALT, alanine aminotransferase; ESR, erythrocyte sedimentation rate; SD, standard deviation.

[a] Results are given as the mean ± SD, or as the number or patients.

[b] Four patients were referred to the other hospitals because of serious complications and removed from the analysis.

still as high as 34%. CRHD currently accounts for <10% of IE cases in industrialized countries.[14] Since the reporting system is not adequate, it is impossible for us to estimate an accurate incidence of acute rheumatic fever (ARF) in Turkey. Available evidence suggests that the incidence of ARF has also been decreasing in Turkey, but it remains higher than that in the developed world. The incidence of ARF is reported to be lower than 10 per 100 000 people in the developed world,[16] whereas it is reported to be 20 per 100 000 people in Turkey.[17] These findings suggest that a comprehensive and sustainable surveillance system for ARF and CRHD should be established to prevent the disease in Turkey.

Other predisposing conditions for IE, such as the presence of intracardiac devices or prosthetic valves, were the same as identified in other studies. However, the incidence of IVDU among the cases of IE (0.9%) was lower than rates reported from the developed world (10%).[1]

In the present study, the four most frequent causative microorganisms were staphylococci, streptococci, enterococci, and *Brucella spp*. Recent studies from the developed world[1] have also reported staphylococci to be the most frequently isolated microorganisms; these have been shown to be the causative agents of 29%, 78%, 44%, 35% and 36% of native valve, pacemaker lead, early prosthetic valve, late prosthetic valve and all of IE cases, respectively in our study. However, the causative microorganisms of IE differ from country to country, depending on the underlying predisposing conditions and place of acquisition of the infection. Streptococci were the leading cause of endocarditis in patients with a native valve endocarditis in the present study. This situation may also be related to the greater presence of patients of younger age with CRHD. Comorbid conditions are low in these patients and they do not need frequent hospitalization; as a result they have a lower risk of healthcare-associated infection such as staphylococcal infection.

In the present study, CoNS, MRSA, Gram-negative rods, *Enterococcus spp*, and *Candida spp* were more frequent in patients with intracardiac prosthetic devices or valves than in patients with no prosthesis. Staphylococci and *Candida spp* were also found more frequently in patients with an intracardiac device or valve in the International Collaboration on Endocarditis (ICE) cohort.[1]

Causative microorganisms were also different among community- and healthcare-associated IE in our study: streptococci and *Brucella spp* were more frequent in patients with community-acquired IE and *S. aureus*, MRSA, Gram-negative rods, and *Candida spp* were more frequently isolated in patients with healthcare-associated IE. *S. aureus*, MRSA, and *Candida spp* were also isolated more frequently from patients with healthcare-associated IE in the study of Lomas et al.[18]

Table 3
Causative microorganisms of 325 cases of infective endocarditis

Causative microorganisms	Native valve	Intracardiac device			Total, *n* (%)
		Pacemaker/ ICD*, *n*	Early prosthetic valve, *n*	Late prosthetic valve, *n*	
Defined causative agent	122	15	47	69	253 (77.8)
Staphylococcus spp	49	14	23	31	117 (36.1)
Staphylococcus aureus	31	10	10	14	65 (20.1)
MRSA	1	0	5	0	6 (1.9)
MSSA	30	10	5	14	59 (17.3)
CoNS	18	4	13	17	52 (16.0)
Methicillin-resistant CoNS	10	1	11	9	31 (9.6)
Methicillin-sensitive CoNS	8	3	2	8	21 (6.5)
Streptococcus spp	52	0	2	9	63 (19.4)
Viridans Streptococcus	44	0	2	9	55 (17.0)
Streptococcus bovis	4	0	0	0	4 (1.2)
Nutritionally variant streptococci	4	0	0	0	4 (1.2)
Abiotrophia defectiva	3	0	0	0	3 (0.9)
Granulicatella elegans	1	0	0	0	1 (0.3)
Enterococcus spp	11	0	0	11	22 (6.8)
Enterococcus faecalis	10	0	0	9	19 (5.9)
Enterococcus faecium	1	0	0	2	3 (0.9)
Brucella melitensis	5	1	0	9	15 (4.6)
Non-fermentative Gram-negative rods	2	0	12	2	16 (4.6)
Pseudomonas aeruginosa	1	0	6	1	7 (2.2)
Stenotrophomonas maltophilia	0	0	5	1	6 (1.8)
Acinetobacter baumannii	0	0	1	0	2 (0.6)
Acinetobacter lwoffii	1	0	0	0	1 (0.3)
Candida spp	1	0	6	1	8 (2.4)
Candida albicans	0	0	5	0	5 (1.5)
Candida parapsilosis	1	0	1	0	2 (0.6)
Other non-albicans *Candida spp*	0	0	0	1	1 (0.3)
Enterobacteriaceae	0	0	4	2	6 (1.8)
Escherichia coli	0	0	1	1	2 (0.6)
Enterobacter cloacae	0	0	1	0	1 (0.3)
Klebsiella pneumoniae	0	0	1	1	2 (0.6)
Serratia marcescens	0	0	1	0	1 (0.3)
HACEK	1	0	0	2	3 (0.9)
Eikenella corrodens	1	0	0	0	1 (0.3)
Actinobacillus actinomycetemcomitans	0	0	0	2	2 (0.6)
Kytococcus schroeteri	0	0	0	1	1 (0.3)
Bartonella henselae	0	0	0	1	1 (0.3)
Bacillus licheniformis	1	0	0	0	1 (0.3)
Undefined causative agents	44	3	5	20	72 (22.2)
Total	166	18	52	89	325 (100)

* ICD, implantable cardioverter defibrillator; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; CoNS, coagulase-negative staphylococci;

Causative microorganisms also differed relative to the age ranges in our study. Streptococci were more frequent among patients aged <40 years and enterococci were more frequent among patients aged >50 years; this is in accordance with the current literature.[19]

It is not always possible to identify fastidious bacteria that cause IE with traditional methods. Molecular methods are particularly useful to show the presence of fastidious bacteria and to identify slow-growing bacteria cultured in blood.[20] We identified HACEK microorganisms, *K. schroeteri*, and *B. licheniformis*

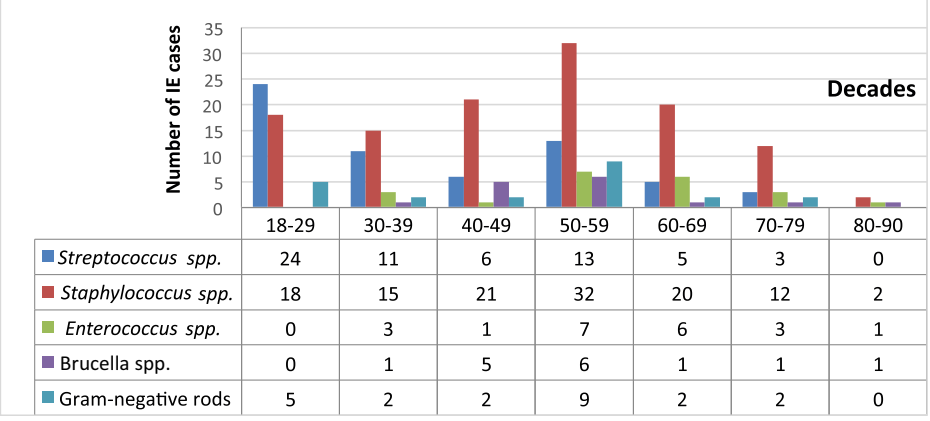

Figure 1. Distribution of the most frequent five causative agents of infective endocarditis according to decades.

Table 4
Demographic and clinical features of patients with infective endocarditis caused by *Streptococcus spp*, *Staphylococcus spp*, and *Enterococcus spp*

Variables[a]	*Streptococcus spp* IE						*Staphylococcus spp* IE						*Enterococcus spp* IE					
				Multivariate analysis						Multivariate analysis						Multivariate analysis		
	Neg $n=262$	Pos $n=63$	Univ. p-value	p-Value	OR	95% CI	Neg $n=208$	Pos $n=117$	Univ. p-value	p-Value	OR	95% CI	Neg $n=303$	Pos $n=22$	Univ. p-value	p-Value	OR	95% CI
Age, years	48 ± 17	40 ± 15	0.001				45 ± 17	49 ± 16	0.035				46 ± 17	56 ± 14	0.001			
>40 years	178	28	0.001				124	82	0.060				188	28	0.063			
>50 years													141	16	0.018	0.029	3.93	1.15–13.40
Sex, male	159	32	0.152				115	76	0.089				176	15	0.383			
Chronic rheumatic heart disease	79	31	0.04	0.001	3.89	1.45–10.41	80	30	0.019				101	9	0.489			
Chronic renal failure	19	0	0.028				12	7	0.937				14	5	0.000			
CHD	44	5	0.078				30	19	0.660				40	9	0.000			
Hypertension	41	5	0.092				27	19	0.304				40	6	0.106			
Diabetes mellitus	28	3	0.151				18	13	0.469				26	5	0.046			
CHF before endocarditis	17	3	0.609				10	10	0.178				19	1	0.745			
History of previous IE	16	2	0.361				13	5	0.455				18	0	0.239			
At least one comorbidity	116	20	0.037				84	52	0.237				120	16	0.007			
Chronic haemodialysis	11	0	0.098				8	3	0.540				7	4	0.004	0.049	6.22	1.007–38.43
Healthcare-associated endocarditis	75	1	0.000				36	40	0.001	0.006	2.26	1.25–4.06	70	6	0.655			
Community- acquired infection	187	62	0.003	0.005	17.93	2.34–137.09												
Presence of any congenital heart defect	25	16	0.001	0.004	4.04	1.78–9.11	30	11	0.191				41	0	0.065			
Presence of intracardiac device	147	11	0.000				90	68	0.010				147	11	0.893			
Native valve (no intracardiac device)	115	52	0.000	0.003	3.68	1.57–8.62												
Presence of prosthetic valve	130	11	0.000				87	54	0.450				130	11	0.517			
Early prosthetic valve endocarditis	50	2	0.002				29	23	0.177				52	0	0.032			
Late prosthetic valve endocarditis	80	9	0.009				58	31	0.778				78	11	0.014	0.034	3.15	1.08–9.13
Pace-maker lead IE	18	0	0.032				4	14	0.000	0.002	6.63	1.99–22.05	18	0	0.239			
Left-sided endocarditis	226	58	0.213				189	95	0.012				163	21	0.238			
CNS emboli	48	6	0.092				32	22	0.427				49	5	0.425			
Peripheral arterial emboli	20	6	0.620				17	9	0.878				24	2	0.845			
Splenic abscess	12	3	0.951				10	5	0.826				14	1	0.937			
Paravalvular abscess	41	7	0.362				35	13	0.163				40	8	0.003	0.000	9.18	2.90–29.04
CHF	85	19	0.727				59	45	0.061				92	12	0.019			
Blood leukocyte count, $\times 10^9$/l	12 ± 6	10 ± 6	0.013				11 ± 6	13 ± 6	0.002				11 ± 6	13 ± 7	0.149			
Blood thrombocyte count, $\times 10^9$/l	245 ± 117	242 ± 82	0.665				247 ± 106	239 ± 120	0.533				244 ± 111	250 ± 107	0.826			
Blood haemoglobin level, gr/dl	10.58 ± 1.96	10.54 ± 2.35	0.539				10.50 ± 2.15	10.69 ± 1.84	0.543				10.6 ± 2.08	10.2 ± 1.39	0.478			
Serum CRP level, mg/l	81 ± 71	72 ± 55	0.844				77 ± 60	82 ± 81	0.680				78 ± 69	88 ± 69	0.485			
Serum creatinine level, mg/dl	1.44 ± 1.51	0.86 ± 0.30	0.001				1.26 ± 1.31	1.47 ± 1.49	<0.001				1.25 ± 1.26	2.41 ± 2.31	0.023			
Serum creatinine level >1.2 mg/dl	74	9	0.014				42	41	0.002	0.008	2.15	1.22–3.78	76	7	0.404			

Table 4 (*Continued*)

Variables[a]	*Streptococcus spp* IE					*Staphylococcus spp* IE					*Enterococcus spp* IE				
				Multivariate analysis					Multivariate analysis					Multivariate analysis	
	Neg $n=262$	Pos $n=63$	Univ. *p*-value	*p*-Value	OR 95% CI	Neg $n=208$	Pos $n=117$	Univ. *p*-value	*p*-Value	OR 95% CI	Neg $n=303$	Pos $n=22$	Univ. *p*-value	*p*-Value	OR 95% CI
Serum blood sugar level, mg/dl	121 ± 48	106 ± 35	0.025			116 ± 46	123 ± 46	0.053			117 ± 45	130 ± 56	0.394		
Serum ALT level, U/l	47 ± 100	28 ± 31	0.041			40 ± 97	49 ± 80	0.071			43 ± 89	54 ± 115	0.436		
ESR, mm/h	64 ± 30	61 ± 31	0.589			65 ± 31	60 ± 30	0.184			63 ± 31	78 ± 25	0.036		
Vegetation area, cm^2	1.35 ± 1.40	1.15 ± 1.09	0.468			1.40 ± 1.61	1.35 ± 1.22	0.58			1.4 ± 1.2	1.5 ± 1.1	0.63		

IE, infective endocarditis; Univ., univariate; OR, odds ratio; CI, confidence interval; CHD, coronary heart disease; CHF, congestive heart failure; CNS, central nervous system; CRP, C-reactive protein; ALT, alanine aminotransferase; ESR, erythrocyte sedimentation rate.

[a] Results are given as the mean ± SD, or as the number or patients.

using 16S RNA analysis; these were cultured from either blood or heart valves of patients with IE and could not be identified with traditional methods. In contrast to other studies, *Brucella spp* was defined as the fourth most frequent cause of IE in our study. In a study from Algeria, where brucellosis is also endemic like Turkey, *Brucella spp* was found to be the causative agent in 1.6% of 62 IE cases.[21] These findings suggest that causative microorganisms may be different among countries. Knowledge of the local epidemiology is required and *Brucella spp* should be considered as a causative agent in cases of IE in Turkey. The Wright agglutination test should be included in the primary serologic testing of IE cases in Turkey.

The rate of determination of causative microorganisms in cases of IE also differs between countries, probably due to the availability of advanced technologies. Causative microorganisms are determined in more than 90% of cases of IE in developed countries,[1,22] but only 41–67% of cases of IE in developing countries.[3–7] A median of 68% (range 50–84%) of the causes of IE have been identified in studies from Turkey[8–12] and we determined the cause in 78% of IE cases. It would be useful to know the risk factors for certain types of causative microorganism in the case of an undefined aetiology among IE cases. The most important features that were found to be useful in estimating the causative agent in cases of IE in our study were patient age, predisposing condition (CRHD, congenital heart disease, presence of intracardiac devices), and whether the infection was acquired from the community or healthcare environment. Community-acquired IE, CRHD or a congenital heart defect as the underlying condition, and the presence of a native valve were found to be independent risk factors for streptococcal IE. Healthcare- or pacemaker lead-associated IE and a higher admission creatinine level in patients (>1.2 mg/dl) were found to be independent risk factors for staphylococcal IE. In a study of 558 patients with *S. aureus*-related IE from the ICE cohort, these patients were also found to be significantly more likely to have healthcare-associated IE than patients with non-*S. aureus*-related IE.[23] Acute renal failure and higher creatinine levels in patients with IE caused by *S. aureus* is a well defined situation.[24] In our study, independent risk factors for enterococcal IE were older age (>50 years), patients with perivalvular abscess, being on dialysis, and late prosthetic valve endocarditis. In recent studies, the most distinctive reported features of enterococcal IE are that it more frequently affects the elderly and patients with a prosthetic valve,[19,25] and more often causes the development of intracardiac abscesses in patients with a prosthetic valve.[25] In a study of IE in 40 haemodialysis patients from Morocco, enterococci were the causative microorganisms in 23% of patients.[26] In accordance with our results, enterococci were identified more frequently in older subjects ($p = 0.02$), *Streptococcus spp* were found to be associated with native valves, and CoNS were associated with intracardiac prosthetic material in a study reported from Israel.[20]

Antimicrobial resistance was not a major problem among the microorganisms isolated from community-acquired endocarditis, but it was in healthcare-associated IE in our study: all of the streptococci were sensitive to penicillin and all of the enterococci were sensitive to penicillin, high-level gentamicin, and vancomycin. Despite increasing reports of strains of viridans group streptococci that are resistant to penicillin and other antibiotics, penicillin-resistant viridans group streptococci are reported very rarely as a cause of IE.[27] No methicillin resistance was seen with *S. aureus* strains isolated from community-acquired IE, but 25% of healthcare-associated *S. aureus* IE strains were resistant to methicillin in our study. Methicillin resistance rates among *S. aureus* strains isolated from healthcare-associated IE cases decreased significantly from 45% to 8%, which was probably related to the control of nosocomial MRSA infections in our hospital after 2006. The rate of methicillin resistance among CoNS strains isolated from 295 patients with IE in the present study was

high in both community- (58%) and healthcare-associated (63%) IE. In the study of Chu et al., the rate of methicillin resistance among CoNS strains isolated from healthcare-associated IE was also very high (58%), but the rate of methicillin resistance among CoNS strains isolated from community-acquired IE was lower (22%) than our results.[28] The higher rate of methicillin resistance among CoNS strains isolated from community-acquired IE cases in our study may be a reflection of the higher rate of consumption of antimicrobials in the community in Turkey.[29] These results suggest that penicillin or ampicillin and ampicillin–sulbactam or cefazolin are still suitable antimicrobials for the treatment of streptococcal or enterococcal and *S. aureus* IE in Turkey, respectively. Because Gram-negative rods, especially non-fermentatives, were the causative microorganisms in 38% and 27% of early prosthetic valve IE cases in our study, we recommend that the empirical therapy for these cases includes an antimicrobial effective against these bacteria, which is compatible with the current treatment guidelines.[30]

The mortality rate of our patients was very high (27.8%). Our hospital is a referral centre for the surgical treatment of IE, thus this higher mortality rate could be due to the referral of more complicated cases. Because findings of progressive and uncontrolled infection such as heart failure or CNS emboli lead to higher mortality in cases of IE, as found in our study and others,[1,2] cases of IE must be monitored closely and managed properly before such complications occur.

Chronic haemodialysis was defined as an independent risk factor for mortality in our study, which is in accordance with the current knowledge. Chronic haemodialysis patients are at higher risk of IE with 50–180 times the incidence compared to the general population.[31] IE causes greater morbidity and mortality in dialysis patients with infection, being second only to cardiovascular disease as the leading cause of death within this patient group. The mortality rate among dialysis patients with IE is at least twice the mortality for IE in the general population and ranges from 30% to 64%.[31–33] Since an increased risk of IE results mainly from vascular access-related bacteraemia, the prevention (preference of native arteriovenous fistula over an indwelling vascular catheter for vascular access, nasal *S. aureus* decolonization of patients, etc.), early detection, and effective treatment of bacteraemia among chronic haemodialysis patients are very important because of the unacceptably high mortality rate of IE among these patients.

The use of a surgical intervention was found to be a protective factor against mortality in our study. Our study was not designed to establish the impact of surgery on the mortality of patients with IE. Although an inverse association was shown between valve surgery and mortality, this does not show a cause–effect relationship between surgery and mortality. Early surgical intervention has been reported repeatedly as a protective factor for mortality in recent studies.[34–36] Although controversies exist, the current literature indicates that valve surgery is associated with significantly reduced mortality in patients with left-sided IE, therefore the management of complicated IE has moved into an era of early surgery.[37,38]

In conclusion, IE occurred in relatively young patients in Turkey. *Brucella spp* should be considered as a frequent cause of IE in Turkey. We should first consider streptococci as the causative agents of IE in young patients (age <40 years), those with ARF or congenital heart valve disease, and those with community-acquired native valve IE. Staphylococci should be taken into consideration first in the case of pacemaker lead IE, when there are high levels of creatinine, and in healthcare-associated IE. Enterococci could be the most probable causative agents of IE particularly in patients aged >50 years, those on dialysis, those with late prosthetic valve IE, and in cases with perivalvular abscess. Early diagnosis and treatment of IE before complications develop is crucial because the mortality rate is high among cases of IE with CNS emboli or CHF. The prevention of bacteraemia with available measures among chronic haemodialysis patients should be a priority because of the higher mortality rates of subsequent IE observed in this group of patients.

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