Clinico-Microbiological Spectrum of Infective Endocarditis in a Tertiary Care Hospital in Eastern India

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Abstract:
Background: *Infective Endocarditis (IE) is a life-threatening disease which predominantly affects those with any underlying structural or congenital heart disease or intravascular prosthetic material. The diagnosis of IE requires a combination of clinical, microbiological and echocardiography results. Culture of valvular tissue is of great use in isolating the causative organisms, particularly when blood cultures are negative. Streptococci, Staphylococci and Enterococci are responsible for majority of IE cases, worldwide.*
Objectives: *To determine the clinico-microbiological profile of Infective Endocarditis by identifying the most common risk factors, isolating the causative organisms from excised cardiac valves and determining the antibiotic susceptibility pattern of those isolates.*
Methods: *This prospective study was conducted among the cases of IE undergoing valve replacement surgery. The excised valves were subjected to gram stain and culture followed by antibiotic susceptibility testing for the isolates by modified Kirby-Bauer disk diffusion method.*
Results: *Methicillin Sensitive Staphylococcus aureus was isolated as the predominant causative organism, mostly sensitive to Vancomycin and Linezolid. Rheumatic heart disease and Diabetes mellitus were found to be frequently associated risk factors.*
Conclusion: *IE is associated with significant morbidity and mortality. There is need for accurate evaluation and early diagnosis of at risk population to prevent disease progression.*
Keywords: *Infective Endocarditis, Rheumatic heart disease, Staphylococcus aureus*

I.   Introduction:

Infective Endocarditis (IE) is an infection of the cardiac valves, or the lining of the heart, i.e. the mural endocardium, and may also involve the heart muscles, caused by bacteria or fungi, producing a number of systemic signs and symptoms, brought about by several mechanisms, like infected or sterile emboli or immunological phenomena. The diagnosis of IE can be done when the patient presents with fever with a combination of investigations like positive blood cultures and detection of vegetation on echocardiography. However, absence of fever, negative blood cultures or no vegetation on echocardiography does not eliminate the possibility of IE. The cases are designated as "definite IE" or "possible IE" according to the various parameters of the Modified Duke's diagnostic criteria. IE needs to be managed aggressively with either antibiotics or surgery. [1,2]

The earliest cases of IE were reported in individuals in the younger age group suffering from rheumatic heart disease. Later, elderly populations with underlying cardiac co-morbidities, were identified as cases of IE. Eventually, there was emergence of IE in intravenous drug users and also nosocomial IE due to invasive procedures like prosthetic valve replacement, intravenous catheterization or insertion of pacemakers. [2] The microbiological spectrum, clinical profile and epidemiology of IE might depend on the type of endocarditis, i.e. prosthetic valve endocarditis or native valve endocarditis. According to studies, 84.5% of all cases of IE are of native valve endocarditis while 7-25% cases are of prosthetic valve endocarditis. [3]

Common organisms causing IE are *Streptococcus spp, Staphylococcus spp, Enterococcus spp* and fastidious gram negative cocco-bacilli. The rare causes include mycobacteria, fungi, *Chlamydia spp* and *Rickettsia spp.* Previously, *Streptococcus spp* was responsible for the majority of cases of IE, but other pathogens have been significantly associated with the disease, of late. *Staphylococcus aureus* is now reported to be the commonest cause of IE in India. There has also been a rise of culture-negative IE. Chronic rheumatic heart disease was identified as a significant risk factor for IE, being associated with 46% of cases. [4]

Despite all the recent advances in diagnostics and therapeutic facilities, IE still remains a major health concern, which is associated with significant morbidity and mortality. This may be due to the fact that there are limited studies on the clinical and microbiological profile of IE in India. This study was undertaken to determine the clinico-microbiological profile of Infective Endocarditis by identifying the most common risk factors, isolating the causative organisms from excised cardiac valves and determining the antibiotic susceptibility pattern of those isolates.

II.   Materials And Methods:

This study was a prospective, observational, descriptive, cross-sectional study conducted for a period of one year, involving patients who were provisionally diagnosed with Infective Endocarditis according to the Modified Duke's criteria and underwent cardiac valve excision surgery due to progressive cardiological deterioration.

For each patient detailed clinical history was taken involving age, sex, underlying cardiological condition, any associated metabolic comorbidity, past history of IE, and presenting signs and symptoms. Transthoracic 2D Echocardiography reports of the patients were studied to determine the existing valvular defect, presence of vegetation, if any, number and site of vegetations, size of the largest vegetation and the left ventricular ejection fraction. Other necessary investigations were correlated including 12-lead Electrocardiogram (ECG), and levels of C - reactive protein (CRP) and Rheumatoid Factor (RF).

At the end of the surgery, the excised cardiac valves were transported to the microbiology laboratory carefully in a sterile container. The excised valves were removed with sterile forceps from the container. Next, they were crushed and homogenized in an autoclaved reusable homogenizer under aseptic precautions. Gram staining and culture was performed immediately from the ground valve tissue. A portion of the tissue was added to brain-heart infusion broth and the rest was inoculated on Mac Conkey agar and Blood agar plates, which were incubated overnight aerobically at 37°C. The brain-heart infusion broth was incubated for 24 hours, and a subculture of the broth was performed if turbidity was detected. All the suspected isolates were further identified by Gram staining and standard biochemical tests.

Antimicrobial susceptibility of isolates was tested by modified Kirby Bauer disk diffusion method as per the recommendations of Clinical and Laboratory Standards Institute (CLSI). Mueller-Hinton agar (MHA) was used as media, it was inoculated with a suspension of organism equivalent to 0.5 McFarland turbidity standard & discs were applied. Inhibition zones were interpreted according to CLSI guidelines.

III.   Results:

150 cases of Infective Endocarditis undergoing cardiac valve replacement were included in this study. Male: female ratio showed a male dominance of cases at 1.5:1. The range of age of cases was 20-70 years. Mean age of patients with IE was 35 years. (**Table 1**)

Fever was the most common presenting complaint (30%) amongst the cases, followed by sudden onset of breathlessness (20%), chest pain (15%), cough (13%) and palpitations (12%). (**Table 2**)

Diabetes mellitus was the most frequently associated metabolic risk factor in 38 of the 150 cases (25%), followed by hypertension in 33 cases (22%).

Most common underlying cardiological risk factor associated with incidence of IE was Rheumatic Heart Disease (60%), followed by ventricular septal defect (20%) and atrial septal defect (18%). (**Table 3**)

Transthoracic 2D- Echocardiography of the cases revealed the presence of vegetations in 78 (52%) out of the 150 cases of IE. Single vegetation was present in 118/150 cases (79%) while the other 21% had multiple vegetations.

Most common site of vegetation was mitral valve (63%) followed by aortic valve (22%). (**Table 4**)

Mitral regurgitation was the most common underlying valvular defect, seen in 90/150 cases (60%), followed by aortic regurgitation (57/150, 38%).

Thrombo-embolic phenomenon occurring due to emboli produced from the valve vegetations was seen in 30/150 cases (20%). All patients had elevated levels of CRP, where 35/150 (23%) had CRP levels above 30 mg/L and rest had above 20 mg/L. (Normal reference range for CRP is <4 mg/L) 12/150 (8%) cases tested positive for Rheumatoid Factor, probably due to immunological cross reactions in sera of IE patients.

47 out of the 150 cases were culture positive (31%). The predominant organism was *Staphylococcus aureus* (77%) (**Fig 1**) followed by *Staphylococcus epidermidis (*15%) (**Fig 2**), *Staphylococcus lugdunensis* (6%) and *Enterococcus faecalis (*2%). (**Table 5**)

All the isolates were sensitive to Vancomycin and Linezolid.(100%) (**Fig 3**). 25 (71%) of the *Staphylococcus aureus* were Methicillin resistant (denoted by Cefoxitin resistance) and 10 were Methicillin sensitive (29%). All isolates of *Staphyloccus epidermidis* and *Staphylococcus lugdunensis* were Methicillin resistant (100%). Highest resistance was seen to Erythromycin (80% of *Staphylococcus aureus* and 100% of *Staphyloccus epidermidis* and *Staphylococcus lugdunensis*). (**Table 6**)

TABLES

Table 1: Age distribution of patients

Age (years)	Number of patients	Percentage (n=150)
20-30	15	10%
31-40	66	44%
41-50	32	21%
51-60	25	17%
61-70	12	8%

Table 2: Distribution of symptoms in cases of IE:

Symptoms	Number of cases	Percentage (n=150)
Fever	60	40%
Sudden onset breathlessness	30	20%
Chest pain	22	15%
Cough	20	13%
Palpitations	18	12%

Table 3: Distribution of cardiological risk factors

Cardiological condition	Number of cases	Percentage (n=150)
Rheumatic heart disease	90	60%
Ventricular septal defect	30	20%
Atrial septal defect	27	18%
Mitral valve prolapse	3	2%

Table 4: Distribution of site of vegetation

Site	Number of cases	Percentage (n=150)
Mitral valve	94	63%
Aortic valve	33	22%
Tricuspid valve	18	12%
Pulmonary valve	5	3%

Table 5: Distribution of causative agents

Organism	Number of isolates	Percentage (n=47)
Staphylococcus aureus	36	77%
Staphylococcus epidermidis	7	15%
Staphylococcus lugdunensis	3	6%
Enterococcus faecalis	1	2%

Table 6: Drug susceptibility pattern of isolates

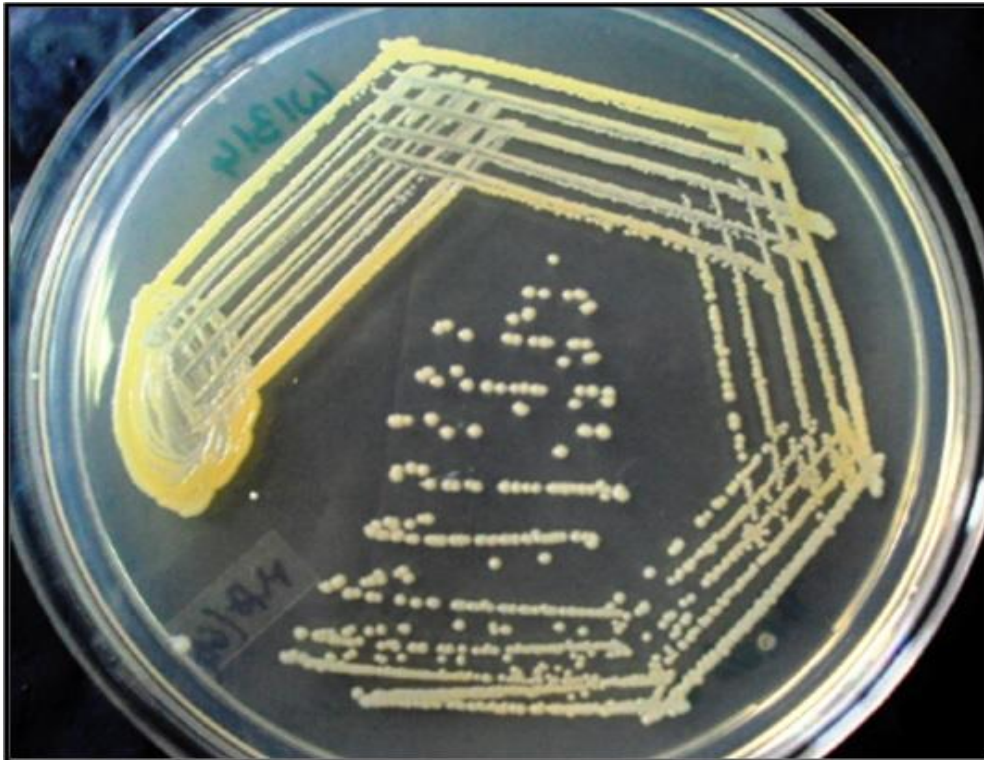|	*S.aureus* (n=36)		*S. epidermidis* (n=7)		*S. lugdunensis* (n=3)	
	No. of sensitive isolates	Percentage	No. of sensitive isolates	Percentage	No. of sensitive isolates	Percentage
Vancomycin	36	100%	7	100%	3	100%
Linezolid	36	100%	7	100%	3	100%
Clindamycin	27	75%	5	70%	2	66.7%
Erythromycin	29	80%	7	100%	3	100%
Ciprofloxacin	9	25%	3	49%	1	33%
Cefoxitin	16	44.5%	0	0%	0	0%

FIGURES

Fig 1 Growth of Staphylococcus aureus on Nutrient agar

Fig 2 Growth of Staphylococcus epidermidis on Blood agar
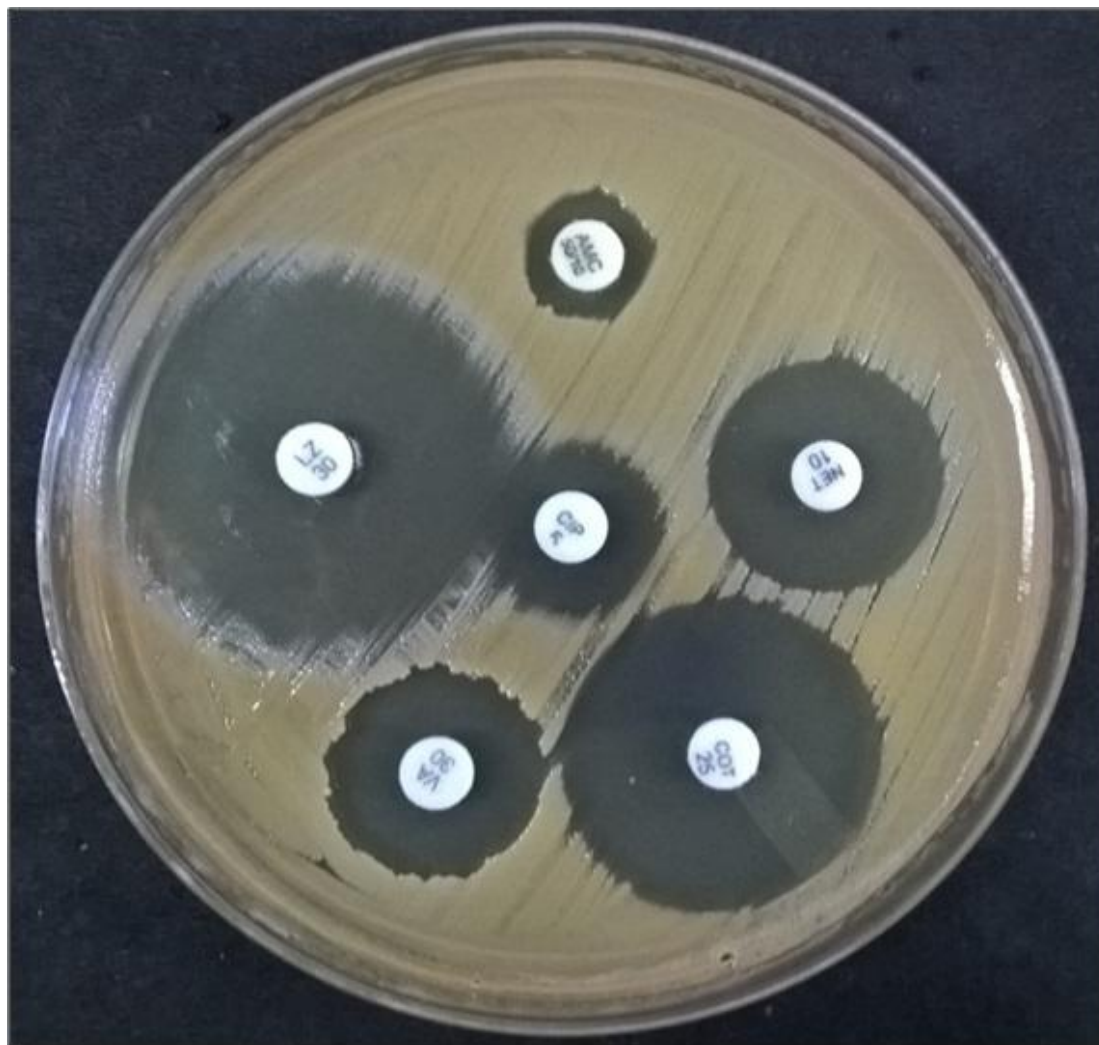
Fig 3 Antibiotic susceptibility testing

IV.   Discussion:

Infective endocarditis is an infection of the cardiac endothelial surface. Even years after its discovery, it still remains a grave problem for modern medicine. This is because IE needs a strong clinical suspicion for its timely diagnosis and also an effective and aggressive treatment at the earliest in order to save the patient. Inspite of the fact that there is an increase in the incidence of IE in recent times, only a limited number of studies have reported the profile of IE in eastern region of India. [3]

In this study male patients were affected more by IE with a male: female ratio of 1.5:1. Kanne Padmaja *et al.* also reported a male preponderance for IE (1.2:1). [3]

In this study, majority of cases were in 31-40 years age group, with a mean age of 35 years. Similar results were obtained by S Ghosh *et al.*[6] and Kothari *et al.* [7] where the mean age of patients with IE was also 31 years and 34 years respectively. This observation is in contrast with that of the western countries where elderly individuals in the 5th and 6th decade reported higher incidence of IE. This may be because of the fact that rheumatic heart disease which predominantly affects the younger population, is the most common cardiological risk factor for IE in India. [7,8] This is also the case in this study where Rheumatic heart disease has been identified as the commonest risk factor(60%).

Fever was the most common presenting complaint in this study (30%). This was comparable with the studies conducted by Hosseini SM *et al.*[5] and Kanne Padmaja *et al.* [3]

Diabetes mellitus was identified as the most common underlying metabolic risk factor (25%). Barrau *et al.* obtained similar results in their studies. [2]

Transthoracic echocardiography 2D-Mode showed that mitral valve was the commonest site of vegetation (63%) and mitral regurgitation was the predominant valvular lesion (60%). Similar results were obtained by Kanne Padmaja *et al.*(54.2% and 89% respectively). [3]

In this study, CRP levels were elevated for all patients of IE. This was comparable to results obtained by S Ghosh *et al.*[6]

Culture positivity in this study was 31% which is in accordance with the study conducted by S. Senthilkumar *et al.* who reported culture positivity to be 23%. [9] Most of the patients in this study had a history of antibiotic intake prior to surgery which could be the cause of high number of culture negative cases. Failure to isolate the organism in culture could also be due to the presence of highly fastidious organisms which did not grow on ordinary media. Other possible reasons are healed endocarditis, haemodilution, systemic hypothermia and cold cardioplegia. [3]

In this study, *Staphylococcus aureus* was most commonly isolated (77%) from the excised cardiac valves followed by *Staphylococcus epidermidis.*(15%). Murdoch *et al.* also observed in his study that *Staphylococcus aureus* is the most common cause of IE worldwide. [10] This might be due to the increasing rate of medical procedures using invasive devices and prosthetic devices and also, the rise of IV drug users, increased survival of the elderly population who are at a higher risk of developing cardiological complications. S Ghosh *et al.* also reported *Staphylococcus aureus* to be the commonest organism causing IE. [6]

All the isolates obtained from excised cardiac valves in this study, were susceptibile to Vancomycin and Linezolid (100%). A similar observation was made by S Ghosh *et al.*who reported an uniform susceptibility to vancomycin among the isolates. [6] Amongst the *Staphylococcus aureus* isolates, a higher number were methicillin resistant (55.5%). This was comparable to the study conducted by Kanne Padmaja *et al.* where more isolates of *Staphylococcus aureus* were methicillin resistant (66%) than sensitive (33%). IE caused by methicillin resistant *Staphylococcus aureus* is often a therapeutic challenge as majority of the strains also show resistance to aminoglycosides. [3]

Despite recent advances in diagnosis and therapy modalities, the mortality associated with IE remains high. More than one thirds of patients suffering from IE, die within a year of diagnosis. Identifying the specific microbial aetiology and risk factors leading to IE is essential for adequate patient management. Delays in culture results may result in delayed initiation of specific antimicrobial therapy, ultimately increasing morbidity and mortality. [11]

In this study, *Staphylococcus aureus* was identified as the leading cause of IE, with rheumatic heart disease being the commonest cardiological and diabetes mellitus being the commonest metabolical risk factor. Fever was the most common presenting feature and mitral valve was predominantly affected. Younger age group was primarily seen to be affected with mean age group in the thirties.

This study emphasizes on the requirement for early clinical suspicion, management of risk factors, quicker diagnosis and adequate treatment of IE with special attention being paid to the changing epidemiology and microbial aetiology of IE in India.

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