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).