

Infective Endocarditis: A Case Series

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Abstract

Infective endocarditis (IE) is an infection of the endocardial surface of the heart. The incidence of IE worldwide is approximately 3 to 10 per 100,000 people annually. Twenty percent of patients die during the hospital stay, and the mortality may reach 25 to 30% six months postinfection. We hereby present our experience of six patients, of whom five survived. The cause of one death was late presentation and lack of coverage for *Burkholderia* in the prescribed empirical antibiotic therapy. One of our patients, with culture-negative endocarditis, responded to doxycycline and did not require any surgery. Five out of six patients who underwent surgery had vegetations more than 10 mm in size, and one patient had an aortic valve abscess (caused by *Staphylococcus haemolyticus*). Both prosthetic endocarditis and native valve endocarditis can be treated successfully with antimicrobial agents and surgery (when indicated). A high index of suspicion is required to diagnose IE caused by fungus and atypical bacteria.

Keywords

- Infective endocarditis
- valve

Introduction

Infective endocarditis (IE) is an infection of the endocardial surface of the heart. It most commonly involves heart valves but may also involve other endocardial sites in the heart. Congenital anomalies such as ventricular septal defect, bicuspid aortic valve (BAV), patent ductus arteriosus, and coarctation of the aorta predispose for the development of IE. The incidence of IE worldwide is approximately 3 to 10 per 100,000 people annually.¹⁻⁴ The incidence of IE remains high in spite of better diagnostic facilities, newer antibiotics, and early surgical intervention.⁵ In India, rheumatic heart disease (RHD) is the most common underlying cardiac condition for developing IE, whereas in the developed countries, congenital heart disease is the predominant underlying pathology.⁶⁻⁸ A recent study in the Indian population revealed that approximately 76% patients with IE were less than 40 years old, with a mean age of 27.6 (± 12) years.⁷ In comparison to adults, IE is less common in children; however, its incidence is on the rise. IE is classified on the basis of location, presence or absence of intracardiac device or prosthetic valve, and mode of acquisition (community-acquired, nosocomial, or intravenous [IV]

drug related). Patients with a prosthetic valve or prosthetic material used for cardiac repair have a high incidence of IE. Prosthetic valve IE can be classified early (<1 year) or late (>1 year) after valve replacement of surgery. The most common causative organism for prosthetic valve endocarditis (PVE) is *Staphylococcus* followed by *Streptococcus* species.⁹

IE is associated with high mortality. Twenty percent of patients die during the hospital stay, and the mortality may reach 25 to 30% six months postinfection.¹⁰⁻¹³ Early mortality is similar between native valve endocarditis (NVE) and PVE and between mitral and aortic valve endocarditis. The mortality is highest (50%) in patients developing infections due to gram-negative bacilli or fungus.^{11,14-17}

Diagnosis of IE requires clinical finding, microbiological analysis, and imaging. The clinical features are often nonspecific and may include fever, chills, fatigue, or weight loss. Fever is the most common clinical manifestation present in approximately 95 to 100% of patients (both in NVE and PVE). The diagnosis of IE is concluded on the basis of the modified Duke criteria (► **Table 1**). The presence of two major, one major and three minor, or five minor clinical criteria is diagnostic of IE.

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Table 1 Modified Duke criteria for diagnosing infective endocarditis³¹

Major criteria	Minor criteria
1. Two positive blood cultures with typical microorganisms collected at least 12 h apart (or one positive culture for <i>Coxiella burnetii</i>)	1. Fever > 38°C
2. Evidence of endocardial involvement (new murmur, echocardiographic evidence of cardiac mass, abscess, valve dehiscence)	2. Vascular phenomenon (systemic emboli, Janeway lesions)
	3. Immunologic phenomenon (Osler nodes, Roth spots)
	4. Predisposition to infective endocarditis (previous infective endocarditis or intravenous drug abuse)
	5. Microbiologic evidence that does not meet major criteria

Laboratory investigations show an increase in the levels of inflammatory markers (erythrocyte sedimentation rate [ESR], C-reactive protein [CRP]) and normocytic normochromic anemia. Urine analysis often reveals microscopic hematuria and occasionally RBC cast or pus cells. The electrocardiogram is essentially normal with infrequent finding of new conduction abnormalities suggestive of paravalvular or myocardial extension of infection. Positive blood cultures are obtained in approximately 60 to 80% in developed countries as compared with developing countries like India, where only 40 to 60% are positive.^{18,19} Echocardiography has become a standard modality for diagnosis of IE. Transesophageal echocardiography has greater sensitivity and specificity than transthoracic echocardiography (TTE) for diagnosing valvular vegetations and abscesses.

We hereby report six patients treated for IE in the Department of Cardio-Thoracic and Vascular Surgery between June 2019 and January 2020.

Case Report

Patient 1

A 17-year-old boy with prosthetic mitral valve (mechanical) was admitted to the Department of Cardio-Thoracic and Vascular Surgery with high-grade intermittent fever and shortness of breath on exertion since 10 days. He had undergone mitral valve replacement four months back for RHD with severe mitral stenosis. TTE showed three sessile structures on the atrial aspect of prosthetic mitral valve annulus suggestive of vegetation. Investigation showed a hemoglobin (Hb) level of 11 g/dL, total leukocyte count (TLC) of 15,640/mm³, CRP of 200.9 mg/dL, procalcitonin of 17.41 ng/mL, and no growth on blood cultures. A diagnosis of prosthetic heart valve endocarditis was made, and treatment was started with parenteral vancomycin, meropenem, and oral rifampicin. The fever persisted even after 1 week of starting the aforementioned antibiotics. Then, oral doxycycline was added to the treatment. After 48 hours, the patient's fever subsided and the aforementioned regime was continued for 6 weeks' duration. The patient recovered completely and was discharged.

Patient 2

A 69-year-old female was admitted to our hospital with high-grade fever and shortness of breath for 1 week. She had undergone aortic valve replacement (AVR) one month back for severe aortic stenosis. One week after AVR, she developed high-grade fever (103°F). At the time of admission her blood pressure (BP) was 90/60 mm Hg, heart rate (HR) was 126 beats per minute, respiratory rate (RR) was 25 breaths/minute, body temperature was 37.5°C, Hb was 9.7 gm/dL, TLC was 22,610/mm³, CRP was 118.53 mg/L, ESR was 35 mm/hour, PCT was 2.62 ng/mL, blood culture showed growth of *Burkholderia cepacia*, and urine culture showed growth of budding yeast cells. TTE showed two aortic valve vegetations (10 × 13 mm and 9 × 12 mm) and paravalvular leak around aortic prosthetic valve. The patient was treated with IV vancomycin, IV gentamicin, and oral rifampicin. She became hemodynamically unstable, following which inotropes and vasopressors were started. She was intubated and put on mechanical ventilation. The patient developed complete heart block, and an emergency permanent pacemaker was implanted. In view of deteriorating clinical status, she was taken up for surgery as a last attempt but she could not be saved and died on the second postoperative day.

Patient 3

A 12-year-old girl was admitted to our hospital with fever between 100°F and 102°F for 3 months not responsive to conventional medical treatment. She had a history of fever and multiple large joint pain four years back. Two years back, she was incidentally diagnosed with mitral valve prolapse during evaluation of her fever. Dental caries was present. On auscultation, pan systolic murmur in the mitral area and early diastolic murmur in pulmonary area was heard. On admission, her BP was 108/60 mm Hg, HR was 130 beats per minute, RR was 14 breaths per minute, temperature was 37°C, Hb was 8.2 g/dL, TLC was 11,060/mm³, CRP was 93.16 mg/L, ESR was 38 mm/hour, and blood cultures were sterile. TTE showed two large vegetations on mitral valve (13 × 10 mm and 12 × 9 mm), prolapsed of anterior mitral leaflet, severe mitral regurgitation, and dilated left atrium (LA). The patient was treated with IV ceftriaxone and gentamicin for four weeks. Patient improved symptomatically and underwent an uneventful prosthetic mitral valve replacement. Following surgery, the patient recovered well and was discharged.

Patient 4

A 54-year-old woman was admitted in our unit with on and off fever for three months. She had a medical history of hypertension and diabetes mellitus and had undergone coronary angiography 3 months earlier for the evaluation of chest pain. The patient developed fever two weeks after coronary angiography. Fundus examination showed a Roth spot, and TTE showed aortic valve vegetation (11 × 6 mm and 8 × 6 mm). The patient was treated with IV ceftriaxone, amikacin, and vancomycin for four weeks, but the fever still persisted. Contrast-enhanced CT scan of the abdomen showed mild hepatomegaly with wedged-shaped infarct in the spleen. Blood cultures did not grow any organism, and

1,3 β -D-glucan was elevated. IV caspofungin was started following which the patient improved symptomatically and later on underwent AVR. After surgery, there was uneventful recovery and the patient was discharged after 1 month.

Patient 5

A 27-year-old male was admitted to our hospital with shortness of breath for 1 month and intermittent fever for 6 months. At the time of admission, his BP was 90/60 mm Hg, HR was 98 beats per minute, RR was 24 breaths per minute, mid-diastolic murmur was present, pedal edema was noted, and there was decreased urine output. Laboratory investigation revealed Hb of 10 g/dl, TLC of 14,500/ μ L, serum creatinine of 6.8 mg/dL, blood urea of 232 mg/dL, and CRP of 125 mg/L. The blood culture showed a growth of *Enterococcus faecium*. The TTE showed a BAV, severe aortic regurgitation, two vegetations on the posterior cusp (11 \times 6 mm and 8 \times 6 mm) of the aortic valve, dilated LA, and mild pericardial effusion. The patient was treated initially with IV gentamicin, IV vancomycin, and oral rifampicin. The antibiotics were later changed to IV meropenem and teicoplanin along with oral rifampicin. The patient improved symptomatically and became afebrile, following which an AVR was performed. The patient had an uneventful recovery and was discharged on postoperative day 40.

Patient 6

A 21-year-old male presented to our hospital with complaints of fever between 101°F and 103°F for four weeks, palpitation, and dyspnea on exertion for 6 months not responsive to conventional medical treatment. At the time of admission, his BP was 110/62 mm Hg, HR was 100 beats per minute, and RR

was 28 breaths per minute. On auscultation, mid-diastolic murmur was found. Laboratory investigation showed Hb of 11 g/dL, TLC of 14,390/ μ L, blood urea of 29 mg/dl, serum creatinine of 0.9 mg/dL, and CRP of 68.3mg/dL. The blood culture showed a growth of *Staphylococcus haemolyticus*. On TTE, there was prolapse and perforation of the noncoronary cusp along with small vegetation over the same cusp of the aortic valve. There was severe aortic regurgitation. The patient was treated with IV ceftriaxone and vancomycin for six weeks and gentamicin for two weeks. An AVR with a mechanical valve was performed, following which the patient had an uneventful recovery and was discharged in stable condition.

Discussion

IE causes significant morbidity and mortality in patients with cardiovascular diseases or postcardiac surgery patients. The risk factors for mortality are development of heart failure, intracardiac abscess, embolism, large mobile vegetation, hemodynamic instability, altered mental status, immunocompromised state, and advanced age.^{12,16,17,20,21} The two challenges when managing a patient with IE are diagnosing the causative organism and deciding when to operate. The laboratory diagnosis of IE is dependent on markers of inflammation and blood cultures. Echocardiography is an important investigation to document vegetation and abscesses, evaluate regurgitant lesions, quantify the heart failure, and serially follow the functional status of heart.

Out of our six patients reported, only one (16.7%) died (**►Table 2**). The cause for death was late presentation and lack of coverage for *Burkholderia* in the prescribed empirical

Table 2 Summary of the six patients diagnosed with infective endocarditis

Patient	Age (years)	Gender	Native/prosthetic valve	Investigations performed	Antimicrobial therapy	Organism	Operation	Outcome
1	17	M	Prosthetic	CBC, LFT, RFT, CRP, PCT, blood C/S, TTE	Vancomycin, meropenem, rifampicin, doxycycline	Culture-negative endocarditis: atypical bacteria	Not performed	Survived
2	69	F	Prosthetic	CBC, LFT, RFT, CRP, PCT, blood C/S, TTE	Vancomycin, gentamicin, rifampicin	<i>Burkholderia cepacia</i>	AVR performed	Died
3	12	F	Native	CBC, LFT, RFT, CRP, blood C/S, TTE	Ceftriaxone, gentamicin	Culture-negative bacterial endocarditis	MVR performed	Survived
4	54	F	Native	CBC, LFT, RFT, CRP, blood C/S, 1,3 β -D-glucan, TTE	Ceftriaxone, amikacin, vancomycin, caspofungin	Fungal endocarditis	AVR performed	Survived
5	27	M	Native	CBC, LFT, RFT, CRP, blood C/S, TTE	Vancomycin, gentamicin, rifampicin, converted to meropenem and teicoplanin	<i>Enterococcus faecium</i>	AVR performed	Survived
6	21	M	Native	CBC, LFT, RFT, CRP, blood C/S, TTE	Ceftriaxone, gentamicin, vancomycin	<i>Staphylococcus haemolyticus</i>	AVR performed	Survived

Abbreviations: AVR, aortic valve replacement; CBC, complete blood count; CRP, C-reactive protein; C/S, culture and sensitivity; F, female; LFT, liver function test; M, male; MVR, mitral valve replacement; PCT, procalcitonin; RFT, renal function test; TTE, transthoracic echocardiography.

antibiotic therapy. The inherent resistance of *Burkholderia* to aminoglycosides and first- and second-generation cephalosporins is well documented. The recommended antibiotics are trimethoprim–sulfamethoxazole, ceftazidime, and meropenem. One of our patients with culture-negative endocarditis responded to doxycycline and did not require any surgery. Five out of six patients who underwent surgery had vegetations more than 10 mm in size, and one patient had an aortic valve abscess (caused by *Staphylococcus haemolyticus*). A high index of suspicion for fungus and atypical bacteria as causative organisms should be maintained for patients not responding to empirical antibiotic therapy within a week. The upgradation or change of antibiotics should be considered once culture reports are received. Five of our patients were alive and well 3 months postdischarge and were not followed any further.

Our unit receives two types of IE patients: NVE and PVE patients. NVE patients are referred from cardiology and are already on antibiotic therapy. Usually, we do not alter these antibiotics unless they develop renal failure, hemodynamic instability, fever, or sepsis. Our first-line antibiotics for NVE are ceftriaxone and gentamicin. Vancomycin is added in patients who do not respond within 72 hours. In patients with renal compromise, meropenem is used instead of vancomycin. Then antibiotics may be altered based on blood culture reports. Serum galactomannan and (1,3)- β -D-glucan are used to rule out fungal endocarditis. In patients with persistent fever for 7 days and raised fungal biomarkers, antifungal agents are added (caspofungin for *Candida*, voriconazole for *Aspergillus*, and liposomal amphotericin B for persistently high serum galactomannan levels in spite of antifungal therapy). The antifungal therapy is administered for at least 6 weeks. In patients with persistent fever for 7 days and normal serum levels of (1,3)- β -D-glucan and galactomannan, doxycycline is added to cover atypical bacteria. In patients responding to doxycycline, the duration of therapy is 6 months. In patients with PVE, the first-line antibiotics are vancomycin, gentamicin, and rifampicin. In select patients of PVE, it is recommended to continue antifungals lifelong. Rest of the protocol is similar to NVE.

Approximately 80 to 90% of IE cases are caused by *Staphylococcus*, *Streptococcus*, and *Enterococcus* spp. *Staphylococcus aureus* is the most frequently isolated microorganism (30%) associated with IE in developed countries.^{10,22} Coagulase-negative staphylococcus is a common cause of hospital-acquired NVE. *Streptococcus viridians* is the most common cause for IE in India.²³ Enterococci are the third most common cause of IE, with approximately 10% of total cases.^{10,22} *Enterococcus faecalis* is the most common species causing both NVE and PVE in elderly or chronically ill patients. Gram-negative bacilli account for approximately 5% of IE cases.²⁴ Approximately 3% patients are infected by HACEK bacteria (*Haemophilus*, *Aggregatibacter*, *Cardiobacterium*, *Eikenella corrodens*, *Kingella*), which are often found as colonizers in the oropharynx.²⁵ Gram-negative bacteria (e.g., *Acinetobacter* spp, *Pseudomonas aeruginosa*), *Mycoplasma* spp, *Legionella* spp, and *Tropheryma whipplei* are rare causes of IE.²⁶

Fungal endocarditis caused either by *Candida* or *Aspergillus* is rare but associated with high mortality. Fungal infections occur in immunocompromised patients or after cardiac surgery, mostly on prosthetic valves.²⁷

The management of IE requires multidisciplinary approach with inputs from cardiologists, cardiothoracic surgeons, intensivists, and infectious disease specialists. Antibiotic therapy should be started on the empirical basis soon after obtaining blood cultures, but a clinician can wait for culture results if the patient is clinically stable. Majority of the patients respond to antibiotic therapy. In such patients, there is a dilemma of whether to replace the infected valve or not. Following are the indications for surgery in NVE and PVE.²⁸⁻³⁰

Indications for Surgery in Native and Prosthetic Valve Endocarditis

1. Patients who develop heart failure due to valve dysfunction require surgery irrespective of antibiotic course status.
2. Patients with IE caused by *S. aureus*, fungal, or other highly resistant microorganisms of the left-sided valves require surgery irrespective of antibiotic course status.
3. Patients with IE who develop heart block, aortic root abscess, or other destructive lesions require surgery irrespective of antibiotic course status.
4. Patients with persistent bacteremia or fever of more than 5 to 7 days even after initiation of appropriate antimicrobial therapy require surgery irrespective of antibiotic course status.
5. Patients with PVE and relapsing infection (recurrence of bacteremia after a complete course of antibiotics and subsequently negative blood cultures) without any other identifiable source of infection may require surgery.
6. Patients with IE who present with recurrent emboli and persistent vegetations despite appropriate antibiotic therapy may require surgery irrespective of antibiotic course status.
7. Patients with NVE or PVE with mobile vegetations more than 10 mm in size and evidence of embolic phenomena despite appropriate antimicrobial treatment may require urgent or emergency surgery.
8. Patients with IE of the right-sided valves with large vegetations and persistent infection (bacteremia or fever more than 5–7 days after starting antibiotics) or with evidence of septic pulmonary embolism may require surgery.

Conclusion

Both PVE and NVE can be treated successfully with antimicrobial agents and surgery (when indicated). A high index of suspicion is required to diagnose IE caused by fungus and atypical bacteria.

Conflict of Interest

None.

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