ORIGINAL ARTICLE

Implications for Diagnosis and Treatment of Infective Endocarditis: Eight year Experience of an Infectious Disease Team in a Private Tertiary Care Centre

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Abstract

Background: The profile of Infective endocarditis (IE) has been evolving continuously. Like other infectious Diseases (ID) syndromes, IE has not escaped from antibiotic resistance issues. The aim of this study was to determine the implications for diagnosis and treatment by studying the clinical profile and outcome of patients admitted with IE in a tertiary care centre in Mumbai during the period from 2007-2015.

Methods: 53 patients having definite or possible IE as per Modified Duke's Criteria (MDC), that were referred to the ID division, were included in this study.

Results: 44 (83%) patients had definite IE and 9 (17%) patients had possible IE. 77.4% of the patients were above 40 years of age. 3 patients presented as euthermic IE. Vegetations were not seen on transthoracic echocardiography (TTE) in 3 patients and were seen only on transesophageal echocardiography (TEE).

15 patients had prosthetic valve IE. 7 patients had rheumatic heart disease. 3 patients had bicuspid aortic valve and 4 had ventricular septal defect (VSD). The rest had no apparent underlying heart disease (45.3%).

41 patients (77.3%) had culture-positive IE and 12 patients (22.6%) had culture-negative IE. *Streptococcus* spp. was found in 14 (26.4%) patients, *Enterococcus spp.* in 9 patients (17%). Other organisms isolated were methicillin-sensitive *S. aureus* (3), Methicillin Resistant *S. aureus* (1), *Eikenella corrodens* (1), *B. cepacia* (2), *Salmonella Typhi* (1), *P. aeruginosa* (1), *M. abscessus* (2) and other rapidly growing mycobacteria (RGM) (5), *Candida parapsilosis* (1), *Candida pelliculosa* (1) and *Aspergillus fumigatus* (1). Notably there was only one case of MRSA.

Among the *Streptococcus* spp., Penicillin MIC testing was done in 11 cases of the 14 cases of Strep spp. 3 of them showed intermediate resistance and 2 were resistant. Among enterococcal IE, 3 had high level aminoglycoside resistance (HLAR) and 2 had β-lactamase producing enterococci with HLAR and 1 had Vancomycin resistance. These were successfully treated with combinations of Ampicillin with Ceftriaxone, Ampicillin-Sulbactam with Imipenem and Daptomycin respectively. The only case of MRSA prosthetic valve endocarditis was successfully treated with Vancomycin and Rifampicin in addition to surgery. Surgery for IE was performed in 26 out of 53 (49%) patients. Early valve surgery (within 15 days of hospital admission) was performed in 6 of these 26 patients.

Conclusion

There is a change in the spectrum and antimicrobial susceptibility of organisms causing IE. We encountered several difficulties with the use of the MDC as 43.5% patients had no predisposing factors for IE and blood cultures were negative in

Introduction

Infective endocarditis (IE), like other syndromes, has not escaped antibiotic resistance issues. Changes in antibiotic susceptibility of 3 major bacterial causes of IE: streptococci, staphylococci, and enterococci is increasingly reported. This may have implications for empiric therapy of culture-negative IE all over the world.

Aim and Objectives

To determine the implications for diagnosis and treatment by studying the clinical profile and outcome of patients with IE, referred to the infectious disease division, in a tertiary care centre in Mumbai from 2007- 2015.

Patients and Methods

Patients admitted with IE between January 2007 to December 2015 and referred to the ID team were reviewed in this observational study. Patients were classified as definite or possible IE as per Modified Duke's criteria. Age, sex, symptoms, signs, duration of symptoms prior to diagnosis, predisposing condition, prior antibiotic therapy, blood cultures- organisms isolated and susceptibility, surgery

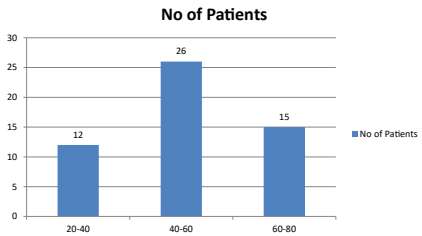

Fig. 1: Distribution of age (yrs.) among study group

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22.6% cases. In our study, PVE was the most common predisposing condition for IE. VGS followed by enterococci were found to be the commonest cause for IE in our setting. Both organisms show variable drug resist patterns. MRSA was isolated in 1 patient only. Thus vancomycin may not be required as empiric treatment in our setting. This is important from the perspective of antimicrobial stewardship Good infection control practices are essential to prevent nosocomial IE due to pathogens such as non-tuberculous mycobacteria (NTM). Important changes in the disease characteristic, treatment, and outcome are noted. Surgery, whenever indicated, helps in improving outcome in these patients thus reiterating the need for a team approach for optimal management of this complex, challenging condition.

for IE, indication and timing for surgery, and clinical outcome of IE were recorded.

Results

44 patients were diagnosed to have definitive IE and 9 patients had possible IE as per the Modified Duke's criteria.

77.4% patients were above 40 yrs of age (Figure 1). There were total 5 cases of right sided IE. Among them 3 had VSD, 1 was following central venous line insertion and 1 patient had SLE. Prosthetic valve (n=15) was a more common risk factor for IE than RHD (n=7) in our study (Figure 2).

The commonest symptoms and signs observed were fever, shortness of breath, weight loss, and pallor. Three patients presented as euthermic IE – one was an immunocompetent patient (n=1), one was a chronic kidney disease patient (n=1) and the third patient had systemic lupus erythematosis (SLE) with *Aspergillus* IE (n=1).

Vegetations were not seen on TTE in 3 patients and were seen only on TEE.

Blood Cultures were positive in 41 of the 53 patients with IE. 12 cases had culture- negative IE. All the culture-negative IE patients had received prior antibiotic therapy. One culture-negative IE was diagnosed as *Aspergillus fumigatus* on valve culture and histopathology.

Viridans Group of streptococci (VGS) was the most common organism isolated followed by enterococci (Figure 3). Among the Streptococcus spp., penicillin minimum inhibitory concentration (MIC) were interpreted as per the American Heart Association (AHA) criteria[1] in 11/14 cases. 3 of them had intermediate susceptibility and 2 were resistant. Among enterococcal IE, 3 had high level aminoglycoside resistance (HLAR), 2 had β-lactamase producing enterococci with HLAR and 1 had Vancomycin resistance (Table 1). These were successfully treated with combinations of Ampicillin with Ceftriaxone, Ampicillin-Sulbactam with Imipenem and Daptomycin respectively (Table 2).

The only case of MRSA prosthetic

Table 2: Antibiotics used for the treatment of enterococcal IE (n=9)

Antibiotic resistance	Treatment
Ampicillin and Gentamicin sensitive (n=2)	Ampicillin and Gentamicin
HLAR (n=3)	Ampicillin and Ceftriaxone
Ampicillin resistant (β-lactamase producing enterococci) with HLAR (n=2)	Ampicillin–sulbactam and Imipenem[7]
Ampicillin and Gentamicin sensitive (n=1)	Ampicillin and Imipenem due to risk of gentamicin nephrotoxicity
Vancomycin resistant (n=1)	Daptomycin

Good outcome was observed in 42 of the 53 patients (79%). Among those who underwent surgery 2 (7.7%) patients had poor outcome out of 26, whereas among medically managed patients 9 (33.33%) out of 27 patients had poor outcome. In-hospital mortality was seen in 4 patients (3 RGM IE and 1 Culture negative endocarditis).

We found a change in spectrum and antimicrobial susceptibility of organisms causing IE. Important changes in the disease characteristics, treatment, and outcome are noted. *Streptococcus* spp. is the commonest cause for IE in our study. Increasing antibiotic resistance may have implications for empiric therapy of culture-negative IE. Also, infection control measures need to be emphasized for preventing nosocomial IE.

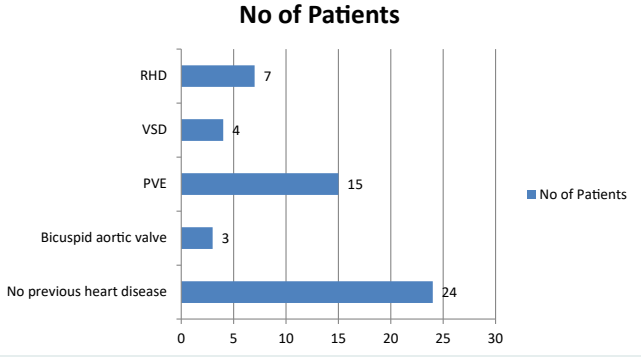

Fig. 2: Predisposing risk factors. VSD: ventricular septal defect; RHD: rheumatic heart disease; PVE: prosthetic valve endocarditis

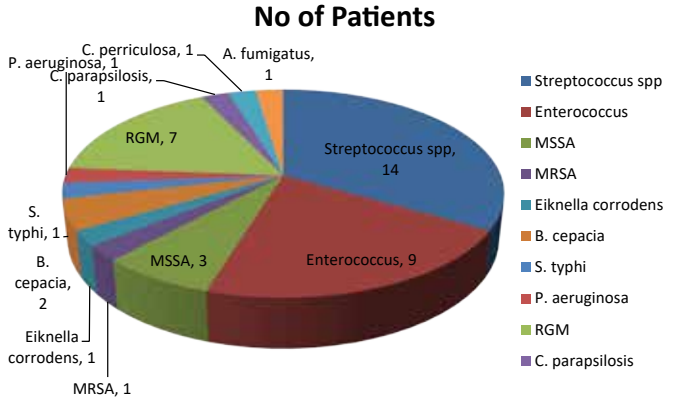

Fig. 3: Microbiological profile of patients causing IE

Table 1: Antibiotic susceptibility of GPC isolated

Organism isolated	Total	Ampicillin	Cefoxitin	Amoxyclav	Ceftriaxone	Gentamicin	Imipenem	Ciprofloxacin	Vancomycin
VGS	14	*	-	100	100	100	100	100	100
Enterococci	9	55	-	67	0	55	100	0	89
MSSA	3	0	100	100	100	0	100	0	100
MRSA	1	0	0	-	-	0	-	0	100

*For VGS IE-Penicillin MICs are recommended

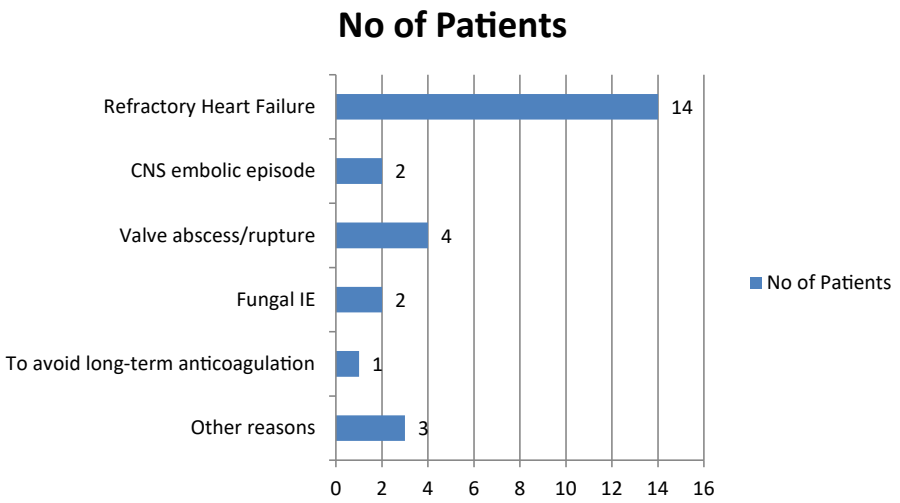

Fig. 4: Indications for surgery for IE

valve endocarditis was successfully treated with Vancomycin and Rifampicin. Gentamicin was avoided due to compromised renal function.

Stent related IE due to rapidly growing Mycobacteria (RGM) IE was identified in 5 patients whereas 1 had *Pseudomonas aeruginosa* after coronary angioplasty. Two patients had RGM IE after coronary angiography. In both of them the coronary angiography was normal. The case of stent related P. aeruginosa IE had resistance to aminoglycosides, carbapenems and all beta lactams except Ceftazidime with intermediate susceptibility to Ciprofloxacin. The patient was managed successfully with a combination of Colistin, Ceftazidime and Ciprofloxacin in addition to surgery. Among patients with RGM IE, 3 patients succumbed to the disease during hospitalization, 3 succumbed post discharge and 1 was successfully managed with combination of surgical and medical treatment.

There was 1 patient who had multiple episodes of IE. The patient was receiving hemodialysis through AV fistula from the same dialysis unit highlighting the role of poor infection control practices leading to increase in episodes of nosocomial IE that we found in our study. This particular patient also had differences in susceptibility of Enterococcal species isolated between the 2 episodes of Enterococcal IE whereas 3rd episode was with Methicillin Resistant Staphylococcus Epidermidis (MRSE). She also had multiple CNS septic emboli causing varying degrees of neurological deficits leading to a poor outcome.

There were 3 cases of Fungal IE. 1 was A. fumigatus in an SLE patient, 1 was C. parapsilosis and 1 C. pelliculosa in patients with prosthetic valve surgery. 2 of 3 patients died after being discharged from hospital.

Surgery for IE was performed in 49% patients with IE (n=26). Most common indication for surgery was refractory heart failure (Figure 4). Early valve surgery (within 15 days of hospital admission) was performed in 6 of these 26 patients.

Clinical cure was observed in 42 of the 53 patients (79%). Among those who underwent surgery 24/26 patients were cured, whereas among medically managed patients only 18/27 patients were cured. In-hospital mortality was seen in 4/44 patients (3 RGM IE and 1 Culture negative endocarditis). 2 patients who had fungal IE died post discharge, increasing the total mortality to 6/44 (13.6%) patients.

Discussion

In the present study most patients (>77%) were over 40 years of age. In our country, younger patients (mean age-25 yrs) were earlier reported to be more commonly affected with IE while our results are comparable to data reported by developed countries.

We encountered several difficulties with the use of the Modified Duke's Criteria. Blood cultures were negative in 22.6% cases. However, most of these patients were on antibiotics. Vegetations were not seen on TTE in 3 patients in whom TEE was required. 43.5% of our patients had no predisposing condition as per the Duke's criteria. Although bicuspid aortic valve is not included as a predisposing condition for IE, we found 3 patients who had bicuspid aortic valve as the only cardiac defect. The use of PET scan for diagnosis of IE was not explored in our study, both due to issues of cost and as it is an evolving recommendation during the study period.

In this study 52.8% of patients had no underlying cardiac risk factors. Amongst those who had risk factors, prosthetic valve IE (28.3%) was more common. RHD was the most common underlying risk factor for IE (present in 46.9% patients) in earlier studies.[2,3]

Left-sided IE is still more common than the right-sided IE as earlier reported. In the present study (VSD and nosocomial procedures such as central venous catheter insertion) are the common causes of right-sided IE where as puerperal sepsis and septic abortion were the commonest causes in earlier studies.[4]

VGS is the most common cause of IE in our study.[5] Enterococcal IE appears to be increasing in frequency (17% vs 8% reported by Garg et al [3]) - more common in elderly pts, associated UTI. Only 1 methicillin-resistant *S. aureus* IE was found during this study period. This microbiological profile has implications on the empirical antibiotic therapy for IE and hence empirical vancomycin for all patients is perhaps not indicated for IE in our setting.

Also, an emerging resistance is noted among a few organisms causing IE. VGS resistance pattern has not been reported in any Indian series previously. Enterococci exhibit various resistance mechanisms including high level aminoglycoside resistance (HLAR) and β-lactamase production.

More patients were managed surgically (49%) vs 23% in earlier reported studies.

IE is associated with high mortality. Patients with heart failure, periannular complications and IE due to *S. aureus* the mortality reaches 79%. Mortality from IE in this study was found to be 21%. This may be attributed to the increase in RGM and fungal IE which had uniformly dismal outcome with only 1 patient with RGM and fungal IE each surviving from our study population.

RGM IE is unusual but at present but it may be observed more in the future because of the increasing use of non-reusable devices in the developing world.[7]

In our study patients managed with surgery in addition to optimum medical treatment had better outcomes than those managed medically alone. This result may be skewed due to survivor selection bias due to selection bias in choosing patients who undergo surgery. High risk patients, but only those who are suitable surgical candidates are chosen for surgery. This bias may favour the perceived benefit of surgery.

This study has limitations. These findings may pertain to a private tertiary care hospital. The epidemiology and resistance patterns may vary in different settings. We recognize that similar facilities for management may not be available and clinicians may have to manage in different ways to suit patient preferences, affordability, available local expertise etc. However, our results show that a team approach is beneficial to optimize the outcome for this complex, challenging condition.

Conclusions

There is a change in spectrum and antimicrobial susceptibility of organisms causing IE. Identifying the organism is the key. In our study, PVE was the most common predisposing condition for IE. 43.5% patients had no predisposing factors for IE as per the MDC. Blood cultures were negative in 22.6% cases. Hence, there are difficulties in applying MDC for diagnosis in our setting.

VGS is still the most common cause for IE but VGS are not uniformly sensitive to penicillin and penicillin MICs are needed. Enterococci exhibit various resistance mechanisms including HLAR and β-lactamase production. β-lactamase production needs to be ruled out by nitrocephin disc even if enterococci is ampicillin sensitive in case of IE. Thus, combination of ampicillin-sulbactam and ceftriaxone and ampicillin-sulbactam with imipenem have potential role in the treatment. This will avoid the use of vancomycin for ampicillin resistant β-lactamase producing enterococci. Also MRSA was isolated in 1 patient only. Thus vancomycin may not be required as empiric treatment in our setting. This is important from the perspective of antimicrobial stewardship

In view of nosocomial IE, due to difficult pathogens such as NTM, infection control practices should be given far more importance than at present.

Important changes in the disease characteristic, treatment, and outcome are noted. Surgery, whenever indicated, helps in improving outcome in these patients thus reiterating the need for a team approach for optimal management of this complex, challenging condition.

References

1. Baddour LM, Bayer AS, Fowler VG, Bolger AF, Levison ME, et al. AHA Scientific Statement Infective Endocarditis: Diagnosis, Antimicrobial Therapy, and Management of Complications. *Circulation* 2015; 132:00-00. DOI: 10.1161/CIR.0000000000000296.
2. Agarwal R, Bahl VK, Malaviya AN. Changing spectrum of clinical and laboratory profile of infective endocarditis. *J Assoc Physicians India* 1992; 40:721-3.
3. Garg N, Kandpal B, Tewari S, et al. Characteristics of infective endocarditis in a developing country-clinical profile and outcome in 192 Indian patients, 1992-2001. *Int J Cardiol* 2005; 15;98:253-60.
4. Grover A, Anand IS, Varma J, et al. Profile of right-sided endocarditis: an Indian experience. *Int J Cardiol* 1991; 33:83-88.
5. Soman R, Gupta N, Sunavala A, Madan S, Shetty A, Rodrigues C. Changing face of infective endocarditis. Program and abstracts of the 51st Annual Meeting of the Infectious Diseases Society of America, San Francisco, California. Oct 2-6, 2013 (Abstract #1271).
6. Soman R, Gupta N, Shetty A, Rodrigues C. Prosthetic Endocarditis due to Non-tuberculous Mycobacteria: A New Problem in the Developing World. Program and abstracts of the 50th Annual Meeting of the Infectious Diseases Society of America, San Diego, California. October 17-21, 2012 (Abstract #1732).
7. Gavaldà J, Torres C, Tenorio C, López P, Zaragoza M, Capdevila JA, et al. Efficacy of ampicillin plus ceftriaxone in treatment of experimental endocarditis due to *Enterococcus faecalis* strains highly resistant to aminoglycosides. *Antimicrob Agents Chemother* 1999; 43:639-46.