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Abstract

Background: The spectrum of infective endocarditis (IE) is significantly different in developed and developing countries. The present study was conducted to study the clinical profile and outcome of infective endocarditis in Pakistan.

Methods: A descriptive cross-sectional study with review of medical records for 188 patients admitted to our teaching hospital with a diagnosis of IE from January 1988 to December 2001. One hundred fifty-nine subjects fulfilled the modified Duke diagnostic criteria.

Results: Definite IE was found in 59.7% (95/159) patients, while the rest had possible IE. One-third of subjects had acute IE 55/159 (34.5%). Subacute IE was found in 62% (99/159) and Nosocomial IE in 3% of the cases. Eighty six (54%) were classified as having culture-negative endocarditis and 73 (46%) as culture positive. Ninty four patients (59%) had an underlying predisposing factor including congenital heart disease (31%) and rheumatic heart disease (21%). The most frequently isolated organisms were streptococci (52%) and followed by staphylococci (29%). Fourteen (8.1%) patients had right-sided cardiac involvement. Using univariate analysis, patients with heart failure, neurologic or renal complications, septicemia, nosocomial endocarditis, and prosthetic valve endocarditis were at increased risk of death ($p \leq 0.05$), however no individual microorganism, or specific site, size, or morphology of vegetation seen on echocardiogram were significantly associated with death. Thirty-seven (23%) patients died of endocarditis or its complications.

Conclusion: Endocarditis continues to be an important contributor to morbidity and mortality in Pakistan, especially in young adults. Our patients differ from the west in terms of epidemiology, predisposing factors, microbiology, complications, and outcome.

Keywords: Infective endocarditis, Pakistan, Epidemiology, Microbiology, Complications, Outcome

Introduction

The epidemiology, clinical, and microbiologic spectrum of infective endocarditis (IE) is significantly different in the developing countries compared to the western world. These differences can be attributable to multiple factors present in poorer countries including significantly higher incidences of rheumatic heart disease and uncorrected congenital heart disease, excessive and improper use of antibiotics, late clinical presentation, and worse outcomes.[1,2] In addition, developing countries may have a higher incidence of 'culture negative endocarditis' than in the west, largely secondary to prior doctor-prescribed or self-administered antibiotic use[3,4], and life-threatening complications from IE are still common despite echocardiographic diagnosis and use of effective antibiotics.[5]

There is a paucity of published reports about IE from developing regions of the world[5,6], and there are no large case series from centers involved in cardiac intervention and surgery. In light of the changing global trends in endocarditis over the last four decades, further insight into the clinical expression of the disease in developing countries and a comparison with western data is warranted. The authors have previously conducted the first case series of endocarditis from Pakistan. The study showed that life-threatening complications from endocarditis are still common despite the use of effective antibiotics and echocardiographic diagnosis.[5] Herein, we present one of the largest case series on IE from the Indian subcontinent

Patients and Methods

We reviewed the medical records of all patients admitted to the Aga Khan University Hospital in Karachi, Pakistan with a diagnosis of IE during the period, January 1988 through December 2001. The Aga Khan University Hospital is a tertiary care hospital serving more than 10 million people of the city, the surrounding province of Sindh, and elsewhere throughout Pakistan. The patient population includes a large number of immigrants from around the country and referrals from underserved rural areas where rheumatic heart disease and undetected congenital heart disease are very common. The mean number of medical adult medicine and pediatric admissions during the study period was more than 13,000 patients annually.

The search was made through electronically-coded medical records and the echocardiography logbook maintained by the Cardiac Diagnostic Laboratory. One hundred and eighty-eight patients were identified with suspected endocarditis. Of these, 159 patients fulfilled the modified Duke criteria[7], and were included in the final analysis. We used the modified Duke criteria in order to validate our results. Cases were defined clinically as "definite" if they fulfilled two of the Duke major criteria, one major plus three minor criteria, or five minor criteria; they were defined as "possible" if they fulfilled one major plus one minor criteria, or three minor criteria. "Acute" endocarditis was defined as beginning suddenly with a high fever (102° to 104°F [38.9° to 40°C]), fast heart rate, fatigue, and rapid and extensive heart valve damage. "Subacute"endocarditis was defined as symptoms of fatigue, mild fever (99° to 101° F [37.2° to 38.3°C]), moderately fast heart rate, weight loss, sweating, a low red blood cell count, all generally occurring for months before diagnosis.

The laboratory workup of the study group included: complete blood count, erythrocyte sedimentation rate, serum creatinine, serum electrolytes, urinalysis and urine culture, chest x-

ray, blood cultures (3-5 sets of aerobic and anaerobic bottles) drawn before the initiation of antibiotics, transthoracic echocardiography (TTE) and, if needed, transesophageal echocardiography (TEE). In cases with negative blood cultures, abdominal ultrasonography, and where appropriate, Mantoux skin testing and sputum for acid-fast bacilli smear and culture were performed. In patients with fever and headache or with neurologic signs, cerebrospinal fluid examination and neuroimaging (computed tomography or magnetic resonance imaging) were conducted. In selected cases, an autoimmune profile was obtained. A peripheral blood smear looking for malarial parasites was performed in all subjects with unexplained fever. Fungal blood cultures were sent in selected cases.

Statistical analysis

Statistical analysis of data was performed using the computerized software program SPSS version 13.0. Descriptive statistics were presented as percentages and as mean +/- standard deviation (SD). Univariate analysis was performed for prognostic factors of mortality using Pearson's chi square test, Fischer's exact test, or student's t test, where appropriate. A p value of < 0.05 was considered statistically significant.

Results

General characteristics

One hundred and fifty-nine patients with IE were identified according to the modified Duke criteria, and their general characteristics are shown in Table 1. The annual number of IE episodes during the study period was 0.87 per 1,000-hospital medical admissions. Mean patient age was 34 years + 21.2 SD (range, < 1 month to 87 years), and 34 (27%) patients were < 16 years of age. The mean age for patients > 16 years was 42 +/- 16.7 (SD). The male: female ratio was 1.8:1. Nosocomial endocarditis was seen in five patients (3%). One-third of subjects had acute endocarditis and the remainder had subacute IE. Of the 159 subjects, 86 (54%) were classified as having culture-negative endocarditis and 73 (46%) as having culture-positive endocarditis. Sixty percent of patients had definitive endocarditis according to the Duke criteria while the rest had possible endocarditis.

Underlying predisposing factors

Overall, 94 patients (59%) had an underlying predisposing factor (Table 2). Most commonly encountered risk factors included congenital heart disease (25%), most commonly a ventricular septal defect and rheumatic heart disease (21%). Other important conditions were mitral valve prolapse with regurgitation (6%), prosthetic valve endocarditis (5%), and stenotic aortic valve disease (2%). Only one patient had documented history of intravenous drug use. Two patients were on dialysis with indwelling central catheters.

Microbiology

Causative microorganisms included streptococci (23%), staphylococci (13%; equally split between Staphylococcus aureus and Staphylococcus epidermidis), Gram-negative bacilli (5%), and Enterococcus faecalis (4%) (Table 3). Eighty-six subjects (54%) had no growth on multiple blood cultures and were thus classified as culture-negative IE.

Echocardiography

Echocardiography was performed in 155 of 159 (97%) patients: TTE in 152 (96%) and TEE in 20 (13%) patients. TTE was positive in 110 of 152 (72%) subjects and TEE in 15 of 20

subjects (75%). Fourteen (8%) patients had right-sided cardiac involvement. The distribution of valves and other significant findings on echocardiography can be seen in Table 3.

Treatment

The antibiotic therapy used in our patients conformed in most cases to the guidelines of the American Heart Association for the treatment of IE. Sixty-eight percent of patients with streptococcal infections were treated with a combination of penicillin plus an aminoglycoside (gentamicin). The remainder received monotherapy with a beta-lactam or a glycopeptide (vancomycin or teicoplanin). Methicillin-sensitive staphylococci (62% of all staphylococci isolated) were treated with cloxacillin; subjects with methicillin-resistant Staphylococcus aureus (MRSA) or Staphylococcus epidermidis (MRSE) received vancomycin. Aminoglycosides were added for synergy in one-third of MRSA subjects, while rifampin was added in only one patient. Sixty-eight percent of patients with culture-negative endocarditis received a combination containing at least one beta-lactam drug (penicillin G with or without cloxacillin) and an aminoglycoside; 12% patients also received vancomycin and 21% also received a 3rd-generation cephalosporin. All patients received 4-6 weeks of antimicrobial therapy. Surgical intervention was required in 18 (11%) of the study group, with the most common indications being heart failure refractory to medical treatment, valve or myocardial abscess, prosthetic valve endocarditis, very large vegetations, systemic embolization, or IE refractory to medical treatment.

Complications and outcome

Complications occurred in about half of the study group and included neurologic (26%), cardiac (25%), renal (13%), hematologic (13%), embolic (10%), pneumonic (8%), and septic (4%) complications (Table 4). Thirty-seven (23%) patients died of IE or its complications. Mean patient follow-up was 3.5 months. Twenty-one patients were lost to follow-up.

Risk factors for mortality

Table 5 demonstrates the risk factors for mortality using univariate analysis. In general, patients with neurological, cardiac, or renal complications or sepsis were at increased risk of dying. Nosocomial endocarditis was also associated with an increased mortality. No individual microorganism, or specific site, size, or morphology of vegetation seen on echocardiogram were significantly associated with death. Patients with previous cardiac surgery, especially those with prosthetic valve endocarditis, were also at increased risk of death.

Discussion

This study represents one of the largest case series of IE reported from the Indian subcontinent, and our data confirm that IE continues to be an important cause of morbidity and mortality in Pakistan. The spectrum of IE in our country differs from the west with respect to epidemiology, predisposing factors, microbiology, and outcome but is similar to that reported from neighboring India.[8-12]

The young age of our study group (mean age, 34 years) is consistent with other studies from the region,[9,10,13], but contrasts an older group (mean age 45-60 years) for patients with IE in the west.[14-17] The reasons for this discrepancy are likely multifactorial and include a higher incidence of rheumatic heart disease and uncorrected congenital heart disease in poorer

countries like Pakistan, and a more aged population with a higher incidence of degenerative heart disease in the west.[13,14,16]

We have previously reported on the impact of prior antibiotic use in culture-negative endocarditis.[18] Prior antibiotic therapy before clinical presentation (seen in 52% of our study group) was the primary contributor to the high incidence (54%) of negative blood cultures in our series. This incidence is consistent with the low yield from blood cultures, ranging from 21 to 67%, reported from elsewhere on the subcontinent.[5,6,10,13,14] In contrast, studies from industrialized counties report a diagnostic yield from blood cultures as high as 90% or more.[13-16] Excessive antibiotic dispensing is common in developing countries; at least one antibiotic may be prescribed for 54%-62% of patients presenting to general practitioners in Pakistan.[3,4] In addition, self-administration of antibiotics is commonplace in many developing countries where drugs are freely available and accessible without a prescription. As in the west, we assume that inadequate microbiologic techniques and infections with highly fastidious bacterial or non-bacterial microorganisms are other less likely reasons for negative blood cultures in our patients.

The Duke and modified Duke criteria both depend on echocardiographic, microbiologic, and pathologic criteria and patients with clinically-suspected IE are classified as "definite", "probable", and "rejected" cases based upon these criteria.[7] The degree of certainty of the diagnosis of IE often depends on the presence or absence of only one criterion. The modified Duke diagnostic criteria are heavily based upon positive blood cultures, and a low microbiologic yield from blood culture raises questions as to the validity of these criteria in diagnosing culture-negative endocarditis in developing countries.[17] More than 60% of our subjects with blood culture-negative endocarditis had 'possible endocarditis' according to the Duke criteria compared to < 15% of patients with positive blood cultures ($p < 0.001$, 95% CI 0.07-0.3). Furthermore, 29 patients diagnosed and treated for clinically presumptive IE were rejected from study entry according to the Duke criteria and negative blood cultures. In a study of the individual value of each of the Duke criteria for the diagnosis of IE, Rognon and colleagues found that the major microbiologic criteria had the highest relative importance.[19] Similarly, Tissieres and coworkers demonstrated the importance of positive blood cultures as a major IE criterion, with echocardiographic findings playing a less important role in diagnosis.[20] A positive blood culture was the only criterion that differentiated "definite" from "possible" IE. Thus, for patients with clinically-suspected IE, but with persistently negative blood cultures (54% of our entire study cohort), the negative predictive value of the modified Duke criteria could be significantly compromised.

During the 1990s, a significant change occurred in the microbiology of IE in the west. By the end of the decade, S aureus had overtaken viridans streptococci as the most frequently isolated pathogen, accounting for nearly 30-40% of cases.[15,16,21] This microbiologic trend may be attributable to an aging population, more frequent intravenous drug use in the community, and an increased frequency of nosocomial, prosthetic valve, and iatrogenic endocarditis. In contrast, rheumatic and congenital heart diseases account for the majority of our IE cases, prosthetic valve insertion is infrequently performed, and thus, streptococci still dominate our patient population, as in other studies from poorer countries.[5,8,22] Previous studies have shown S aureus to be an independent predictor of mortality.[15,16,21] We did not encounter an increased mortality in patients with S aureus IE, and this may be because

staphylococcal infection in the west is seen in different, high-risk patient populations, occurring in individuals with nosocomial, iatrogenic, hemodialysis-related or prosthetic valve infection.

Like elsewhere on the Indian subcontinent, rheumatic heart disease and congenital heart disease continue to be the most important causes of IE in Pakistan. This is consistent with other studies from this part of the world.[8-10] Right-sided endocarditis has a prevalence of 5-10% in the west, and most of these cases are attributed to parenteral drug abuse.[23,24] Fourteen (9%) of our patients had right-sided endocarditis but only one subject had a history of iv drug use. More than half of these patients had congenital heart disease and one-quarter had prior corrective cardiac surgery. Right-sided endocarditis in non-iv drug users has been previously reported from the Indian subcontinent and attributed to anatomic cardiac defects largely from congenital heart disease.[25-27] These defects are generally corrected in early life in developed countries; usually in pre-school years and thus do not manifest as IE in later years. We found no particular microorganisms associated with right-sided endocarditis, in contrast to the west where S aureus and P. aureginosa are the major causes of tricuspid valve infection.[23-24]
Unlike in the west where addict-associated IE generally has a better prognosis, subjects in our study cohort with right-sided endocarditis had no difference in mortality compared to patients with left-sided IE. They did, however, have fewer neurologic complications and peripheral emboli, and more pneumonia and larger vegetations.

Studies from industrialized countries have shown a consistent improvement in survival of patients with IE over the past four decades, with mortality recently reported between 15%–33%.[11,14,28,29] A similar decrease in mortality is also seen in patients from the Indian subcontinent: 42% in 1970[12], 20.3% in 1981[10], 21%–25% in 1992[9,30], 13.9% in 1998[31], and 13% in 2001[6]. The higher in-hospital mortality in our study (23%) may be explained by the fact that the Aga Khan University is a tertiary care referral center representing a skewed population of complicated cases. We did not find valve site or vegetation size or morphology to significantly correlate with mortality, stroke, or peripheral embolism. As expected, prosthetic valve endocarditis, and neurologic, renal, cardiac, and peripheral complications were all associated with an increased risk of death.[32-34] Other authors have observed similar associations with kidney and heart complications and prosthetic valve infection[9,32,34,35], and in 1992 Choudhry and colleagues reported from India that patients with neurologic complications had a higher incidence of death from IE.[9] Others have also reported prosthetic valve endocarditis and systemic embolism as independent risk factors of mortality.33,35 Death in five patients who developed IE >72 hrs in the hospital was very high (60%). This is consistent with a recent series from Madrid, where nosocomial infection accounted for 22% of IE patients, and resulted in a very high mortality (>50%).[36] These infections are often related to intravenous catheters or surgical procedures, and fewer than 50% of patients have underlying structural heart disease.[16]

Our study has several limitations. First, the 'true' microbiology of our cases could not be determined because many of the patients received prior antibiotic therapy prior to diagnosis, and because serology and polymerase chain reaction testing for fastidious organisms such as Brucella, Bartonella, Coxiella, and other rare causes of endocarditis were not performed. Second, only 20 patients (13%) underwent transesophageal echocardiography; the prevalence of culture-negative endocarditis may have increased if TEE had been performed on all

patients. Finally, being a tertiary care referral center our data may not truly represent endocarditis in the general community and may be skewed towards a sicker patient population, although they may be comparable to results from other academic centers.

Conclusion

In conclusion, endocarditis continues to be an important contributor to morbidity and mortality in Pakistan, especially among young adults. Our patients differ from those seen in the west in terms of epidemiology, predisposing factors, microbiology, complications, and outcome. Culture-negative endocarditis continues to have a high prevalence in developing countries like Pakistan, largely due to prior antibiotic use before clinical presentation. We believe that this practice may lead to a decreased sensitivity of the Duke criteria in diagnosing endocarditis. Further studies are needed to validate the negative predictive value of the Duke criteria in developing countries. Clinicians in countries like Pakistan should be advised to maintain a high index of suspicion of endocarditis and send blood cultures or refer appropriately before prescribing antibiotics.

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Table 1: General characteristics of 159 patients with infective endocarditis, Pakistan 1988-2001

Characteristic	**Value**
Number of patients	159
Age in years (mean +/- SD*)	34.6 +/- 21.2
Male:female ratio	103:56
'Definite endocarditis'	95 (59.7)
'Possible endocarditis'	64 (40.3)
Nosocomial endocarditis (after > 72 hrs in-hospital)	5 (3)
Acute endocarditis	55 (34.5)
Subacute endocarditis+	99 (62)

* SD = standard deviation
\+ Subacute endocarditis defined as symptoms >10 days.

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Table 2: Predisposing factors in 159 patients with infective endo-carditis

Predisposing factor	**No. of patients (%)**
Congenital heart disease (CHD)	39 (25)
Cyanotic congenital heart disease	6 (15)
Teratology of Fallot	3 (8)
Transposition of great arteries	2 (5)
Supraventricular pulmonary stenosis	1 (3)
Acyanotic congenital heart disease	33 (85)
Ventricular septal defect	14 (36)
Atrioventricular cushion defects	3 (8)
Patent ductus arteriosus	2 (5)
Atrial septal defect	2 (5)
Bicuspid aortic valve	4 (10)
Coarctation of aorta	1 (3)
Cleft mitral valve	1 (3)
Congenital mitral stenosis	1 (3)
Others	5 (12)
Surgically-corrected CHD	7 (18)
Rheumatic heart disease (RHD)	34 (21)
Mitral valve	16 (47)
Aortic valve	11 (32)
Aortic and mitral valve	2 (6)
Pulmonic valve	1 (3)
Undetermined	4 (12)
Surgically-treated RHD	1 (3)
IV drug user	1 (1)
Mitral valve prolapse with murmur	10 (6)
Prosthetic valve	8 (5)
Degenerative/stenotic aortic disease	2 (1)
Indwelling dialysis catheter	2 (1)
No predisposing factors	65 (41)

Table 3: Microorganisms recovered from blood cultures of patients with infective endocarditis

Organism	**No. of patients (%)**
GRAM-POSITIVE	
Streptococci	38 (23)
viridans Streptococci	24 (15)
Streptococcus bovis	1 (1)
Streptococcus mitis	1 (1)
Streptococcus intermedius	1 (1)
Others	11 (7)
Staphylococci	21 (13)
Staphylococcus aureus	10 (6)
Staphylococcus epidermidis	11 (7)
Enterococcus faecalis	7 (4)
GRAM-NEGATIVE	
Pseudomonas species*	3 (2)
Enterobacter+	3 (2)
Serratia	1 (1)
No growtha	86 (54)

* P. cepaciae and P. maltophilia.
\+ Enterobacter cloacae and E. agglomerans.
a At least three (3) blood cultures.

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Table 4: Echocardiographic findings in patients with endocarditis

Finding	**No. of patients (%)**
Site of involvement*	
Mitral valve	71 (45)
Aortic valve	52 (33)
Tricuspid valve	9 (6)
Pulmonic valve	4 (3)
Ventricular septal defect	8 (5)
Other findings	
Moderate to severe valvular insufficiency	80 (49)
Mobile vegetation	43 (27)
Large vegetation+	20 (13)
Perivalvular abscess	4 (2)
Intramyocardial abscess	1 (1)
Sinus of valsalva aneurysm	1 (1)

***** Includes patients with multi-valvular involvement.
\+ >10 mm in size.

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Table 5: Complications and mortality observed in patients with infective endocarditis

Complications	**No. of patients (%)**
Died	37 (23)
Surgery required	18 (11)
Neurologic complications	41 (26)
Stroke	23 (15)
Intracranial hemorrhage	6 (4)
Seizures	7 (4)
Meningitis	4 (3)
Brain abscess	1 (1)
Renal complications	20 (13)
Renal insufficiency*	18 (11)
Interstitial nephritis	2 (1)
Glomerulonephritis	4 (2)
Hemolysis	20 (13)
Cardiac	40 (25)
Heart failure	35 (22)
Cardiac abscess+	5 (3)
Peripheral embolism	16 (10)
Pneumonia	13 (8)
Sepsis	7 (4)

* Serum creatinine > 2.0 mg/dL.
\+ Includes intramyocardial (1) and perivalvular (4) abscesses.

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Table 6: Risk factors for mortality in patients with infective endocarditis

Characteristics	Died (n = 37)	Recovered (n = 122)	p value	95% CI
GENERAL				
Age	37.6 +/- 22	33.7 +/- 21	NS*	-
Sex (M:F)	23/14	80/ 42	NS	-
Acute endocarditis+	13 (35)	42 (34)	NS	-
Prosthetic valve IE	5 (13)	3 (2)	**0.017**	**1.4 - 27.3**
Nosocomial	3 (8)	2 (2)	0.054	**0.85 - 26.7**
Culture-positive	15 (41)	58 (48)	NS	-
Definitive endocarditis	25 (67)	70 (57)	NS	-
PRESENTATION				
Fever	35 (95)	114 (93)	NS	-
Splenomegaly	8 (22)	20 (16)	NS	-
Anemia	20 (54)	65 (53)	NS	-
Thrombocytopenia	4 (11)	16 (13)	NS	-
Leukocytosis	8 (21)	38 (31)	NS	-
PREDISPOSING FACTORS				
Rheumatic heart disease	7 (19)	27 (22)	NS	-
Congenital heart disease	9 (24)	30 (25)	NS	-
MVP with murmur	1 (3)	9 (7)	NS	-
Intravenous drug use	0 (0)	1 (1)	NS	-
Previous cardiac surgery	8 (21)	12 (10)	0.055	0.95-6.75
MICROBIOLOGY				
Streptococci	2 (5)	9 (6)	NS	-
Staphylococcus aureus	3 (8)	7 (6)	NS	-
Pseudomonas spp	2 (5)	1 (1)	NS	-
Enterococci	2 (5)	7 (6)	NS	-
COMPLICATIONS				
Neurologic complications	18 (48)	23 (18)	**< 0.001**	**1.85 - 8.9**
Renal failureo	9 (24)	9 (7)	**0.004**	**1.44 - 11.1**
Hemolysis	5 (14)	6 (5)	0.07	-
Peripheral embolism	7 (19)	9 (7)	0.056	0.94 - 9.8
Heart failure	16 (43)	19 (16)	**< 0.001**	**1.83 - 9.3**
Cardiac abscess	2 (5)	3 (3)	NS	-
Large vegetationa	5 (14)	15 (12)	NS	-
Pneumonia	5 (14)	8 (7)	NS	-
Sepsis	4 (11)	3 (2)	**0.03**	**.02 - 22.5**
Surgery for endocarditis	3 (8)	15 (12)	NS	-

* Not significant.
\+ Defined as symptoms <10 days.
o Serum creatinine >2 mg/dL.
a >10 mm in size.