Clinical profile and outcome of children admitted with infective endocarditic at Tikur Anbessa Specialized Hospital

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Abstract

***Back ground**: Infective endocarditis (IE) is an infection of the endocardial surface of the heart. Infective endocarditis is associated with substantial morbidity and mortality. The diagnosis of IE is based upon a careful history and physical examination, blood culture and laboratory results, an electrocardiogram, a chest radiograph, and an echocardiogram. Several sets of criteria for IE have been described. The most commonly accepted are the Duke criteria.*

***Objective**: To study clinical features and etiologic agents, treatment and mortality of children admitted in the hospital with infective endocarditis. To study the predisposing or risk factor and isolated organism in blood culture for infective endocarditis.*

***Methodology**: A retrospective analysis was conducted on the hospital medical records of pediatric patients under 15 years with the discharge diagnosis of IE who were admitted to Tikur Anbessa Specialized hospital between September 2005 and August 2009*

***Result**: There were 66 episodes of infective endocarditis 20/63 (32%) were male and 43/63(68%) were female. The ages ranged from 4 to 168 months. Thirty eight (60.3%) of them had underlying chronic rheumatic valvular heart disease and 24(38.1%) had Congenital heart disease. Clinical presentations included: fever, pallor, congestive heart failure, Splenomegaly, clubbing, renal complication and neurological findings. Laboratory findings include: A haematocrit of less than 10mg/dl, Leukocytosis >12,000, Erythrocyte sedimentation rate >30mm/hr s, hematuria, blood culture was positive only in 18 episodes of IE (27.3%). Coagulase negative staphylococcus aureus and staphylococcus aureus were the two most commonly isolated bacteria. Transthoracic Echocardiography was done in 58/66 (87.9%) episodes. Vegetation was found in 31(53.4%) of the Echocardiography done and one non- oscillating thrombus. Ampicilline, cloxacilline and gentamycin was used to treat 31(37.9%) episodes of IE. Twenty five (37.9%) were treated for 4 weeks. Fifty-four patients (81.8%) survived. There were 5 deaths and overall mortality was 7.6%. Patients died during therapy (cause of death; were thromboembolism, sudden death, cardio respiratory failure 2^0 to massive pericardial effusion and acute renal failure. Seven (10.6%) patients went against medical advice before completing their treatment.*

***Conclusion:** This study describes the presentation, treatment and outcome of IE in Tikur Anbessa hospital. Infective endocarditis remains a challenging problem. Chronic rheumatic heart disease remains to be the major predisposing factor. Culture negative infective endocarditis still represents larger proportion of our patients. In addition to cross sectional echocardiography, additional clinical and laboratory parameters are required to make the diagnosis. Penicillin and gentamycin are still important drugs. Cloxacilline can be added if staphylococcus is strongly suspected. Embolic episodes are still important cause of high mortality and morbidity.*

INTRODUCTION

Background information and Statement of the problem

Infective endocarditis (IE) is an infection of the endocardial surface of the heart. The intracardiac effects of this infection include severe valvular insufficiency, which may lead to intractable congestive heart failure and myocardial abscesses. IE also produces a wide variety of systemic signs and symptoms through several mechanisms, including both sterile and infected emboli and various immunological phenomena [(1)].

Infective endocarditis is associated with substantial morbidity and mortality. Although it is relatively rare in children, its incidence may be increasing. The epidemiology of heart disease in children has changed during the past 3 to 4 decades. because of the increased survival rate of children with congenital heart disease(CHD) and the overall decrease in rheumatic valvular heart disease(RHD) in developing countries, CHD now constitutes the predominant underlying condition for IE in children over the age of 2 years in these countries[(2)].

A number of factors predispose to the development of IE. These include structural heart disease, prosthetic heart valves, and injection drug use (IDU). Other factors, especially related to invasive procedures, have been postulated to increase the risk and form the theoretical basis for antimicrobial prophylaxis. However, a population based case control study from Philadelphia failed to identify pulmonary, cardiac, gastrointestinal, genitourinary procedures or surgery as risk factors for the development of community-acquired endocarditis. Patients with teeth who did not floss were at slightly higher risk for endocarditis caused by mouth flora than those who did floss and those without teeth [(3)].

In the developing world, where rheumatic heart disease is still prevalent ,antibiotic prophylaxis for potential septic procedure is not a routine and late referral is common, infective endocarditis is an important cause of morbidity and mortality[(4)].

Infective endocarditis is caused by viruses, fungi, and other microbiologic agents. Viridians-type streptococci (a-hemolytic streptococci) and Staphylococcus aureus are the leading causative agents responsible for endocarditis in pediatric patients. Other organisms cause endocarditis less frequently; approximately 6% of cases, blood cultures are negative for any organisms. Staphylococcal endocarditis is more common in patients with no underlying heart disease; viridians group streptococcal infection is more common after dental procedures, group D enterococci are seen more often after lower bowel or genitourinary manipulation, Pseudomonas aeruginosa or Serratia marcescens is seen more frequently in intravenous drug users, and fungal organisms are encountered after open heart surgery. Coagulase-negative staphylococci are common in the presence of an indwelling central venous catheter [(14).]

The diagnosis of IE is usually based upon a constellation of clinical findings rather than a single definitive test result. The diagnosis is usually obvious when a patient has the characteristic findings of IE: Numerous positive blood cultures in the presence of a well recognized predisposing cardiac lesion and evidence of endocardial involvement. However, some patients with IE do not have positive blood cultures (i.e., culture-negative endocarditis), cardiac lesion at disease onset [(6, 7).]

The diagnosis of IE is based upon a careful history and physical examination, blood culture and laboratory results, an electrocardiogram (ECG), a chest radiograph, and an echocardiogram. Several sets of criteria for IE have been described. The most commonly accepted are the Duke criteria [5, 6].

During the initial assessment of patients with suspected endocarditis, a careful history should be performed with special attention given to a history of prior cardiac lesions and historical clues pointing toward a recent source of bacteremia, such as indwelling intravascular catheters or intravenous drug use. The physical examination should include a careful cardiac examination for signs of new regurgitant murmurs or heart failure. Classic clinical stigmata and complications of endocarditis [5, 6, 7] :

Antibiotic therapy should be instituted immediately once a definitive diagnosis is made. When virulent organisms are responsible, small delays may result in progressive endocardial damage and are associated with a greater likelihood of severe complications. A total of 4–6 wk of high dose treatment is recommended for each specific virulent organism. Follow up should continue with, 48 to 72 hr blood culture and clinical evaluation for any complication, improvement or therapy related side effects [5, 6, 7].

Surgical intervention for IE is indicated for severe aortic or mitral valve involvement with intractable heart failure. Rarely, a mycotic aneurysm, rupture of an aortic sinus, or dehiscence of an intracardiac patch requires an emergency operation. Other surgical indications include failure to sterilize the blood despite adequate antibiotic levels, myocardial abscess, recurrent emboli, and increasing size of vegetations while receiving therapy. Mortality is 20 – 25% even with management. There are predictor of death like; Low serum albumin, Infection with S. aureus, Heart failure, Diabetes mellitus, Embolic events , Paravalvular abscess, Vegetation size, Female sex [5, 7, 8].

Antimicrobial prophylaxis before various procedures, including dental cleaning and other forms of dental manipulation, reduces the incidence of infective endocarditis in susceptible patients. Continuing education regarding prophylaxis is important, especially in teenagers and young adults, who often have poor knowledge of their own heart lesion. Proper general dental care and oral hygiene are most important in decreasing the risk of infective endocarditis in susceptible individuals. Vigorous treatment of sepsis and local infections and careful asepsis during heart surgery and catheterization reduce the incidence of IE [5].Various articles studying methods of preventing IE were reviewed, primarily the AHA's revised guidelines published in April 2007. Lists of reference articles were examined to cross reference relevant information regarding antibiotic prophylaxis for the prevention of IE. A major influence for revisions to the guidelines is that studies show a very small fraction of IE cases are preventable with prophylaxis with antibiotic therapy prior to dental procedures. IE is more likely to result from daily activities, such as brushing and flossing teeth, than from bacteremia caused by dental procedures. Patients with underlying cardiac conditions, who are associated with the most detrimental outcome if IE develops, should receive prophylaxis prior to dental procedures. Maintenance of oral health is more effective in reducing the risk of IE than prophylactic antibiotics for dental procedures. An increased lifetime risk of developing IE alone is not a basis for prophylaxis, especially considering that adverse events stemming from antibiotic use exceed the benefit of antibiotic prophylaxis [6].

Objective :To study clinical features and etiologic agents, treatment and mortality of children admitted in the hospital with infective endocarditis.

Materials and methods

A retrospective analysis was conducted on the hospital medical records of pediatric patients under 15 years with the discharge diagnosis of IE who were admitted to Tikur Anbessa Specialized hospital between September 2005 and August 2009. The medical record of the patients retrieved from statistics bureau. Tikur Anbessa Specialized hospital is the largest tertiary referral center and the major teaching hospital in Ethiopia. All cases were diagnosed by the pediatric residents and attending cardiology consultants.

The Duke criteria were used in the diagnosis of endocarditis. Major criteria include:-

(1) Positive blood cultures (two separate cultures for a usual pathogen, two or more for less typical pathogens) and

(2) Evidence of endocarditis on echocardiography (intracardiac mass on a valve or other site, regurgitant flow near a prosthesis, abscess, partial dehiscence of prosthetic valves, or new valve regurgitant flow).

Minor criteria include predisposing conditions, fever, embolic-vascular signs, immune complex phenomena (Glomerulonephritis, arthritis, rheumatoid factor, Osler nodes, and Roth spots), a single positive blood culture or serologic evidence of infection, and echocardiographic signs not meeting the major criteria. Two major criteria, one major and three minor, or five minor criteria suggest definite endocarditis.

A modification of the Duke criteria may increase sensitivity while maintaining specificity. Two more minor criteria are added to those already listed: The presence of newly diagnosed clubbing, Splenomegally, splinter hemorrhages, and petechiae; anemia; A high erythrocyte sedimentation rate; a high C-reactive protein level; and the presence of central nonfeeding lines, peripheral lines, and microscopic hematuria [15,16].

The other routine investigations like haematocrit, erythrocyte sedimentation rate, white blood cell count & urine for microscopic hematuria, renal function test, electrolytes or chest x-ray was retrieved from each patient's cards. Transthoracic Echocardiography was done for the patients by cardiologists. Vegetations were defined as typical if a mobile echo-dense mass is found attached to valves or their supporting structures in path of jets of blood passing through regurgitant or stenotic valves or intracardiac shunts. The number and nature of antibiotic used, their dosage and duration will be carefully recorded. The outcome of medical treatment, any complications, was recorded. A X^2 test was used when applicable. The records of all patients with discharge diagnosis of IE were checked to verify if they satisfy the above mentioned criteria. Those who did not were excluded.

RESULT

Patient population

The medical records of 63 patients under 15 yrs of age admitted to Tikur Anbessa hospital with IE was seen over 5 years period to provide an overview of the spectrum of IE during infancy and childhood.

There were 66 episodes of infective endocarditis in 63 these patients of which 20 0f them were males and 43 females. Patients' ages ranged from 4 to 168 months (mean age 92.9$\pm$45months), 7 patients were under 12 month ,9 patients

(13.6%) were under 2 years of age and 27 patients were ≥10 yrs of age at onset.

Surgical status

A definite predisposing factor could be identified in only 9(13.6%) patients. Post cardiac surgical sepsis and hospital acquired sepsis accounted for 4 and 5 cases respectively. Infective endocarditic occurred within 6 months after the surgery of which 2 were post valve replacement for CRVHD and 2 were surgical repair (one post PDA ligation and the other after TOF repair). There was no patient who had history of intravenous drug abuse. No patient was found to have IE following dental procedure, lower bowel or genitourinary manipulation.

Signs and symptoms

Clinical presentations in 66 episodes of IE included: subjective fever in 56(84.8%), fever ≥38^0c in 45(68.2%), pallor in 29(43.9%), Splenomegally in 37(56.1%), clubbing in 20 (30.3%). Congestive heart failure was present in 47(71.2%), neurologic finding in 2 (3%), renal complication in 5(7.5%), *Table 1 and 2.*

Table 1*: Selected demographic, clinical and laboratory features of 66 treated episodes with the diagnosis of infective endocarditis*.

Characteristics	CRVHD	CHD*	TOTAL ((n,%)
Demographic			
Number of episodes	39	27	66 (100)
Female	23	22	45 (68.2)
Male	16	5	21(31.8)
Female/male ratio	1.43	4.4	2.14
Age ,mean ± SD in months	112.4 ± 31.8	64.8 ± 46.9	92.9 ± 45
Mean duration of hospitalization, in days	38.3	35.7	37.2
Laboratory			
Hemoglobin ≤10 mg/gl	22	16	38 (57.6)
White blood cell count ≥ 12,000 /mm^3	11	10	21 (31.8)
ESR ≥ 30mm/hr	31	18	49 (74.2)
Microscopic hematuria	23	12	35 (53)
Growth in blood culture	7	11	18 (27.3)
Clinical			
Fever ≥ 38^0 c	22	23	45 (68.2)
Pallor	20	9	29 (43.9)
Splenomegally	18	19	37 (56.1)
Petechiae	4	1	5 (7.6)
Clubbing	11	9	20 (30.3)
Conjunctival hemorrhage	0	1	1 (1.5)
Valve replacement or surgical repair	2	2	4 (6)
Previous history of IE	1	2	3 (2)
Nosocomial	2	3	5 (7.6)
Previous antibiotic use before 7 days	5	8	13(19.7)
Mortality	3	2	5 (7.6)

*The patient with TR with dilated right sided of the heart was added with the group of CHD

TABLE: 2 ***Complications of 66 treated episodes with the diagnosis of infective endocarditis.***

Systems	Complications	Frequency (out of 66 episodes of IE)	Percentage %
Cardiac	CHF	47	71.2
	AV block	1	1.5
CNS involvement	Stroke	1	1.5
	Encephalopathy	1	1.5
Renal impairment	Renal failure	2	3
	Glomerulonephritis	3	4.5

Laboratory findings included: A haematocrit of less than 10mg/dl was found in 38(57.6%). Leukocytosis >12,000 was present in 21(31.8%). Erythrocyte sedimentation rate was found to be >30mm/hr in 49(74.2%) patients, hematuria in 29(43.9%) , Table 1.

Pathogens

Blood culture was positive in 18 episodes of IE (27.3%). Coagulase negative staphylococcus aureus (CONS) 8(12.1%) and staphylococcus aureus 7(9.1%) were the two most commonly isolated bacteria, bar Graph 1.

Prior medical condition

Out of the 63 patients, 38(60.3%) of them had underlying chronic rheumatic valvular heart disease (CRVHD) and 24(38.1%) had CHD. One patient was found to have severe tricuspid regurgitation with dilated right atrium and ventricle and RV dysfunction .No patient was found to have normal cardiac finding, or dilated cardiomyopathy, Table 3.

TABLE : 3 underlying heart disease *in* 63 children treated with the diagnosis of infective endocarditis.

Underlying heart disease	Frequency	Percentage %
♦ CRVHD	38	60.3
Mitral regurgitation	6	9.5
Mixed (Aortic ,Mitral and tricuspid)	30	47.6
Mitral stenosis	1	1.6
Mitral valve prolapsed + Mitral regurgitation	1	1.6
*TR	1	1.6
♦ CHD	24	38.1
VSD	6	9.5
TOF	3	4.8
PDA	9	14.3
VSD+PDA	2	3.2
VSD +ASD	1	1.6
VSD+ASD+PDA	1	1.6
TR+ PFO+ dilated ascending aorta	1	1.6
AV valve defect +AV canal defect	1	1.6
TOTAL	63	100%
+Associated pulmonary Hypertension	12	19

CRVHD=chronic rheumatic heart disease, CHD=congenital heart disease ,VSD=ventricular septal defect, ASD=atrial septal defect, TOF=tetralogy of Fallot, PDA=patent ductus arteriosus , AV= atrio-ventricular, PFO=patent foramen ovale TR=tricuspid regurgitation * the patient had markedly dilated right atrium & ventricle with RV dysfunction,

Treatment

Ampicilline, cloxacilline and gentamycin was used to treat 31(37.9%) episodes of IE, in 15 patients (22.7%) Ampicilline and gentamycin was used. Twenty five (37.9%) were treated for 4 weeks and 14 (21.2%) for 5 weeks. The Eight patients treated for less than 4 weeks were discharged against medical advice or had died within 4 weeks after admission. Tuberculosis was diagnosed additionally in 7 (10.6%) and rheumatic recurrence was found in 4 (6.1%) episodes of IE, Table 4 & 5.

TABLE 4 Antibiotics used to treat 66 episodes of infective endocarditis.

ANTIBIOTIC USED	Frequency	Percentage %
AMPICILLINE/CLOXACILLIN/GENTAMYCIN	31	47
CEFTRIAXONE/ CLOXACILLIN/GENTAMYCIN	5	7.6
CEFTRIAXONE	7	10.6
AMPICILLINE / GENTAMYCIN	15	22.7
CEFTRIAXONE / CLOXACILLIN	4	6.1
AMPICILLINE / CLOXACILLIN	1	1.5
CLOXACILLIN / GENTAMYCIN	1	1.5
AMPICILLINE /CHLORAMPHENICOL/ GENTAMYCIN	1	1.5
CRY.PENICILLINE/ CLOXACILLIN / GENTAMYCIN	1	1.5

TABLE : 5 Duration of treatment *in* 66 treated episodes with the diagnosis of infective endocarditis.

Duration of treatment	Frequency	Percentage %
Less than 4 weeks	8	12.1
For 4 weeks	25	37.9
For 5 weeks	14	21.2
For 6 weeks	10	15.2
More than 6 weeks	9	13.6

Morbidity and mortality

Fifty-four patients (81.8%) survived. There were 5 deaths and overall mortality was 7.6%. Patients died during therapy (cause of death; were thromboembolism, sudden death, cardio respiratory failure 2^0 to massive pericardial effusion and acute renal failure. Seven (10.6%) patients went against medical advice before completing their treatment, Table 6 and pie chart 1.

PIE CHART : 1 **condition at discharge *in* 66 episodes treated with the diagnosis of infective endocarditis.**

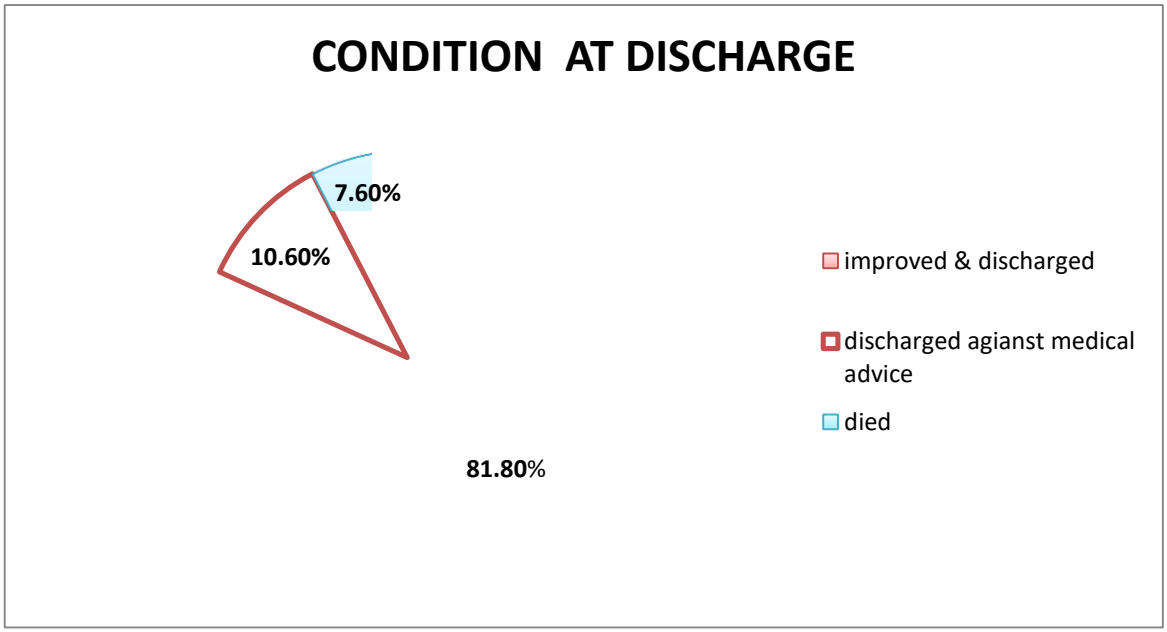

TABLE: 6 **Cause of death *in* 66 treated episodes with the diagnosis of infective endocarditis.**

Cause of death	Frequency	Percentage %
Thromboembolism	2	3
Sudden cardiac arrest	1	1.5
Cardiorespiratory failure 2^0 to massive pericardial effusion	1	1.5
Cardio respiratory 2^0 to acute renal failure	1	1.5
TOTAL	5	7.5%

Table 7: Additional diagnosis

Additional dx	n	%
Tuberculosis	7	10.6
Pneumonia	2	3
hospital acquired sepsis	1	1.5
Rheumatic recurrence	4	6.1
Severe acute malnutrition	3	4.5
Hepatitis	1	1.5
Seizure disorder	1	1.5

Discussion

Comparing the study of pediatric endocarditis patients with similar studies, both similarities and differences were noted.

Epidemiology and risk factor

Patients with definite IE had a mean age of 92.9±5.5 months. Infective Endocarditis unrelated to heart disease is more common in neonates, infants and IV drug abusers or indwelling catheter use. While this is well reported in the west [17,18], no neonates were noted in this study, probably because of lack of utilization of central venous lines in the neonatal period in our hospital, or because of under diagnosis. Only 7 patients were under 1 year of age and there was no IV drug abuser identified. All patients included in the study had underlying heart disease. Only 4 patients (6.1%) had IE after surgery. The population at risk in our set up is different from that reported from west [17, 18]. Studies from Pakistan [4] showed Rheumatic heart disease was the underlying lesion in 24(53%) while congenital heart lesions occurred in 20 patients (45%). Rheumatic heart disease is still the most common underlying lesion in our study.

Clinical manifestation

The clinical pattern of infective endocarditis observed in our study suggested that the most common presentation in the 66 episodes of infective endocarditis were subjective fever and splenomegally. These findings were similar to the study done in India [9].when compared to similar study; clinical pallor and clubbing were less prevalent in our study. This could be due to subjective variation in clinical detection. Previous antibiotics treatment was given in 19% of the episodes of IE which is less than the study done in Pakistan [4]. This may be due to inefficient history extraction from patients and / or since most patients are from country side antibiotics may not be readily available. Thus patients might present to Tikur Anbessa hospital directly before presenting to other health centers.

Congestive heart failure was the commonest complication that the patients present with. Compared with the studies done in India [9] and Beirut [10] the percentage is much higher. This may be due to late presentation of the patients to our hospital or most of them might have borderline cardiac condition which decompensate during the time of infection. Renal failure and cerebral embolism are predictors of mortality in IE (4) .Our study shows the neurology and renal complications to be by far lower than other similar studies done at India and Beirut. Because of high mortality, patients with renal and cerebral complications might die at home before presenting to our hospital. A variety of nonspecific laboratory findings may be present in children with IE. Anemia, leukocytosis, hematuria and elevated acute phase reactant (ESR) are present in a large proportion of the patients [2]. Our study shows similar laboratory findings.

Echocardiography

The diagnostic use of echocardiography in identifying clinically definite cases of IE have been confirmed in several studies [2-4]. This is particularly true in our set up where blood culture yield is low. Transthoracic echocardiography done in our study has picked vegetation in 53.4% of the patients whom echocardiography was done. This figure is slightly less than what is documented in several studies which might reach as high as 60-80 %[4, 10, 13]. But if it is done transoesophageal, because of its' to identify vegetation less than 1 cm, the yield increases to 90% [15]. Our study has a low rate of vegetation. Despite the unavailability of transoesophageal echocardiography, this study reflects the general picture of

infective endocarditis in developing country.

Microbiology

Of the 66 episodes of IE blood culture result was collected and documented in only 59 patients. Etiological diagnosis could be established in only 18 (27.3%) patients of the total episodes of IE. There are some studies done from Indian subcontinent which have the comparable figure, varying from 21 to 47 % [13, 19]. But the figure is still very low when compared to published data and international standards [2-5,7,14]. The association between prior antibiotics treatment and negative blood culture in our study was statistically not significant with 95% Confidence Interval (0.83, 2.118), but prior antibiotics treatment is the major cause of negative blood culture in other published studies [2,4,]. Inadequate microbiological techniques, infection with highly fastidious bacteria or non-bacterial microorganisms could be other reason for failure to culture. Usual culture methods do not recover anaerobes as well. The pattern of isolated organisms is also different from what is reported in the literature [15]. Streptococcus viridans and staphylococcus aureus are the commonest organisms isolated in most of the published data [2, 4, 9, 10, 12]. CONS and staphylococcus aureus are the most common organisms isolated in our study. There are other published papers with staphylococcus predominance like in our study [20]. Streptococcus viridans was not isolated in our study. This could be due to inadequate microbiological techniques and culture media.

Antimicrobial treatment

As recommended Penicillin, cloxacilline and gentamycin were mostly used in our study [2, 4, 14]. In a disease requiring long term antibiotics therapy there are serious cost complications in developing country where there is no medical insurance and the government cannot provide free medical treatment for all patients.

Mortality

The mortality rate for pediatric endocarditis in this study (n=5, 7.6%) is lower than previous reports done in developing country which reaches 30 % [4, 9]. As mentioned above, there were 7(10.6%) patients who left the hospital against medical advice and those patients were critically sick. We still don't know the outcome of those patients and that could be the reason why the mortality rate became lower than developing countries. Other reason could be due to improper death chart keeping.

Conclusion

This study describes the presentation, treatment and outcome of IE in Black lion hospital. Infective endocarditis remains a challenging problem. Chronic rheumatic heart disease remains to be the major predisposing factor. Culture negative infective endocarditis still represents larger proportion of our patients. In addition to cross sectional echocardiography, additional clinical and laboratory parameters are required to make the diagnosis. Penicillin and gentamycin are still important drugs. Cloxacilline can be added if staphylococcus is strongly suspected. Embolic episodes are still important cause of high mortality and morbidity.

Recommendation

1. Since CRHD is common in our set up bacterial endocarditis prophylaxis should be continued to be given.
2. Either the technique of blood culture taking or the culturing in the laboratory should be revised and standardized to minimize the shortcomings.

3. Most of the patients cannot afford for echocardiography and exact diagnosis was difficult. Some patients might be over treated or under treated for IE. The availability of Transthoracic or transoesophageal echocardiography for free in the pediatric ward would simplify the problem.
4. The hospital chart keeping should also be revised with certain code of a disease.
5. In the future, surveillance using administrative databases and more detailed prospective studies may be useful to know the real prevalence and to change the outcome of pediatric infective endocarditis.

Limitation of the study

1. The number of patients was small because most cards were not returned to the statics office.
2. There were some results which were not collected or documented in the patient's card.
3. History from the patients was not thorough enough to help fill some of the questioner. Around 10 patients' card was not included in the study because there was no enough information needed for the study.

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