

Changing profile of infective endocarditis during 31-year time course in a tertiary care hospital

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ABSTRACT

Aim: Infective endocarditis (IE), infection of the endocardial surface of heart, may cause mortality up to 30% despite advancements in medical care. Epidemiology of IE and profile of causative organism has changed in the last years. We aimed to investigate the changing profile of IE over a 31-year period in a tertiary care hospital

Material and Method: Medical records of 290 patients treated with the diagnosis of IE between 1974 and 2005 were re-evaluated according to Modified Duke criteria. Forty seven cases were classified as rejected cases.

Results: Of the 243 patients 109 was female (44.8%) and 134 male (55.2%). The mean age of the patients was 38±16.4 years (Table). The mean age of the patients showed an increasing trend throughout the time ($p < 0.001$); it was 29 years between 1974-1980 but increased to 54 years in 2001-2005 period. Rheumatic valvular disease (RVD) was the most frequent underlying heart disease (60%) but showed a declining trend especially in the last years. *S. aureus* was the most common pathogen in all the time periods (15.2%). Blood cultures were negative in 90 (43%) patients. But the percentage of blood culture negativity decreased significantly from 63% in 1981-1985 periods to 28% in 2001-2005 period. ($p: 0.02$). Mitral valve was the most common affected valve (52, 44%). Surgery was performed in 74 of the 243 cases (30.5%). In-hospital mortality rate was 30.6. Mortality rate was significantly lower in patients who underwent surgery compared to ones who did not (19.2% vs. 35.8%, $p < 0.005$). Mortality rate was also lower in patients with community acquired infection compared to ones with nosocomial infection (27% vs 45%). Embolic events, nosocomial infections and surgery were independent risk factors for mortality.

Conclusion: The mean age of IE population is increasing, RVD disease is less commonly seen as an underlying heart and *S. aureus* is the most common pathogen. These findings are compatible with the reports from developed countries. Surgery displays a protective effect on the prognosis of IE

Keywords: Infective endocarditis, mortality, epidemiology

INTRODUCTION

Infective endocarditis (IE) is an infectious disease that affects the endocardial surface of the heart. Native or prosthetic valves and also implanted intracardiac devices may be involved (1). Annual incidence of IE approaches 10/100,000 of the general population where mortality risk may reach 30% despite the advancements in medical care (2,3).

Epidemiology of the disease has changed in the last years. Rheumatic valvular disease is currently less common in developed countries but is still an important predisposing factor in developing countries. On the other hand prosthetic valves and intracardiac devices constitute major risk factors for IE in developed countries. In industrialized countries older individuals are more

commonly affected; the percentage of younger individuals affected by IE is higher in developing countries or in low socioeconomic groups. Intravenous drug use in young individuals is also an increasing risk factor (1,4).

Staphylococcus aureus has become more prominent among causative microorganisms, accounting for up to %30 percent of cases (1). This may be due to the fact that most cases of IE are hospital acquired or health care related (5). Due to the decreased incidence of rheumatic heart disease, incidence of viridians group *streptococci* causing subacute IE has also decreased. Growing incidence of *enterococcal* IE is also seen worldwide (2).

In this study we aimed to investigate the changing profile of IE during 31-year time course in a tertiary care hospital.

MATERIAL AND METHOD

The study was a thesis study. It was completed with the approval of Academic Board of Department of Internal Medicine, Hacettepe University (Date: 2014, Decision No: 87). This study was a retrospective thesis study for Internal Medicine residency graduation which was approved by Department of Internal Medicine of Hacettepe University in 05.05.2006. All procedures were performed in accordance with the ethical rules and principles of the Helsinki Declaration.

Study Population

Medical records of patients treated in Hacettepe University Hospital with the diagnosis of IE between January 1974 and June 2005 were retrospectively examined.

Data collected were as follows: age, sex, signs, duration of hospitalization, comorbidities, source of infection, haemoglobin level, white-blood cell counts (WBC), erythrocyte sedimentation rate (ESR), C-reactive protein, rheumatoid factor, presence of; any murmurs, petechiae, splinter haemorrhage, conjunctival haemorrhage, Janeway lesions, splenomegaly, Roth spots, Osler's nodes, clubbing, neurological signs, embolic phenomena, transthoracic echocardiography (TTE) and transoesophageal echocardiography (TEE) findings, blood culture results, history of prior antibiotic treatments, medical or surgical treatment and mortality.

Cases were re-evaluated according to modified Duke Criteria.

Statistical Analysis

SPSS software version 10.0 was used for statistical analysis. Data were presented as mean±standard deviation for continuous variables. For categorical variables frequencies were calculated. Chi-square test (χ^2) was performed for comparing qualitative variables. Mann-Whitney U test was used to establish the relationship between mean age and mortality. Spearman Correlation test was applied for demonstrating the relationship between age and mortality. For time trends, linear ratios were analyzed by χ linear trend test (χ^2_{LT}).

RESULTS

Two hundred and ninety cases treated between January 1974 and June 2005 with IE diagnosis was identified during the search. When these cases were re-evaluated using modified Duke Criteria: 145(50%) cases were classified as definite endocarditis, and 98(33%) cases were as possible endocarditis. Forty-seven cases (16.2%) were rejected as they did not fulfil the criteria.

Of the 243 patients 109 were female (44.8%) and 134 male (55.2%). The mean age of the patients was 38±16.4 years (Table 1). The mean age of the patients showed an

increasing trend throughout the time ($p < 0.001$); it was 29 years between 1974- 1980 but increased to 54 years in 2001-2005 period (Figure 1).

Table 1. Baseline characteristics of patients with infective endocarditis

Age, mean±SD	38±16
Gender; Female/Male n (%)	109/134 (44.8/55.2)
Predisposing factors	n (%)
Rheumatic valvular disease	124 (60)
Prosthetic valve	51 (21)
Congenital heart disease	14 (5.7)
Sclerotic aortic disease	9 (3.6)
Previous IE	2 (0.8)
Cardiac pacemaker	2 (0.8)
Intravenous drug abuse	1 (0.4)
Laboratory findings	
Haemoglobin (g/dl), mean	10.3± 1.86
White blood cells (/mm ³), mean	12.1± 2.45
Erythrocyte sedimentation rate (mm/hour), mean	71±27.8
Rheumatoid factor positivity, %	37
Clinical findings	n (%)
Fever	219 (90)
Murmurs	218 (89)
Splenomegaly	108 (44)
Petechiae	23 (9.4)
Splinter hemorrhage	22 (9)
Clubbing	14 (5.7)
Roth's spots	8 (3.2)
Osler nodes	7 (2.9)
Janeway lesions	4 (1.6)
Embolic event	89 (36)
Involved valve	n (%)
Mitral valve	52 (44)
Aortic valve	36 (40)
Mitral + aortic valve	11 (9.6)
Prosthetic valve	16 (13.5)
Pulmonary valve	1 (0.9)
Tricuspid valve	2 (1.7)
Causative microorganism	n (%)
<i>S. aureus</i>	37 (15.2)
<i>S. viridans</i>	25 (10.3)
<i>S. epidermidis</i>	16 (6.6)
<i>E. faecalis</i>	18 (7.4)
<i>Brucella</i>	13 (5.3)
<i>P. aeruginosa</i>	7 (2.9)
<i>S. haemolyticus</i>	4 (1.6)
Prior antibiotic use, n (%)	120 (49)
Nosocomial infection, n (%)	45 (18.5)
Surgical treatment, n (%)	74 (30)
Mortality, n (%)	71 (29)

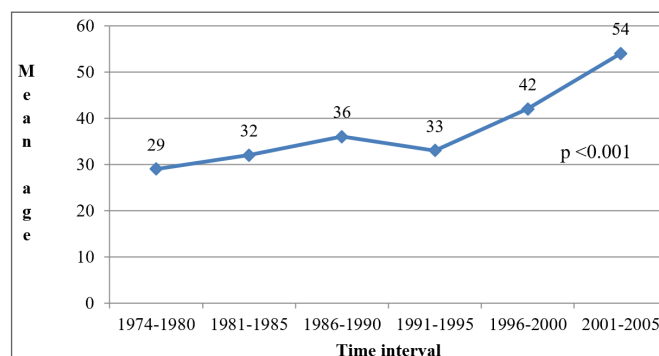


Figure 1. Mean age of patients in consecutive time periods

Underlying Heart Disease

In 207 cases (85%) at least one underlying heart disease was identified; rheumatic valvular disease (RVD) was the most frequent underlying heart disease (60%) followed by prosthetic valve (21%). Underlying heart diseases are shown in **Table 1**. While rheumatic valvular disease seems the most frequent underlying heart disease, substantial changes have occurred throughout the time; a decrease has been observed in the frequency of RVD. In the 2001-2005 periods prosthetic valves have become more frequent than RVD. In this last period no structural heart disease has been identified in 40% of the cases (**Figure 2**).

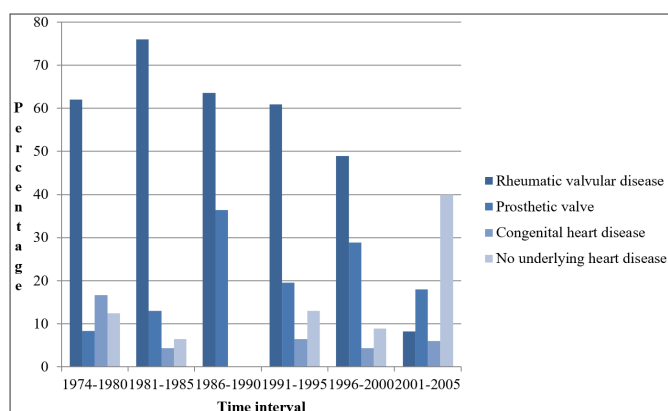


Figure 2. Distribution of underlying heart diseases in consecutive time periods

Causative Microorganisms

Blood cultures were positive in 138/243 (57%) of patients with diagnosis definite or possible IE. The most common pathogen was *S. aureus* in 37 patients (15.2%), followed by *S. viridans* in 25 patients (10.3%), *E. faecalis* in 18 patients (7.4%) and *Brucella* in 13 patients (5.3%) (**Table 1**). In all time periods *S. aureus* was more common than *S. viridans* except for the 1986-1990 period (**Figure 3**).

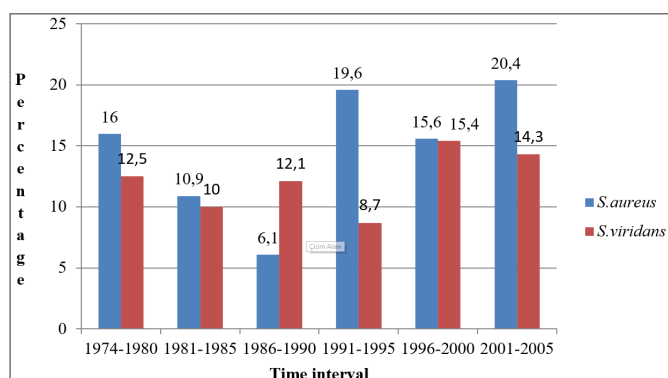


Figure 3. Comparison of incidences of *S. aureus* and *S. viridans* in consecutive time periods

Blood cultures were negative 90 patients (43%). The percentage of culture negative cases decreased throughout the time, from 63% in 1981-1985 period to 28% in 2001-

2005 period (**Figure 4**). The decrease was statistically significant ($\chi^2_{LT} = 3.26, p=0.002$).

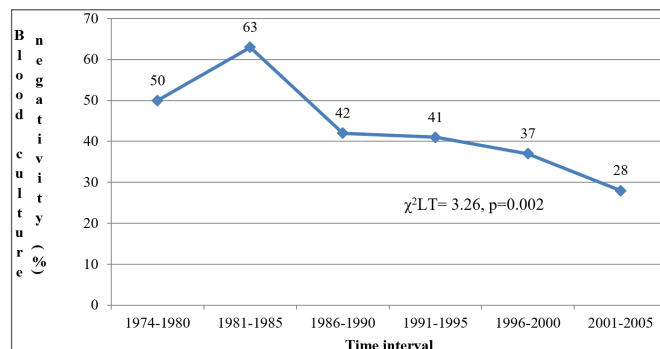


Figure 4. Percentage of blood culture negativity in consecutive time periods

Echocardiographic Findings

From 1990 all cases were evaluated by transthoracic echocardiography (TTE). Transoesophageal echocardiography (TE) was available since 1995. Since then TEE was performed in 56 /110 (50%) of cases. Echocardiographic findings compatible with modified Duke criteria was found in 118 patients of the 243 patients (48%) classified as IE. TEE detected vegetations in 24(20%) cases which could not be detected by TTE. Vegetations were most commonly seen on mitral valve in 52(44%) patients followed by aortic valve in 36(30%) patients (**Table 1**).

Complications

Complications were present in 111 of the 243 cases (**Table 2**). The most frequent complication was embolic events (96, 39.5%). Heart failure was the second most frequent complication (16, 6%). Cerebral embolism was the most common embolic events occurring in 65 cases (26.7%). Spleen (13 cases, 5.3%), extremities (10 cases, 4.1%) and lungs (3 cases, 1.2%) were also affected by embolic events.

Surgery

Surgery was performed in 74 of the 243 cases (30.5%) diagnosed with IE. Surgery was indicated most commonly for heart failure (21.6%) followed by embolic events (18.9%), valve dysfunction (17.6%), prosthetic valve failure (14.9%). Indications for surgery are given in detail in **Table 2**.

Mortality

In-hospital mortality rate was 30.6%. Major causes of death were as follows: sudden death (14 cases, 19.7%), cerebral embolism (13 cases, 18.3%), cardiogenic shock (9 cases, 12.6%), pulmonary embolism (2 cases, 2.8%). A marked decrease in mortality has been observed over the time. Mortality rate decreased from 47.5 % in the 1974-1980 periods to 22.7 % in 1996-2000 periods. But

in 2001-2005 period there was an unexpected increase in the mortality rate (Figure 5).

Table 2. Complications of infective endocarditis and indications for surgery	
Complication	n, (%)
Embolic event	93 (38.3)
Congestive heart failure	13 (5.3)
Embolic event +congestive heart failure	3 (1.2)
Chordae tendineae rupture	2 (0.8)
Indications for surgery	
	n, (%)
Congestive heart failure	16 (21.6)
Embolic events	14 (18.9)
Valve dysfunction	13 (17.6)
Prosthetic valve failure	11 (14.9)
Mobile vegetation > 10 mm	6 (8.1)
Congenital heart defect	4 (5.4)
Perivalvular abscess	2 (2.7)
<i>Brucella endocarditis</i>	1 (1.4)
Uncontrolled infection	1 (1.4)
Prosthetic valve failure + perivalvular abscess	1 (1.4)
Candida endocarditis	1 (1.4)
Valvular obstruction	1 (1.4)

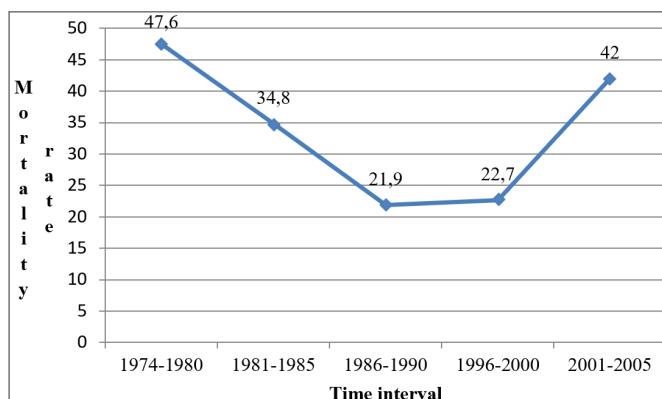


Figure 5. Mortality trend in consecutive time periods

Mean age of patients who died were higher compared to the surviving patients (42.44 ± 16.70 vs. 37.79 ± 16.15 , $p < 0.005$)

Mortality rate was significantly lower in patients who underwent surgery compared to ones who did not (19.2% vs. 35.8%, $p < 0.005$). Mortality rate was also significantly lower in patients with community acquired infection compared to ones with nosocomial infection (27% vs 45%, $p < 0.005$). Mortality rate was higher but not significant in patients >60 years compared to patients ≤ 60 years (38.9% vs 29.3%, $p = 0.078$).

Multivariate analysis (Table 3) showed that embolic events (OR=3.304, 95% CI: 1.703-5.404, $p = 0.047$) nosomial infection (OR=2.24, 95% CI: 1.140-4.396, $p = 0.019$) and surgery (OR=0.425, 95% CI: 0.218-0.827, $p = 0.012$) were independent risk factor for mortality, but not *S. aureus* (OR=3.304, 95% CI: 0.499-1.856, $p = 0.901$)

or blood culture positivity (OR=1.7, 95% CI: 0.655-3.054, $p = 0.071$).

Table 3. Multivariate analysis of factors predicting in-hospital mortality of patients with infected endocarditis			
	Odds'ratio	95%CI	p-value
Embolic events	3.034	1.703-5.404	0.047
Nosocomial infection	2.24	1.140-4.396	0.019
Surgery	0.425	0.218-0.827	0.012
<i>S. aureus</i>	0.962	0.499-1.856	0.901
Blood culture positivity	1.7	0.655-3.054	0.071

DISCUSSION

The features of IE over a 31-year period in a tertiary care hospital are analyzed in this retrospective study. The mean age was 38 ± 16.4 years in this period but showed an increasing trend throughout the time. In 2001-2005 period mean age increased to about 54 years. The mean age was found to be 45 in a study from our country which included 2002- 2004 period (6). In a recent study of IE from our country median age was 58 (7). The increase in age is considered to be associated with the decrease in rheumatic heart diseases and increase in degenerative heart diseases (5). In our series RVD was the leading predisposing factor until 2000, but a striking decrease in the incidence of RVD was observed in 2001-2005 period which is in concordance with the literature (1,4). Interestingly in the last period most of IE cases occurred in patients with no underlying structural heart disease. In this period the mean age of the patients increased to about 54 years. We may postulate that the individuals in this group may have more chronic illnesses necessitating more medical interventions predisposing them to IE.

S. aureus was the most common isolated microorganism in IE cases. It was followed by viridians group *streptococci*. Our results are in concordance with a pooled analysis of 1270 IE cases in Turkey (8) and a consensus report on IE (9). *S. aureus* is also the most common pathogen in Western countries and United States of America (2,5). In the study by Correa et al. (10), which included the period between 1970 and 2006, a similar period to our study, viridians group *streptococci* was more common than *S. aureus* except for the 2001-2006 period. The decrease in the incidence of viridians group *streptococci* was suggested to be associated with significant decrease in the proportion of rheumatic heart disease as a result of successful treatment of streptococcal pharyngitis. But unlike their findings *S. aureus* was more common than viridians group *streptococci* in all periods in our study, except for the 1986-1990 periods.

Overall, blood cultures were negative in 43.2% of cases. Although we observed a significant decrease in culture negative cases throughout the time; in 2001-2005 period culture period cases consisted 28% percent of all the cases, the number is still high. Recent European and American studies report rates ranging between 5%-20% (11,12). In our study group 58% of blood culture negative cases had a history of antibiotic use in two weeks time prior to diagnosis which may explain such high rate. In the above mentioned pool analysis of IE cases in Turkey, incidence of negative blood culture was 31.1 % (8). In two studies conducted at tertiary care hospitals from Turkey culture negative cases were reported at similar high rates 48% (4,7). Authors explain this undesired high rate as a consequence of being a referral hospital where patients have a history of antibiotic use prior to referral.

Surgery was performed in 30.5% of the cases, comparable to the rate reported (36.9%) in a study from Portugal (13). In that study main indication for surgery was heart failure similar to our study. Higher surgery rate (69.7%) was reported in a study from our country which is explained as a possible result of selection bias by the author (7).

Embolic events were the most frequent complication identified in our study. Most emboli were seen in the brain. Mostaghim et al. (2) also reported a similar finding. They have two explanations for this finding. First one is ordering more brain imaging as result of increased awareness of physicians for the neurologic symptoms. Second one is the upward direction of the branches of aorta supplying the brain which makes it easier for embolism .

In-hospital mortality rate found in our study (30.6%) was within the limits reported in the literature (2,3). Over the 31-year period a substantial decrease was observed in mortality rate in our patients except 2001-2005 periods where mortality rate increased to 42%. This unexpected increase may be explained by the fact that the patients in this period were older; older age is associated with more chronic medical conditions making individuals more vulnerable.

Surgical therapy in IE was reported to be lower mortality rates in the literature (13,14). We found a significant lower mortality rate in patients who underwent surgery.

This study is not without limitations. Retrospective nature of this study is the major limitation. The high rate of culture negative cases may have precluded us detecting the real incidence of microorganisms, especially viridians group *streptococci*. As the study is conducted at a tertiary care hospital, it will not be proper to generalize the results

to the whole population. But 31-year study period in our study gives a good perspective to observe the changes occurred in the profile of IE.

CONCLUSION

We studied the changing profile of IE over a 31-year period in a tertiary care hospital. We found out that the mean age of patients with IE has dramatically increased evidently increased and that the incidence or RVD has decreased. The rate of culture negative cases has also decreased. Embolic events and nocomial infections were independent predictors of mortality. But it was encouraging to see the improvement in survival rates throughout the time; surgery was associated with improved survival rates.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was a thesis study. It was completed with the approval of Academic Board of Department of Internal Medicine, Hacettepe University (Date: 05.05.2006, Decision No: 2).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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