



CULTURE NEGATIVE INFECTIVE ENDOCARDITIS – A CASE SERIES IN A TEACHING HOSPITAL IN RURAL INDIA

Paediatrics

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ABSTRACT

Background- Infective endocarditis (IE) is an infection of endocardial surface of the heart. It commonly involves heart valves but may also involve other endocardial sites in heart. The incidence is 3 to 10 per one lakh with mortality of 30%. Viridian streptococci and staph aureus are common causative organism, 6% of cases are culture negative IE. **Aims and Objectives-** To report 5 cases of culture negative infective endocarditis and to study predisposing factors, response to treatment and outcome. **Materials And Methods-** The study was conducted in patients admitted in Department of Pediatrics, Dr. Vitthalrao Vikhe Patil Pravara Rural Hospital, Loni from January 2022 to June 2022 and diagnosed as IE by modified Duke's criteria, detailed history was taken to assess the risk factors and clinical examination, 2d echocardiography, serial blood culture, careful monitoring is done to look for response treatment and outcome. **Results-** During the study period total 8 cases were diagnosed as infective endocarditis out of which 5 cases were found to be culture negative IE. Out of 5 cases, 4 patient had congenital heart disease and 1 patient had RHD as predisposing factor, 4 survived and 1 patient expired. 3 patient responded to empirical antibiotic treatment, while 1 patient was referred to higher center for surgery due to failure of medical management. **Conclusion-** Infective endocarditis prophylaxis in patient with risk factors is appropriate step in prevention and proper blood culture technique, prompt clinical examination and imaging remains the mainstay in diagnosis of IE. Antibiotic policy according to the protocol and 2d echocardiographical surveillance reflects the outcome.

KEYWORDS

Infective endocarditis, Blood culture negative endocarditis, congenital heart disease.

INTRODUCTION:

Infective endocarditis (IE) is an infection of endocardial surface of the heart. It commonly involves heart valves but may also involve other endocardial sites in heart. The incidence is 3 to 10 per one lakh. The mortality of infective endocarditis is 30% in the first 6 months after diagnosis. It can be bacterial as well as non bacterial like virus, fungus. Viridian streptococci and staph aureus are common causative organism but 6% of cases are culture negative IE. In developed countries congenital heart disease is the most common predisposing factor in development of infective endocarditis but in India rheumatic heart disease remains the mainstay risk factor. The patients with congenital heart disease where there is turbulent blood flow because of stenotic orifice or shunt, especially if there is a high pressure gradient across the defect are most susceptible to infective endocarditis. 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 remains high in spite of better diagnostic facilities, newer antibiotics, and early surgical intervention. 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) after valve replacement of surgery. The most common causative organism for prosthetic valve endocarditis (PVE) is Staphylococcus followed by Streptococcus species.⁹

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

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.

Laboratory investigations show positive blood culture. 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} Elevated erythrocyte sedimentation rate; may be low with heart or renal failure, elevated C-reactive protein, Anemia, Leukocytosis, Immune complexes, Hypergammaglobulinemia, Hypocomplementemia, Cryoglobulinemia, Rheumatoid factor, Hematuria, Renal failure: azotemia, high creatinine (glomerulonephritis), Chest radiograph: bilateral infiltrates, nodules, pleural effusions, Echocardiographic evidence of valve vegetations, prosthetic valve dysfunction or leak, myocardial abscess, or new-onset valve insufficiency.

Transesophageal echocardiography has greater sensitivity and specificity than transthoracic echocardiography (TTE) for diagnosing valvular vegetations and abscesses.

We hereby report case series of five out of six patients treated for IE in our Department of Pediatrics between January 2022 and June 2022.

Patient 1

A 6 year old child was admitted to our hospital with complaints of fever since 5-6 days. On admission his heart rate was 112 beats per minute, respiratory rate was 28 breaths per minute, saturation was 70 % on right upper limb. Upon examination child had peripheral cyanosis and breathing comfortably. On auscultation child had single S2 and ejection systolic murmur was present in the pulmonary area. Lab parameters were hb is 14.1 gm/dl, platelets were 1,50,000, pcv is 45, erythrocyte sedimentation rate was 84, C reactive protein turns out to be positive. On 2d echo it was diagnosed as tetralogy of fallot with vegetations on the mitral valve, suggestive of infective endocarditis { ECHO POSITIVE FOR IE (major), FEVER & PREDISPOSITION (minor)}. Child was started on antibiotics ceftriaxone and gentamycin. Three site blood cultures were sent. After the completion of the course, child became asymptomatic and afebrile. Thereafter went for the higher centre for tetralogy of fallot repair.

Patient 2

A 9 year old male child came to our hospital complaining of fever since

15 days. On admission his vitals were like , heart rate is 134 beats per minute , respiratory rate was 30 cycles per minute , blood pressure was 105/84 mm of hg . On examination child had increased precordial activity & hyperdynamic apex.lab parameters were like hemoglobin was 15.6 gm/dl , white blood cells were 8600 , platelets were 2,54,000 , c reactive protein was positive . On 2d echo – it shows large atrial septal defect, which measures 25mm and 2 echogenic foci { vegetations measuring 20 x 12 mm } in the right atrium , suggestive of infective endocarditis. 1 major and 3 minor criteria of dukes criteria is met { ECHO POSITIVE FOR IE (major) , FEVER & PREDISPOSITION (minor)}. Child was started on iv antibiotics ceftriaxone , gentamycin and later upgraded to cefepime . After the course of the treatment , child became asymptomatic and afebrile . Went to the higher centre for atrial septal defect closure.

Patient 3

A 5 year old male child was brought to our hospital complaining of fever since 5 days. Child is a known case of atrial septal defect with congenital mitral stenosis , for which he got operated 14 days before the presentation.lab parameters were like hemoglobin was 13.6 gm/dl , white blood cells were 11,600 , platelets were 1,97,000. On 2d echo – 3 echogenic foci were present { vegetations } , suggestive of infective endocarditis { ECHO POSITIVE FOR IE (major) , FEVER & PREDISPOSITION (minor)}. Child was started on iv antibiotics ceftriaxone and gentamycin. Gradually child became afebrile and asymptomatic. Went to the operated hospital for further management.

Patient 4

A 10 year old male child came to our hospital complaining of fever since 8 days and breathing difficulty since 3 days . Child was a known case of tetralogy of fallot and underwent surgery 5 years back. Chest x-ray pa view suggestive of cardiomegaly . 2d echo was done , which was suggestive of congestive cardiac failure and shows large vegetation on the mitral valve leaflet , suggestive of infective endocarditis { ECHO POSITIVE FOR IE (major) , FEVER & PREDISPOSITION (minor)}. Child was started on iv antibiotics ceftriaxone , gentamycin and was given oxygen support. upon completion of the course of treatment , child was discharged

Patient 5

12 year old male child was brought with complaints of fever since 20 days. Child was a known case of rheumatic heart disease and was treated for the same and prophylaxis was also taken 5 years back. On echocardiography vegetation measuring 16x20mm in the mitral valve leaflet is present. According to modified dukes criteria 1 major and 3 minor criteria is present (echo findings, fever, predisposing factors, roth spot). Child was started on IV antibiotics ceftriaxone , gentamycin , upon completion of treatment course , child was discharged .

DISCUSSION:

Isolated positive blood cultures are inconclusive for IE, however, persistent bacteraemia in multiple culture bottles of a typical organism is highly suggestive. If blood cultures demonstrate no growth and the clinical suspicion of IE remains high, especially if there has been no prior antibiotic exposure, prolongation of blood culture bottle incubation and serological testing should be undertaken following consultation with an infection specialist. Causes of culture negative endocarditis such as *Bartonella* spp, *Coxiella burnetii*, *Tropheryma whippelii* and some fungi (especially *Aspergillus* spp) need to be considered.

In our set up 5 out of 6 patients with infective endocarditis were culture negative. All these patients are already on antibiotic therapy by the time they are referred to us as our hospital is tertiary care centre. In a study done by Bhandari S et al⁷ (50%) patients were culture negative. They ascribed the high proportion of negative cultures to previous antibiotic therapy, fastidious organisms with difficult culture requirements, very low numbers of circulating organisms, and less than meticulous culture techniques. In a study by Dinesh K et al⁵ 57.1% had culture negative infective endocarditis and this was expected by them as all enrolled patients in their study received antibiotics before admission. However, in the West, it usually represents 2.5 to 31% of infective endocarditis. ^c

The sensitivity of Duke's clinical criteria decreased further in the presence of culture-negative endocarditis. Lamas and Eykyn have reported a sensitivity of 21% in bacterial culture-negative endocarditis.^d Since predisposing cardiac conditions is a minor

criterion for IE, the increasing occurrence of infective endocarditis in a normal heart will likely further decrease the sensitivity of Duke's criteria. Easy availability of over the counter antibiotics and high rate of prior antibiotic use (such as prevalent in our setting), inevitably leads to high rates of blood culture negativity and difficulty in fulfilling Duke's microbiological criteria. In the context of frequent prior antibiotic use and detection of vegetation on echocardiography, a case can be made for considering even a single positive blood culture (especially for *S. aureus*) as a major criterion. Role of other imaging like fluorodeoxyglucose (FDG) positron emission tomography (FDG PET) should be evaluated in blood culture negative Infective Endocarditis and possibly incorporated in the modified Duke criteria. Since pediatric IE has such a low incidence, multi-center, prospective collaborative studies are required to collect data on this subject.

Out of 5 cases, 4 patient had congenital heart disease and 1 patient had RHD as predisposing factor. 4 of them survived and 1 patient expired. Out of 4 survived patient, 3 patient responded to empirical antibiotic treatment, while 1 patient was referred to higher center for surgery due to failure of medical management.

CONCLUSION:

In our study we showed the changing trend and aetiology of infective endocarditis. There must be consistent efforts in identifying the emerging and atypical organisms in future. And judicious antibiotic use especially in children with risk factors will also reflect the outcome in identifying organisms involved in the disease. Monitoring of response to treatment must be done clinically as well as guided by echocardiography.

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