Indian Heart Journal 73 (2021) 711–717

Contents lists available at ScienceDirect

Indian Heart Journal

journal homepage: www.elsevier.com/locate/ihj

Original Article

Changing spectrum of infective endocarditis in India: An 11-year experience from an academic hospital in North India

Navneet Arora [a], Prashant Kumar Panda [b], Pruthvi CR [b], Lipi Uppal [b], Atul Saroch [a], Archana Angrup [c], Navneet Sharma [a], Yash Paul Sharma [b], Rajesh Vijayvergiya [b], Manoj Kumar Rohit [b], Ankur Gupta [b], Bhupinder Kumar Sihag [b], Himanshu Gupta [b], Neelam Dahiya [b], Ajay Bahl [b], Parminder Singh [b], Saurabh Mehrotra [b], Parag Barwad [b], Ashok Kumar Pannu [a, *]

[a] Department of Internal Medicine, Postgraduate Institute of Medical Education and Research, Chandigarh, India
[b] Department of Cardiology, Postgraduate Institute of Medical Education and Research, Chandigarh, India
[c] Department of Medical Microbiology, Postgraduate Institute of Medical Education and Research, Chandigarh, India

ARTICLE INFO

Article history:
Received 8 March 2021
Received in revised form
24 August 2021
Accepted 8 September 2021
Available online 16 September 2021

Keywords:
Endocarditis
Epidemiology
Injection drug use
Rheumatic heart disease
Staphylococcus
Echocardiography

ABSTRACT

Objective: Several studies have demonstrated a shift in the spectrum of infective endocarditis (IE) in the developed world. We aimed to investigate whether demographic and microbiologic characteristics of IE have changed in India.
Design: A retrospective analysis of patients with in north India between 2010 and 2020.
Methods: The clinical and laboratory profiles of 199 IE admitted to an academic hospital patients who met the modified Duke criteria for definite IE were analysed.
Results: The mean age was 34 years, and 84% were males. The main predisposing conditions were injection drug use (IDU) ($n = 71$, 35.7%), congenital heart disease ($n = 46$, 21.6%), rheumatic heart disease ($n = 25$, 12.5%), and prosthetic device ($n = 19$, 9.5%). 17.1% of patients developed IE without identified predispositions. Among 64.3% culture-positive cases, the most prevalent causative pathogens were *Staphylococcus aureus* (46.1%), viridans streptococci (7.0%), enterococci (6.0%), coagulase-negative staphylococci (5.5%), gram negative bacilli (5.5%), polymicrobial (5.5%), and *Candida* (1.0%). The tricuspid (30.3%), mitral (25.6%), and aortic (21.6%) valves were the most common sites of infection, and 60.3% had large vegetations (>10 mm). Systemic embolization occurred in 55.3% of patients at presentation. Cardiac surgery was required for 13.1%. In-hospital mortality was 17.1% and was associated with prosthetic devices (p-value, 0.001), baseline leucocytosis (p-value, 0.036) or acute kidney injury (p-value, 0.001), and a microbial etiology of gram negative bacilli or enterococci (p-value, 0.005).
Conclusion: IDU is now the most important predisposition for IE in India, and *S. aureus* has become the leading cause of native valve endocarditis with or without IDU.

1. Introduction

Infective endocarditis (IE) refers to microbial infection of the heart valves or endocardium. Despite advancements in diagnostic techniques, antimicrobial therapy, and surgical facilities, IE remains a challenging disease for clinicians worldwide and is associated with high morbidity and mortality.[1–5] The disease has been continuously evolving in its epidemiology, predisposing conditions, and clinical spectrum in recent years. It was traditionally associated with structural heart diseases, such as rheumatic heart disease (RHD) or congenital heart disease (CHD); however, in the current

* Corresponding author. 4th floor, F block, Nehru Hospital, PGIMER, Chandigarh, 160012, India.
E-mail addresses: aroranavneet1045@gmail.com (N. Arora), prashantpanda85@gmail.com (P.K. Panda), drpruthvicr@gmail.com (P. CR), drlipiuppal@gmail.com (L. Uppal), atulsaroch@gmail.com (A. Saroch), archanaangrup@yahoo.com (A. Angrup), navneetsharma@hotmail.com (N. Sharma), ypspgi@gmail.com (Y.P. Sharma), rajeshvijay999@hotmail.com (R. Vijayvergiya), cardiopgimerchd@gmail.com (M.K. Rohit), agpgi@yahoo.com (A. Gupta), drbhupndrasihag@gmail.com (B.K. Sihag), himanshu2883@gmail.com (H. Gupta), drneelamdahiya@gmail.com (N. Dahiya), drajaybahl@hotmail.com (A. Bahl), psotaal@gmail.com (P. Singh), rhythmdivine46@yahoo.com (S. Mehrotra), paragaims@gmail.com (P. Barwad), gawaribacchi@gmail.com (A.K. Pannu).

https://doi.org/10.1016/j.ihj.2021.09.008

era, injection drug use (IDU) and health-care-associated factors are the primary risk factors.[3–11] *Staphylococcus aureus*, rather than the more insidious viridans group streptococci, is now the leading infecting organism in most industrialized countries.[4,5,12–14]

Evaluating local epidemiology and continued monitoring of patterns of an infectious disease is essential for clinical management, including prompt recognition and empirical therapy. The studies addressing IE trends in India are scarce and have not been regularly updated.[15–22] The marked change in IE spectrum is expected to occur in Indian patients given altered predisposing conditions (declining incidence of RHD, increasing IDU among the young population, and increased survival of patients with CHD), advancement in diagnostic testing (culture methods, growing echocardiography availability), and improved infection control practices in recent decades.[23–25] Therefore, in the current study, we aimed to investigate the clinical, microbiological, and echocardiographic characteristics, predisposing conditions, and treatment outcomes of IE patients admitted to a tertiary care academic institute in north India.

2. Materials and method

Study design and population: A retrospective review of the medical record of all patients 13 years old and older with IE who were admitted to the Emergency Department (Department of Internal Medicine) and the Department of Cardiology of Postgraduate Institute of Medical Education and Research, Chandigarh (India), from January 2010 to December 2020 was performed. This academic hospital has 1948 beds, serving a large population of north India. The diagnosis of IE was made according to the modified Duke's criteria, and only definite IE cases were included in the study.[26] For the patients with more than one IE episode during the study period, only the first episode was recorded to preserve the assumption of independence of observations.

Data collection: Each record was reviewed by one of the authors by completing a clinical research form detailing a clinical profile (socio-demographic data, predisposing conditions, clinical presentation, physical examination), laboratory data (complete blood counts, biochemical panel, blood cultures (automated system using BACTEC™ method), antibiotic susceptibility testing), imaging studies (echocardiography and radio-imaging), disease-related complications during the course, length of stay, and in-hospital mortality. The embolic complications were defined based on clinical or radiological characteristics, i.e., clinically symptomatic or asymptomatic. The empirical antimicrobial therapy and management of IE patients were following standard guidelines and the local epidemiological data. The antimicrobial agents were modified according to the available culture results or the development of IE complications or hospital-acquired infections during the course.

Ethical consideration: The institutional ethics committee approved the study (No. INT/IEC/2020/SPL-1464). Informed consent was waived as the study involved the anonymized retrospective patient data.

Statistical analysis: The patients were divided into three primary forms of IE - native valve endocarditis (NVE) (without IDU), IDU-related IE (IDU-IE), and prosthetic valve endocarditis (PVE) (including implantable cardiac devices). We used SPSS (version 25 for Mac) for statistical analysis. Discrete variables were described as frequency (n) and percentage (%). According to the normalcy of data, continuous data were recorded as median with interquartile range (IQR) or mean ± standard deviation (SD). Analysis of variance was used to determine the differences between the outcome groups, i.e., died and survived. A two-sided *p*-value of less than 0.05 was taken statistically significant for all statistical tests.

3. Results

3.1. Baseline characteristics

We reviewed 199 patients with definite IE according to modified Duke's criteria admitted over 11 years. The patients were 13–86 years old (mean ± SD, 34.1 ± 13.7 years), with only 10 cases >60 years. There were 167 males and 32 females (ratio, 5.2:1). The median duration of the IE at presentation was 4 weeks (IQR, 3–8 weeks; range, 3 days to 1 year). About one-fourth of cases (24.6%) started symptoms within two weeks. Fever was the most common symptom (93.5%), followed by chills or sweating (72.9%). 70.5% of patients had shortness of breath on admission. History of loss of appetite (57.8%) or weight (46.7%) was common. Chest pain (13.1%) and peripheral edema (4.5%) occurred occasionally. The mean haemoglobin level of the patients at admission was 9.6 g/dL (± 2.2), and 13.3% had severe anemia with a haemoglobin of <8 g/dL. The median leucocyte count was 11850/μL (IQR, 8325–18375), and leucocytosis (>11000/μL) was present in 56.6%. Median value of serum creatinine at presentation was 1.0 mg/dL (IQR, 0.7–1.8).

3.2. Predisposing conditions

Nearly 17% of IE patients did not have any predisposing condition, such as pre-existing cardiac conditions or portals of entry for blood stream infection (e.g., IDU) (Table 1). Fig. 1 shows the increasing proportion of IDU-IE in total cases of IE over the years. IDU-IE was exclusively seen in males, contributing to 42.5% IE episodes in them. Usual predisposition in females were CHD ($n = 13$), RHD ($n = 7$), and PVE ($n = 5$).

3.3. Echocardiography

One hundred ninety-three patients had a positive echocardiogram. Transesophageal echocardiography was available in 36

Table 1
Predisposing conditions in infective endocarditis ($n = 199$).

Predisposing conditions	n (%)
Heart conditions	**86 (43.2%)**
Congenital heart disease[a]	45
Rheumatic heart disease	19
Prosthetic valve endocarditis	12
Prior infective endocarditis	3
Prosthetic valve endocarditis and Rheumatic heart disease	2
Prosthetic valve endocarditis and Prior infective endocarditis	2
Prosthetic valve endocarditis and Double-chambered right ventricle with ventricular septal defect[a]	1
Rheumatic heart disease and Prior infective endocarditis	1
Degenerative mitral regurgitation	1
Injection drug use	**63 (31.7)**
Both heart condition and Injection drug use	**8 (4.0%)**
Rheumatic heart disease and Injection drug use	3
Prior infective endocarditis and Injection drug use	3
Prosthetic valve endocarditis and Injection drug use	2
Miscellaneous	**8 (4.0%)**
Chronic kidney disease receiving hemodialysis	3
Catheter-related blood stream infection	2
Post-abortion	1
Malignancy	1
Post renal transplantation	1
No predisposition	**34 (17.1%)**

[a] Congenital heart disease lesions ($n = 46$) include Bicuspid aortic valve ($n = 18$), Mitral valve prolapse ($n = 16$), Ventricular septal defect ($n = 5$), Double-chambered right ventricle with ventricular septal defect ($n = 3$), Patent ductus arteriosus ($n = 1$), Tetralogy of Fallot ($n = 1$), Aortic stenosis ($n = 1$), and Pulmonary valve stenosis ($n = 1$).

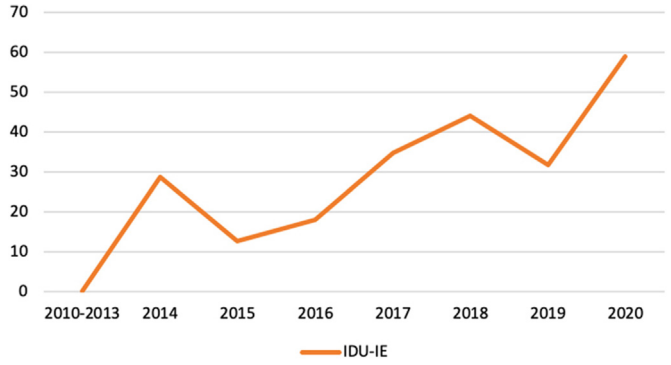

Fig. 1. Shows the increasing proportion (%) of IDU-IE in total cases of IE over the study period (years).

(18.1%) cases. Table 2 shows echocardiographic findings with involved sites and the size of the vegetation in different IE types.

3.4. Microbiology

Table 3 shows blood culture positive IE cases ($n = 128$). Most common causative organism was *S. aureus* ($n = 68$, including 9 polymicrobial cases) in both IDU-IE ($n = 44$) and non-IDU NVE ($n = 22$). 10/22 NVE patients had no predisposition; the rest occurred with mitral valve prolapse (MVP) ($n = 3$), bicuspid aortic valve (BAV) ($n = 2$), congenital aortic stenosis ($n = 1$), pulmonary valvular stenosis ($n = 1$), RHD ($n = 2$), catheter-related blood stream infection (CRBSI) ($n = 2$), previous IE ($n = 1$), and malignancy ($n = 1$). 61.8% ($n = 42$) *S. aureus* were methicillin resistant strains. Coagulase-negative staphylococci (CoNS) ($n = 14$) infected the patients with PVE ($n = 2$), IDU ($n = 2$), RHD ($n = 2$), BAV ($n = 2$), MVP ($n = 1$), double-chambered right ventricle with ventricular septal defect ($n = 1$), degenerative mitral regurgitation ($n = 1$), no predisposing factors ($n = 3$). Five CoNS strains were methicillin resistant.

Viridans streptococci were second common organisms ($n = 18$), isolated from BAV ($n = 4$), MVP ($n = 3$), double-chambered right ventricle with ventricular septal defect ($n = 1$), ventricular septal defect ($n = 1$), patent ductus arteriosus ($n = 1$), RHD ($n = 2$), PVE ($n = 2$), IDU-IE ($n = 1$), and NVE without any predisposition ($n = 3$). 7/18 viridans streptococci were beta-lactam sensitive, 6 had beta-lactam resistance (including one vancomycin resistant strain), and in the rest five, sensitivity pattern was not available. Enterococci (*E. faecium*, $n = 13$; *E. gallinarium*, $n = 1$) were implicated with IDU ($n = 4$), MVP ($n = 1$), tetralogy of Fallot ($n = 1$), RHD ($n = 1$), degenerative mitral regurgitation ($n = 1$), and no predisposition identified ($n = 4$). Only four *E. faecium* strains were ampicillin resistant (but vancomycin sensitive), remaining all enterococci were beta-lactam sensitive. *Streptococcus gallolypticus* (previously called *Streptococcus bovis* biotype 1) infected one patient with MVP.

Pseudomonas aeruginosa caused 10/15 gram negative bacilli (GNB)-related IE, including five aminoglycoside sensitive strains, three aminoglycoside resistant (but sensitive to piperacillin-tazobactam and ceftazidime), and sensitivity pattern was not available in the remaining two. Each of *Stenotrophomonas maltophilia*, *Burkholderia cepacia*, *Enterobacter kobei*, and *Achromobactor xylosidans* were aminoglycoside sensitive, but *Klebsiella pneumoniae* was carbapenem-resistant with sensitivity only to polymyxins. All three cases of *Brucella* species had a history of consumption of unpasteurized milk products.

3.5. Complications and in-hospital outcomes

Septic embolization was seen in 55.3% ($n = 110$) at admission. IDU-IE had higher rates of pulmonary emboli, and NVE had more cerebral and splenic emboli (Table 4, Supplementary Figure 1). Cardiac surgical treatment was performed in 13.1%, 61.5% of whom had left-sided IE. The in-hospital mortality was 17.1% ($n = 34$). PVE had high complication rates and was associated with death

Table 2
Echocardiography findings in IE ($n = 199$).

Parameter	Total ($n = 199$)	NVE ($n = 111$)	IDU-IE ($n = 71$)[a]	PVE ($n = 19$)[a]
Site involved				
Tricuspid valve	60 (30.2)	11 (9.9)	48 (67.6)[a]	3 (15.8)[a]
Mitral valve	51 (25.6)	38 (34.2)	7 (9.9)	6 (31.6)
Aortic valve	43 (21.6)	30 (27.0)	8 (11.3)	5 (26.3)
Pulmonary valve	4 (2.0)	3 (2.7)	–	1 (5.3)
Right ventricular outflow tract	2 (1.0)	2 (1.8)	–	–
Multi-valve involvement	27 (13.6)	21 (18.9)	5 (7.0)	1 (5.3)
Mitral and Aortic valves	12 (6.0)	10 (9.0)	1 (1.4)	1 (5.3)
Mitral and Tricuspid valves	7 (3.5)	5 (4.5)	2 (2.8)	–
Mitral, aortic and Tricuspid valves	3 (1.5)	2 (1.8)	1 (1.4)	–
Tricuspid and Pulmonary valves	2 (1.0)	1 (0.9)	1 (1.4)	–
Tricuspid and Aortic valves	2 (1.0)	2 (1.8)	–	–
Aortic valve and Right ventricular outflow tract	1 (0.5)	1 (0.9)	–	–
Miscellaneous	6 (3.0)	3[b] (2.7)	–	3[c] (15.8)
No vegetation detected	6 (3.0)	3 (2.7)	3 (4.2)	–
Vegetation size (at maximum dimension)				
Small (<10 mm)	63 (31.7)	43 (38.7)	14 (19.7)[a]	7 (36.8)[a]
Large (10–30 mm)	77 (38.7)	39 (35.1)	31 (43.7)	7 (36.8)
Very large (>30 mm)	43 (21.6)	21 (18.9)	21 (29.6)[a]	2 (10.5)[a]
Valvular abscess	2 (1.0)	–	1 (1.4)	1 (5.3)
Both small and large (in multi-valve IE)	2 (1.0)	1 (0.9)	1 (1.4)	–
Size not mentioned	6 (3.0)	4 (3.6)	–	2 (10.5)

Abbreviation: IE-infective endocarditis; IDU- injection drug use; NVE-native valve endocarditis; PVE-prosthetic valve endocarditis.
Values are given as n (%).
[a] Two patients had both IDU and PVE. Both had tricuspid valve involvement. The vegetation size was small in one case and was very large in the other.
[b] Right coronary cusp ($n = 1$), Left ventricle apex ($n = 1$), Left atrial appendages ($n = 1$).
[c] Cardiovascular implantable electronic device ($n = 1$), Right ventricular lead ($n = 1$), Ventricular septal defect patch ($n = 1$).

Table 3
Microbiological etiology of IE (n=199).

Microorganism(s)	Total (N=199)	NVE (n=111)	IDU-IE			PVE (n=19)[b]
			Total (N=71)[a,b]	Right side (n=53)	Left side (n=16)	
Culture positive IE	**128 (64.3)**	**63 (56.8)**	**57 (80.3)**	**45 (84.9)**	**10 (62.5)**	**9 (47.4)**
Staphylococcus aureus	**59 (29.6)**	**19 (17.1)**	**40 (50.6)**	**34 (64.2)**	**6 (37.5)**	–
Viridans streptococci group	**14 (7.0)**	**11 (9.9)**	**1 (1.4)**	–	**1 (6.2)**	**2 (10.5)**
S. sanguinis	6	4	1	–	1	1
S. oralis	3	3	–	–	–	–
S. gorodonii	3	3	–	–	–	–
S. mitis	1	1	–	–	–	–
S. parasanguinis	1	1	–	–	–	–
S. anginosus	1	–	–	–	–	1
Granulicatella adiacens[c]	2	2	–	–	–	–
Enterococcus faecium	**12 (6.0)**	**8 (7.2)**	**3**[a] **(4.2)**	**1 (1.9)**	**1 (6.2)**	**1 (5.3)**
Coagulase-negative staphylococci	**11 (5.5)**	**7 (6.3)**	**2 (2.8)**	**2 (3.8)**	–	**2 (10.5)**
S. epidermidis	4	2	–	–	–	2
S. haemolyticus	4	2	2	2	–	–
S. homonis	3	3	–	–	–	–
Gram negative bacilli	**11 (5.5)**	**4 (3.6)**	**6 (8.4)**	**5 (9.4)**	–	**2 (10.5)**
Pseudomonas aeruginosa	7	1	6[a,b]	5	–	1[b]
Stenotrophomonas maltophilia	1	–	–	–	–	1
Klebsiella pneumoniae	1	1	–	–	–	–
Achromobacter xylosoxidans	1	1	–	–	–	–
Enterobacter kobei	1	1	–	–	–	–
Polymicrobial	**11 (5.5)**	**6 (5.4)**	**4 (5.6)**	**3 (5.7)**	**1 (6.2)**	**1 (5.3)**
S. aureus and P. aeruginosa	3	1	2	1	1	–
S. aureus and Candida species	2	1	–	–	–	1
S. aureus and E. faecium	1	–	1	1	–	–
S. aureus and S. parasangunis	1	1	–	–	–	–
S. aureus and S. epidermis	1	1	–	–	–	–
S. aureus and Burkholderia cepacia	1	–	1	1	–	–
S. epidermidis and Streptococcus gallolyticus	1	1	–	–	–	–
S. epidermidis and E. gallinarum	1	1	–	–	–	–
Miscellaneous						
Brucella species	3	3	–	–	–	–
Candida species	2	1	1	–	1	–
Diphtheroids	1	1	–	–	–	–
Lactobacillus rhamnosus	1	–	–	–	–	1

Abbreviation: IE – infective endocarditis; IDU – injection drug use; NVE – native valve endocarditis; PVE – prosthetic valve endocarditis
Values are given as n (%)
[a,b] Two patients had both IDU-IE and PVE, and two IDU-IE cases had both right and left sides involvement
[a] Both right and left-sided IE
[b] One of the two IDU-IE patients with both right and left sides involvement was culture-positive (*P. aeruginosa*)
[c] Nutritionally Variant Streptococci

Table 4
Septic emboli at admission and in-hospital outcomes in IE patients (n = 199).

Parameters	Total (n = 199)	NVE (n = 111)	IDU-IE (n = 71)	PVE (n = 19)
Septic emboli at presentation				
Pulmonary	71 (35.7)	27 (24.3)	42 (59.2)	3 (15.8)
Cerebral	28 (14.1)	20 (18.0)	7 (9.9)	1 (5.3)
Splenic	25 (12.6)	15 (13.5)	7 (9.9)	3 (15.8)
Peripheral extremities	13 (6.5)	6 (5.4)	4 (5.6)	3 (15.8)
Renal	11 (5.5)	3 (2.7)	2 (2.8)	6 (31.6)
Hepatic	2 (1.0)	–	2 (2.8)	–
Multiple (more than one) sites	32 (16.1)	17 (15.3)	11 (15.5)	4 (21.0)
Total events	110 (55.3)	49 (44.1)	52 (73.2)	10 (52.6)
Major complications during course				
Acute kidney injury	34 (17.1)	19 (17.1)	8 (11.3)	7 (36.8)
Circulatory shock	18 (9.0)	10 (9.0)	3 (4.2)	5 (26.3)
Cerebrovascular accident	12 (6.0)	6 (5.4)	3 (4.2)	3 (15.8)
Valvular rupture or perforation	3 (1.5)	3 (2.7)	–	–
Pulmonary thromboembolism	2 (1.0)	1 (0.9)	1 (1.4)	–
Cardiac tamponade	1 (0.5)	1 (0.9)	–	–
Need of cardiac surgical treatment	26 (13.1)	17 (15.3)	7 (9.9)	2 (7.7)
In-hospital mortality	34 (17.1)	17 (15.3)	9 (12.7)	9 (47.4)

Values are given as n (%).
Abbreviation: IE-infective endocarditis; IDU- injection drug use; NVE-native valve endocarditis; PVE-prosthetic valve endocarditis.

(Tables 4 and 5). Mortality was similar in NVE and IDU-IE outcomes were similar between culture-positive IE and culture-negative IE. The median duration of hospital stay was 2 weeks (IQR, 1–4 weeks) and was similar in the three IE forms.

Table 5
Univariant analysis for the predictors of mortality in infective endocarditis ($n = 199$).

Variable	Survived ($n = 165$)	Died ($n = 34$)	*p*-value
Demographics			
Age (years) (mean, SD)	33.5 (±13.8)	37.2 (±13.4)	0.152
Male sex (n, %)	138 (82.6)	29 (17.4)	1.000
Presenting features			
Duration of illness (weeks) (median, IQR)	4.0 (2.0–12.0)	4.0 (3.0–8.0)	0.707
Septic emboli (n, %)	89 (80.1)	21 (19.9)	0.452
Severe anemia (hemoglobin <8 g/dl) (n, %)	33 (71.7)	12 (28.3)	0.073
Leukocytosis (n, %)	86 (77.5)	25 (22.5)	**0.036**
Acute kidney injury (n, %)	21 (61.8)	13 (38.2)	**0.001**
Predisposition			
Prosthetic device (n, %)	10 (52.6)	9 (47.4)	**0.001**
Presence of injection drug use in native valve endocarditis (n, %)	61 (88.4)	8 (11.6)	0.516
Microbiology			
Culture positive endocarditis (n, %)	109 (85.2)	19 (14.8)	0.326
Microbial etiology (n, %)			
Staphylococci	67 (91.8)	6 (8.2)	**0.005**
Streptococci	13 (92.9)	1 (7.1)	
Polymicrobial etiology	10 (90.1)	1 (9.1)	
Enterococci	7 (58.3)	5 (42.7)	
Gram negative bacilli	7 (63.6)	4 (37.4)	
Echocardiography			
Valve involved (n, %)			
M itral valve	41 (80.4)	10 (19.6)	0.353
T ricuspid valve	54 (90.0)	6 (10.0)	
Aortic valve	37 (86.0)	6 (14.0)	
Multi-valve involvement (n, %)	20 (74.1)	7 (25.9)	0.189
Left-side involvement (n, %)	86 (79.6)	22 920.4)	0.163
Large vegetation (>10 mm) (n, %)	103 (83.1)	21 (16.9)	1.000
Need of cardiac surgery (n, %)	22 (84.6)	4 (15.4)	1.000

Note: Bold values are statistically significant.

4. Discussion

This study, to our knowledge, is one of the largest-yet Indian series of IE covering 11 years in a large academic medical center. It demonstrates a significant shift in the spectrum of IE. IDU has emerged as the most critical risk factor. While CHD remained constant predisposing heart conditions, the proportion of RHD cases trended downward. *S. aureus* replaced viridans streptococci as the principal agent in NVE with or without IDU. Viridans streptococci, enterococci, and CoNS were the following common organisms, concurring with worldwide data. PVE was uncommon (<10%) and frequently culture-negative. The overall mortality of 17% showed a decrease but remained substantial. The risk was associated with PVE, culture-positive with enterococci or GNB, andbaseline leucocytosis or acute kidney injury.

Globally, the opioid epidemic has led to increasing admissions for IDU-IE, with substantial health and cost implications.[4,5,10,21,27,28] Our study, along with a recent study from Punjab, detected an alarming increase in the proportion of IDU-IE in India compared to the previous major IE series (Supplementary Table 1).[15–22] A continuously increasing ratio of IDU-IE was demonstrated over the years in our study, except for a significant decline from 2014 to 2015 (Fig. 1), which was mainly attributed to active anti-drug use campaigns during the elections in north India. A recent declining trend of RHD in India and improved survival of CHD patients have resulted in the flipping of the contributions of predisposing heart conditions causing IE.[22,23] Gynecological procedures or puerperal sepsis typically predisposed IE in young or middle-aged women in previous reports; however, only one case (post-abortion) in our series seems parallel to the improved infection control practices in India.[15] Albeit the study was limited to geographic regions of north India; a similar situation likely exists to a large extent across the country.

Because illicit drug use is almost exclusively occurring in males, a high proportion of IDU-IE in our study, along with the less prevalence of RHD (more commonly affects females) and uterine factors, attributed to the striking male preponderance. Indian IE population continued to remain young, given the principal etiologies being IDU, CHD, or RHD.[15–22] This contrasts with western cohorts' median age of the sixth decade, mainly attributing to increased use of implantable cardiac devices and other invasive diagnostic and therapeutic interventions in patients with advanced age.[4,5,29] PVE accounted for <10% of our cases, and other healthcare-associated factors (e.g., hemodialysis, CRBSI) contributed less.

Microbial organism identification is crucial in defining the optimal therapy regimen in IE. Blood culture positivity in about two-thirds was fair in this cohort compared to previous studies, though it left considerable room for improvement.[4,5,15–22] Most culture-negative patients can be explained by recent antibiotic exposure; however, it may reflect infections (e.g., fastidious organisms, fungus) requiring better diagnostic techniques.[30] Concurring with many studies from the developed world, we have demonstrated a shift in the microbiological profile of IE, with *S. aureus* surpassing viridans streptococci as the most frequently isolated species in India.[4–22] The increase in the proportion of *S. aureus* in the western countries was mainly attributed to health care contact and prosthetic device use.[4,5,12–14,31] However, in this study, PVE was not caused by *S. aureus*, and excluding those instances where the infection was acquired by IDU, the mode of acquisition in our NVE cases could not be ascertained. Moreover, given this data is from a referral-based center, the results may not reflect overall trends. Thus, the emergence of *S. aureus* as the single predominant entity for IE in India needs confirmation by population-based prospective studies.

As anticipated, most viridans streptococci (14/18) were isolated from patients with a previously damaged valve due to CHD, RHD, or

prosthetic valve.[4,5,32] Streptococcal species such as *S. pneumoniae* and *S. pyogenes* carry the lowest risks for IE and did not cause IE in this cohort.[32] Both *S. aureus* and viridans streptococci were frequently beta-lactam resistant. Enterococci were the third most common etiologic agents. In contrast to the previous experience, *E. faecium*, not *E. faecalis*, was the predominant species in our cohort, and the majority remained susceptible to ampicillin.[4,5,33] The relatively high proportion of susceptible strains of enterococci and CoNS was perhaps because most were community-acquired. The polymicrobial group was more likely to have infections from *S. aureus*, CoNS, *Candida*, GNB, and enterococci. The relative contributions of GNB and fungi showed no significant variation over time.[15–22] *P. aeruginosa* remained next common to *S. aureus* in IUD-IE. Overall, this study's microbiological and antibiotic susceptibility patterns reassure the western world's recommendations for empirical treatment (pending culture results) with the combination of vancomycin and gentamycin for IDU-IE and ceftriaxone plus vancomycin for NVE without IDU in Indian patients.[1,2,34] Small numbers, low culture positivity, and a heterogeneous bacteriological profile limit interpretation for PVE.

Fever, dyspnea, and other constitutional symptoms were the chief presenting features in most cases. More than half of patients had systemic emboli at admission, most frequently in IVD-IE (about 75%). These embolic phenomena might serve as the initial clinical clue for diagnosing IE, e.g., in febrile patients with IDU with pulmonary involvement or stroke.[35–37]Besides cardiorespiratory manifestations, AKI, cerebrovascular complications, and anemia were frequent, and AKI was associated with poor outcomes. Overall in-hospital mortality was 17% which showed a decline comparing previous Indian studies but remained substantial.[4,5,15–22] This report provided bedside risk stratification of four baseline features associated with mortality - PVE, leucocytosis, AKI, and a microbial etiology of GNB or enterococci. Notably, the presence of embolic events, size or site of vegetations, and a polymicrobial etiology did not predict deaths.[37–39] In contrast to worldwide data, our IE patients had a low likelihood to undergo surgical interventions to improve outcomes despite being at risk for high complications (e.g., large vegetation) and being in a large referral academic institute. Although our study does not provide information about the benefits of surgery, the emerging data showing less adverse events and improved outcomes emphasize the need for improved IE cardiac surgery practices in this part of the world.[37,38,40,41]

4.1. Limitation

Our major limitations were single-center data, retrospective design, and referral bias of a tertiary-care hospital. Because some clinical features (e.g., orthopnea, paroxysmal nocturnal dyspnea, cardiac murmur, added heart sounds, elevated jugular venous pulsation, splenomegaly) had variable documentation in the patient records, we had to exclude them in the analysis. Similarly, laboratory investigations including, inflammatory markers (e.g., C-reactive peptide, erythrocyte sedimentation rate), cardiac biomarkers (e.g., pro-B-type natriuretic peptide), and serological markers (e.g., for hepatitis B, hepatitis C, and human immunodeficiency virus infections associated with IDU), were not available in the databases of all patients.

Given the variable documentation of clinical features (e.g., dyspnea, orthopnea, crackles, lung infiltrates) and their attribution to either cardiac or respiratory failure, along with the unavailability of adjunctive biomarkers, we could not define the exact prevalence of heart failure or respiratory failure in this cohort. Clinical outcomes would also require more exposition on the clinical information, such as treatment details (partial oral treatment, outpatient parenteral antibiotic treatment, surgical procedures undertaken) that may be limited by the data collection design of this audit.

5. Conclusion

This retrospective study, spanned over a decade, captures the changes in IE profile among Indian patients due to the growing opioid epidemic and the declining RHD trend. *S. aureus* emerges as the single predominant entity in NVE with or without IDU. PVE is uncommon and has a high mortality rate. Although these results require confirmation from multicentre prospective studies, our study highlights the need for effective policy interventions to address growing IDU, adherence to infection-control practices, management of drug dependence, and appropriate patient selection for valve surgery.

Acknowledgment

The corresponding author (AKP) wishes to thank Dr. Arjun Lakshman (a friend and colleague during the senior residency) for being a constant source of initiation and inspiration to carry out this study. Authors thank Mrs. Sunaina Verma for help in statistics.

Author contributions

NA: patient management, collected patient data, drafted the manuscript, PKP: patient management, revised the manuscript, PCR, LU: patient management, collected patient data, AS, AA, NS, YPS, RV, MKR, AG, BKS, HG, ND, AB, PS, SM, PB: patient management, AKP: conceived the idea, patient management, collected patient data, drafted and revised the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ihj.2021.09.008.

References

1. Chambers HF, Bayer AS. Native-valve infective endocarditis. *N Engl J Med*. 2020;383(6):567–576.
2. Wang A, Gaca JG, Chu VH. Management considerations in infective endocarditis: a review. *J Am Med Assoc*. 2018;320(1):72–83.
3. Cahill TJ, Baddour LM, Habib G, et al. Challenges in infective endocarditis. *J Am Coll Cardiol*. 2017;69(3):325–344.
4. Shah ASV, McAllister DA, Gallacher P, et al. Incidence, Microbiology, and outcomes in patients hospitalized with infective endocarditis. *Circulation*. 2020;141(25):2067–2077. Erratum in: Circulation 2020;141(25):e960.
5. Murdoch DR, Corey GR, Hoen B, et al. International collaboration on endocarditis-prospective cohort study (ICE-PCS) investigators. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the international collaboration on endocarditis-prospective cohort study. *Arch Intern Med*. 2009;169(5):463–473.
6. Sandre RM, Shafran SD. Infective endocarditis: review of 135 cases over 9 years. *Clin Infect Dis*. 1996;22(2):276–286.
7. Tornos P, Iung B, Permanyer-Miralda G, et al. Infective endocarditis in Europe: lessons from the Euro heart survey. *Heart*. 2005;91(5):571–575.
8. Siddiq S, Missri J, Silverman DI. Endocarditis in an urban hospital in the 1990s. *Arch Intern Med*. 1996;156(21):2454–2458.
9. Tleyjeh IM, Steckelberg JM, Murad HS, et al. Temporal trends in infective endocarditis: a population-based study in Olmsted County, Minnesota. *J Am Med Assoc*. 2005;293(24):3022–3028.
10. Schranz AJ, Fleischauer A, Chu VH, Wu LT, Rosen DL. Trends in drug use-associated infective endocarditis and heart valve surgery, 2007 to 2017: a study of statewide discharge data. *Ann Intern Med*. 2019;170(1):31–40.
11. Hoen B, Alla F, Selton-Suty C, et al. Association pour l'Etude et la Prévention de l'EndocarditeInfectieuse (AEPEI) Study Group. Changing profile of infective endocarditis: results of a 1-year survey in France. *J Am Med Assoc*. 2002;288(1):75–81.
12. Fowler Jr VG, Miro JM, Hoen B, et al. ICE Investigators. Staphylococcus aureus endocarditis: a consequence of medical progress. *J Am Med Assoc*. 2005;293(24):3012–3021. Erratum in: JAMA 2005;294(8):900.

13. Selton-Suty C, Célard M, Le Moing V, et al, AEPEI Study Group. Preeminence of Staphylococcus aureus in infective endocarditis: a 1-year population-based survey. *Clin Infect Dis*. 2012;54(9):1230–1239.
14. Federspiel JJ, Stearns SC, Peppercorn AF, Chu VH, Fowler Jr VG. Increasing US rates of endocarditis with Staphylococcus aureus: 1999-2008. *Arch Intern Med*. 2012;172:363–365.
15. Choudhury R, Grover A, Varma J, et al. Active infective endocarditis observed in an Indian hospital 1981-1991. *Am J Cardiol*. 1992;70(18):1453–1458.
16. Garg N, Kandpal B, Garg N, et al. Characteristics of infective endocarditis in a developing country-clinical profile and outcome in 192 Indian patients, 1992-2001. *Int J Cardiol*. 2005;98(2):253–260.
17. Math RS, Sharma G, Kothari SS, et al. Prospective study of infective endocarditis from a developing country. *Am Heart J*. 2011;162(4):633–638.
18. Senthilkumar S, Menon T, Subramanian G. Epidemiology of infective endocarditis in Chennai, South India. *Indian J Med Sci*. 2010;64(4):187–191.
19. V R RM, Nambi PS, Ramakrishnan B, Gopalakrishnan R, Sathyamurthy. Profile of infective endocarditis: at a tertiary care referral centre. *J Assoc Phys India*. 2018;66(6):60–65.
20. Padmaja K, Sudhaharan S, Vemu L, Satish OS, Chavali P, Neeraja M. Clinicomicrobiological spectrum of infective endocarditis - from a tertiary care centre in south India. *Iran J Microbiol*. 2017;9(5):257–263.
21. Goyal A, Mohan B, Kumar P, et al. Clinical characteristics and outcome of infective endocarditis among intravenous drug abusers in India. *Indian Heart J*. 2020;72(6):547–551.
22. Gupta A, Gupta A, Kaul U, Varma A. Infective endocarditis in an Indian setup: are we entering the 'modern' era? *Indian J Crit Care Med*. 2013;17(3):140–147.
23. Negi PC, Sondhi S, Asotra S, Mahajan K, Mehta A. Current status of rheumatic heart disease in India. *Indian Heart J*. 2019;71(1):85–90.
24. Saxena A. Congenital heart disease in India: a status report. *Indian Pediatr*. 2018;55(12):1075–1082.
25. National AIDS Control Organization. *HIV Sentinel Surveillance 2016-2017: Technical Brief*. New Delhi, India: Ministry of Health and Family Welfare, Government of India; 2017. Available at: http://naco.gov.in/sites/default/files/HIV%20SENTINEL%20SURVEILLANCE_06_12_2017_0.pdf. Accessed May 3, 2020.
26. Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis*. 2000;30(4):633–638.
27. Fleischauer AT, Ruhl L, Rhea S, Barnes E. Hospitalizations for endocarditis and associated health care costs among persons with diagnosed drug dependence - North Carolina, 2010-2015. *MMWR Morb Mortal Wkly Rep*. 2017;66(22):569–573.
28. Suzuki J, Johnson JA, Montgomery MW, et al. Long-term outcomes of injection drug-related infective endocarditis among people who inject drugs. *J Addiction Med*. 2020;14(4):282–286.
29. Terpenning MS, Buggy BP, Kauffman CA. Infective endocarditis: clinical features in young and elderly patients. *Am J Med*. 1987;83(4):626–634.
30. Lamas CC, Eykyn SJ. Blood culture negative endocarditis: analysis of 63 cases presenting over 25 years. *Heart*. 2003;89(3):258–262.
31. Wang A, Athan E, Pappas PA, et al. International Collaboration on Endocarditis-Prospective Cohort Study Investigators. Contemporary clinical profile and outcome of prosthetic valve endocarditis. *J Am Med Assoc*. 2007;297(12):1354–1361.
32. Chamat-Hedemand S, Dahl A, Østergaard L, et al. Prevalence of infective endocarditis in streptococcal bloodstream infections is dependent on streptococcal species. *Circulation*. 2020;142(8):720–730.
33. McDonald JR, Olaison L, Anderson DJ, et al. Enterococcal endocarditis: 107 cases from the international collaboration on endocarditis merged database. *Am J Med*. 2005;118(7):759–766.
34. Baddour LM, Wilson WR, Bayer AS, et al. American heart association committee on rheumatic fever, endocarditis, and kawasaki disease of the council on cardiovascular disease in the young, council on clinical Cardiology, council on cardiovascular surgery and anesthesia, and stroke council. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American heart association. *Circulation*. 2015;132(15):1435–1486. Erratum in: Circulation 2015;132(17):e215. Erratum in: Circulation 2016;134(8):e113. Erratum in: Circulation 2018;138(5):e78-e79.
35. Kaku DA, Lowenstein DH. Emergence of recreational drug abuse as a major risk factor for stroke in young adults. *Ann Intern Med*. 1990;113(11):821–827.
36. Heiro M, Nikoskelainen J, Engblom E, Kotilainen E, Marttila R, Kotilainen P. Neurologic manifestations of infective endocarditis: a 17-year experience in a teaching hospital in Finland. *Arch Intern Med*. 2000;160(18):2781–2787.
37. Rodger L, Glockler-Lauf SD, Shojaei E, et al. Clinical characteristics and factors associated with mortality in first-episode infective endocarditis among persons who inject drugs. *JAMA Netw Open*. 2018;1(7), e185220.
38. Hasbun R, Vikram HR, Barakat LA, Buenconsejo J, Quagliarello VJ. Complicated left-sided native valve endocarditis in adults: risk classification for mortality. *J Am Med Assoc*. 2003;289(15):1933–1940.
39. Mügge A, Daniel WG, Frank G, Lichtlen PR. Echocardiography in infective endocarditis: reassessment of prognostic implications of vegetation size determined by the transthoracic and the transesophageal approach. *J Am Coll Cardiol*. 1989;14(3):631–638.
40. Kang DH, Kim YJ, Kim SH, et al. Early surgery versus conventional treatment for infective endocarditis. *N Engl J Med*. 2012;366(26):2466–2473.
41. Delahaye F, Célard M, Roth O, de Gevigney G. Indications and optimal timing for surgery in infective endocarditis. *Heart*. 2004;90(6):618–620.