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INFECTIVE ENDOCARDITIS: A 10-YEAR STUDY IN SHIRAZ UNIVERSITY HOSPITALS

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ABSTRACT

The medical records of all patients discharged with the diagnosis of "infective endocarditis", "subacute bacterial endocarditis (SBE)," "acute bacterial endocarditis (ABE)," and "bacterial endocarditis" from March 1977, to February 1987, were reviewed. 84 cases fulfilled the criteria of endocarditis. Sixty-one percent were male and the mean age was 25.7 years. 57% were culture-negative and among culture-positive cases, *S. aureus* was predominant (44%). Culture-positivity was associated with higher mortality. Multiple valve involvement was most common (36%). Among fatal cases, mitral involvement was most common (33%) and mitral involvement was associated with the highest mortality (22%). 92% of the patients showed evidence of abnormal heart before development of endocarditis, rheumatic heart disease being the most common (73%). The mortality rate was 21% and CNS complications were the major cause of death. Although much of our results are consistent with published data, there are some major differences. Points which might explain these differences are: high incidence of rheumatic heart disease among Iranians, delay in seeking medical care, indiscriminate use of antibiotics prior to adequate cultures, and shortcomings in laboratory techniques.
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INTRODUCTION

Infective endocarditis is a disease that has fascinated students of medicine and infectious disease experts; there has been a vast compilation of data ever-since Osler delivered the famous lectures about "Malignant Endocarditis" more than a century ago,[1] and modern medical literature abounds in numerous excellent reviews concerning various aspects of infective endocarditis. Nevertheless, despite the many advances, it remains a disease with significant morbidity and mortality.

Endocarditis is an evolving disease with changes in the age of the patient, underlying heart disease, and becteriology. Extensive data have been gathered from various institutions regarding the epidemiology, pathogenesis, diagnosis, bacteriology, and other facets of infective endocarditis. Some have specifically dealt with the changing spectrum of this disease.[2,3]

To our knowledge, there has, as of yet, been no published review of this subject among the Iranian population and the present study is an attempt to review as many aspects of endocarditis as possible among patients admit-

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ted during the past ten years in Shiraz University Hospitals and to compare these with other published reports.

PATIENTS & METHODS

Shiraz University Hospitals employ the International Classification of Disease (ICD) coding system. The medical records of all patients discharged with the diagnosis of "Infective Endocarditis", "SBE", "ABE" and "Bacterial Endocarditis", from March 1977 to Feb. 1987 were reviewed at two major Shiraz University Hospitals: Nemazee Hospital (NH), and Faghihi Hospital (FH).

Cases were categorized as "definite" (n=10), "probable" (n=32), or "possible" (n=42) infective endocarditis according to the widely-accepted criteria proposed by Pelletier and Petersdorf[4] and modified by Von Reyn.[5] Resulting data were statistically analyzed by the chi-square method.

RESULTS

Of the 96 records reviewed, 84 cases fulfilled the above mentioned criteria as infective endocarditis. Both hospitals were similar regarding the number of cases, mortality, and mean age. There was a predominance of males in FH (74%) in comparison to NH (46%) (X^2= 7.19; $p<0.05$). There was a slight, but non-significant predominance of *S. aureus* cases in FH and of *S. Viridans* in NH

There were 51 males (61%) and 33 females (39%). The age range was 1-58 years with a mean of 25.66±2 years (Fig.1). No significant difference in mortality was observed between males (22%) and females (21%). The mean age of males was similar to the mean age of females.

57% of our patients had persistently negative blood cultures; of these, ten patients had received antibiotics before cultures were drawn. Culture-positivity was associated with significantly higher mortality (31% vs. 15%) (X^2= 4.56; $p\leq 0.001$). Table I shows the results of blood cultures and mortality.

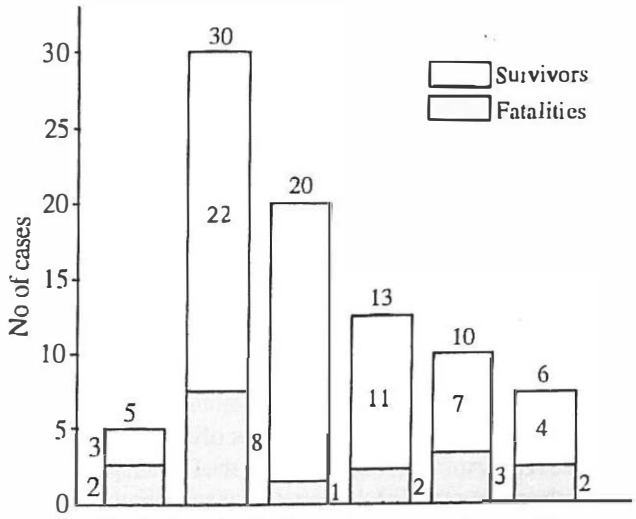

Fig. 1. Age distribution and age-related mortality.

Determinations of site of endocarditis was based on clinical assessment, echocardiography, and observations at surgery and autopsy. As shown in Table II, no definite

Table I. Organisms and mortality

Organism	Patients	Patient deaths
S. aureus	16	8
S. epidermidis	3	0
S. viridans	10	1
Enterococci	1	0
Non-hemolytic Streptococci	1	0
Pneumococcus	2	0
B. subtilis	2	1
Diphtheroids	1	1
Culture-negative	48	7
Total	84	18

Table II. Site of involvement

Location	Number	Fatal cases
Aortic	14	2
Mitral	27	6
Aortic + mitral	27	2
Mitral + tricuspid	2	0
Aortic + tricuspid	1	1
Congenital (non-valvular	4	1
Other	2	1
Unkown	7	5
Total	84	18

site of involvement was found in seven cases, despite complete physical examinations, echocardiography, and inferences from the patient's history. Mitral involvement was associated with the highest mortality (22%).

Ninety-two percent showed evidence of abnormal hearts before development of endocarditis. Rheumatic heart disease (RHD) was the most common underlying disease (73%). Twenty-eight percent had history of clinically-documented rheumatic fever. The number of patients with congenital heart disease (CHD) was 12; among these, there were four with pure mitral valve prolapse (MVP), three cases of ventricular septal defect (VSD), and one with tetralogy of Fallot. There were only three patients with prosthetic valves. Five patients had a previous history of endocarditis. For one of the patients who had a positive blood culture, no evidence of pre-existing heart disease other than mitral dysfunction during the course of acute myocardial infarction was found and the underlying heart disease was considered to be atherosclerosis (Table III).

Table III. Pre-existing heart disease

RHD	50	11	61
CHD	11	1	12
Atherosclerotic	1	0	1
Prosthetic	2	1	3
None	2	5	7
Total	66	18	84

Table IV. Physical Findings

Signs	Total number (percent)
Fever	74(88%)
Murmur	72(86%)
Splenomegaly	47(56%)
Skin lesions	24(29%)
Hemiplegia	17(20%)
Clubbing	16(19%)
New Murmur	12(14%)
Hepatomegaly	11(13%)
Arthritis	9(11%)
Splinter hemorrhage	8(10%)
Roth's spot	6(7%)
Osler's node	6(7%)
Changing murmur	5(6%)
Conjunctival hemorrhage	3(4%)

An apparent protal of entry was present in 16 patients (19%). Dental infection and manipulations were the most common events related to the development of endocarditis, noted among five patients. Four patients had recent ENT procedures, and four developed endocarditis following gynecological procedures. There was one patient who had undergone urethral catheterization and another had an orthopedic prosthesis prior to development of endocarditis.

The frequency of specific physical findings at the time of admission are detailed in Table IV. Fever and heart murmur were the most frequent signs.

Anemia was commonly present, with a mean hematocrit of 31.3±0.7%. Thirty-seven percent had initial hematocrits less than 30%. The mean initial hematocrit of survivors was not significantly higher than that of fatalities.

Total WBC counts ranged widely, with a mean of 13,400±1,900/mm^3. Sixty percent of the patients had mean WBC counts more than 10,000/mm^3. The mean WBC count of fatalities (19,900±3,000) was significantly higher than that of survivors (11,200 ±900) (X^2= 3.8; p≤ 0.005).

Admission erythrocyte sedimentation rates (ESR) were usually elevated, in 81% of cases being greater than 30 mm/h. The mean ESR at the time of admission was 51.5± 10 mm/h. The mean ESR in survivors was similar to the mean ESR in fatalities.

Platelet counts varied between 30,000 and 600,000, with a mean of 318,000±30,000. The mean platelet count for fatalities (238,000±45,000) was significantly lower than that of survivors (355,000±30,000) (X^2=3.3; p<0.025).

Test for rheumatic factor was positive in eight of the 15 patients of whom this test was performed (53%). The VDRL test was performed for nine, all revealing negative results. LE-cell was positive in one of eight patients for whom it was performed. C-reactive protein was determined for twelve and in nine (75%), it was positive.

The incidence of microscopic hematuria was 56%, and significantly higher among fatalities (70%), than survivors (51%) (X^2=4.6; P≤0.001). Lumbar puncture was done in 11 cases and was abnormal in 10. The most common abnormality was increased protein (seven patients), followed by polymorphonuclear predominance (five patinets) and xanthochromia (four patients). The WBC counts ranged from 12 to 350 per mm^3 and only three patients had cell

Table V. Echopositivity as related to mortality

	Survivors	Fatalities	Total
Echopositive	17	5	22
Echonegative	16	0	16
Total	33	5	38

Table IV. Presumable causes of death

	Number (%)
C.N.S.	5(28%)
Septic embolism	2
Mycotic aneurysm	3
C.H.F.	4(22%)
Renal failure	4(22%)
Sepsis	3(17%)
Unknown	2(11%)
Total	18(100%)

counts above 100/mm^3.

M-mode echocardiography was obtained for 38 patients and vegetations were detected in twenty-two (58%). As related to mortality, "echo-positivity" was associated with a significantly higher mortality (X^2= 7.04; $p \leq 0.001$) (Table V).

Overall, central nervous system (CNS) complications were most common (17 patients), consisting of septic embolization (eight patients). Overwhelming sepsis was present in 13 patients, congestive heart failure in nine, and eight patients developed renal failure. Two patients developed pulmonary embolization and one was noted to have multiple splenic abscesses. Two patients required emergency valve replacement surgery.

There were 18 deaths (mortality= 21%). Presumable causes of death are shown in Table VI.

DISCUSSION

In our series, there was a significant male predominance (61%), fitting into the previously reported incidence of 51 to 73%.[1,5] Mean age was nearly twenty years younger than all reports.[2,3] The youngest reported mean age of patients with infective endocarditis in the world literature is 30 years in a study involving the years 1932-1943.[6] The rise in the age of patients with endocarditis in American studies has been attributed to the decreasing frequency of rheumatic fever in the United States.[7] Thus, the younger age of our patients might be explained by the persistently high incidence of rheumatic fever and rheumatic heart disease among Iranians. The mean ages of males and females in our study are not significantly different and this is in contrast to other reports which reveal males to be six years older.[8] In confirmation of previous reports indicating higher mortality among the young and the old, we also found a significantly higher mortality rate in the 1-19 year-old range and the 40-59 year-old population.

Our cases revealed a very high incidence of culture-negativity, as compared with the 10-12% incidence reported by others;[2,4,5] an important contributory factor might be the difficulty in recovering slow-growing fastidious gram-negative rods and anaerobes. Anaerobic cultures are only rarely performed in Shiraz hospitals. Ten patients had definite history of antibiotic treatment immediately prior to drawing blood cultures. Reports indicate up to 62% of patients with culture-negative endocarditis of having received antibiotics before cultures.[9] Another possible explanation for the higher incidence of culture-negativity might be the prolonged duration of illness before patients have sought medical care ("bacteria-free state"). Of the culture-positive cases, there was a significant predominance of *S. aureus*. This might again be explained by the facility of recovering *S. aureus* as in comparison to other organisms. In general reviews of endocarditdes, nearly 90% of culture-positive endocarditis are caused by staphylococci and streptococci;[3,10] this is also true in our patients. The relative frequency of staphylococcal endocarditis has increased in recent years, and this has been attributed to the increasing frequency of intravenous drug abuse;[11] none of our patients being addicted. According to Washington, prior administration of antibiotics especially reduced the positivity of cultures in cases of streptococcal endocarditis.[12] The incidence of culture-negative infective endocarditis in the 35 reviews studied by Pesanti ranged from 3% to 64%, reflecting variations in defining endocarditis as well as culture procedures.[9]

One of the problems encountered is the distinction between staphylococcal bacteremia and staphylococcal endocarditis. Although various methods including echocardiography, teichoic acid antibodies, or circulating immune complexes have been used, the distinction is at times almost impossible.[13] We mainly relied on clinical criteria and echocardiography to make this distinction.

Pneumococci account for 1-5% in most series.[14,15] Some reprts have noted gonococci to account for 4-10%.[16] In our study, there were two patients with pneumococcal endocarditis and none with gonococcal endocarditis.

Ninety-two percent showed evidence of abnormal hearts. This is in contrast to the 60-70% reported by others.[17] The high incidence of RHD in Iran might explain this difference. RHD was the underlying problem in 73% of cases as compared to recent reports of 25-40%.[3,17,18] The rather older review by Kerr has the highest published percentage of RHD (80-90%).[19]

The incidence of congenital heart disease among patients with infective endocarditis has ranged from 6% to 26%;[20] our data shows an incidence of 14%. Five percent of our patients had pure mitral valve prolapse; the incidence has been reported to be about 5 to 17 percent.[21,22]

The incidence of prosthetic valve endocarditis (PVE) among patients with endocarditis is quite variable, ranging from seven to thirty-three percent.[4,7,23] Among our patients, there were only three with PVE. This reflects the fact that valve replacement surgery had been performed sporadically in the study period.

The majority of our patients had no apparent bacterial portal of entry. The single most common portal of entry has been noted to be dental infection, and this was true among our patients.

Of the physical findings fever and heart murmurs were the most common, consistent with previous reports.[4,5,24] The incidence of splenomegaly has been noted to range from 28 to 57 percent.[4,5] It correlates with the chronicity of disease and our data reveals 55%, relating to the time-interval our patients take to refer to hospitals. Recent reports indicate clubbing to occur in 7-13% of case;[4] our data reveal 19%, again reflecting the rather chronic nature of endocarditis among our patients. No clubbing occurred among patients with CHD.

Considering the laboratory data, the mean hematocrit was significantly lower than that noted by others.[4,5] 81% of our patients had erythrocyte sedimentation rates higher than 30 mm/h, which is comparable to other reports.[4,5] The incidence of positive rheumatoid factor and microscopic hematuria is similar to other reports.[4,5,25]

The accuracy of a positive echocardiogram has been noted to be 76%, that of a negative test to be about 80%; and "echopositivity" has been correlated with the development of congestive heart failure (CHF), need for valve replacement, risk of embolization, and mortality.[3,13,26-29] Among our patients, "echopositivity" correlated with significant mortality.

The overall mortality of infective endocarditis has been noted to be ten to fifty percent,[4,5,10,30,31] the most common cause of death being CHF, followed by CNS complications.[3,4,5,10,32,33] Our data shows a mortality rate of 21% and the most common presumable cause of death to be CNS complications.

In conclusion, although much of our results are consistent with published data, there are some major differences such as age, underlying heart disease, microbiology and the high incidence of CNS complications. Points which might explain, to some extent, these differences are: the high incidence of rheumatic heart disease among Iranians, delay in seeking medical care, the indiscriminate use of antibiotics prior to adequate cultures, and shortcomings in laboratory techniques.

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