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Profile of Infective Endocarditis in Nigerian Children

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Authors' contributions

This work was carried out in collaboration between all authors. Author OOI designed the study, wrote the protocol, analyzed data and wrote the first draft of the manuscript. Authors CSY, UD and FBT designed the study and wrote the protocol. Authors HOA, MB and FB managed the literature searches and contributed in writing the first draft of the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Background: Infective endocarditis (IE) was initially thought to be uncommon in children but is on the increase due to improved cardiac services in the developing world.
Aims: Aims of this study is to describe the profile of IE in children in Jos, Nigeria and identify the peculiarities of the disease in the locality.
Methods: Case records of children diagnosed with IE based on the modified Duke's criteria over a seven year period were retrospectively reviewed in a tertiary hospital. Their clinical manifestations, blood culture isolates, presence or absence of vegetations and clinical outcomes were documented and analyzed using Epi Info 7.
Results: Case records of thirty children were reviewed. The number of children managed increased yearly with 10 (33.3%) of them seen in the last year of the study. The clinical features were mainly non-specific - fever (70.0%), congestive cardiac failure (63.3%) and anorexia (63.3%) being the major findings. *Staphylococcus aureus* was the commonest isolate, present in 5 (45.5%) of the 11 blood culture-positive cases. Other organisms isolated were Klebsiella species in

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3 (27.3%), *Pseudomonas aeruginosa* in 2 (18.2%) and *Acinetobacter baumami* in 1 (9.1%) child. Vegetations were detected in 12 (40.0%) children, most of them located on the mitral valve. Mortality occurred in 8 (26.7%) children and was significantly higher in males – $P = 0.02$.

Conclusion: There is a marked increase in the number of children admitted and managed for IE in the last year of the study possibly due to an increased index of clinical suspicion of IE. A high index of suspicion is required for diagnosis because many children presented with nonspecific clinical features.

Keywords: Children; congenital heart disease infective endocarditis; rheumatic heart disease.

1. INTRODUCTION

Infective endocarditis (IE) occurs as a result of infection of the endocardium which is the inner lining of the heart. [1] The incidence of IE varies widely from country to country and also within the same region. IE is still an important cause of childhood morbidity and mortality in developing countries, especially where rheumatic heart disease (RHD) is very common and mortality rates as high as 47% have been reported, compared with global rates of 15 - 25% [2-5]. Some individuals with a clinically normal heart can also acquire IE but surgical inspection usually shows evidence of mild structural abnormalities [6].

IE which was initially thought to be uncommon in children is now thought to be on the increase due to improved diagnosis of cardiac diseases using echocardiography, better medical care and the availability of cardiac surgical services in more parts of the developing world. Children with cardiac diseases are therefore surviving longer, thus increasing their risk for the development of IE [7]. Rapid diagnosis and effective treatment plays a vital role in significantly reducing morbidity and mortality of IE. However, the diagnosis of IE in Nigeria remains a challenge mainly due to widespread antibiotic use/misuse before hospitalization, late referral and a low index of suspicion [5].

In a resource constrained environment with poor health seeking behavior, we sought to identify the features of IE in children and to describe the profile of the disease in those managed over the past 7 years in our hospital so as to encourage a higher index of suspicion among clinicians.

2. MATERIALS AND METHODS

2.1 Study Design

This was a 7 year retrospective study where records of all paediatric patients admitted and managed for infective endocarditis from January 2010 to December 2016, at the Jos University Teaching Hospital, Jos, Nigeria, were reviewed.

2.2 Study Location

This is a tertiary hospital located on the outskirts of Jos, the capital of Plateau State in Nigeria and serves as a major referral center for other hospitals in Plateau and neighbouring states. On the average, 600 children are admitted into the Paediatric medical ward every year in this tertiary facility.

2.3 Study Procedure

Children with a clinical suspicion of IE are usually admitted to the Emergency Paediatric Unit (EPU) or directly to the Paediatric medical ward through the Paediatric cardiology clinic. A transthoracic echocardiogram and three aerobic blood cultures are performed on all suspected cases and those identified as 'Definite', 'Probable' or 'no' IE using the modified Dukes criteria are commenced on empiric intravenous antibiotics while blood culture results are awaited. [8] The therapy is subsequently adjusted based on clinical response and blood culture and sensitivity results, with the aim of treating for four to six weeks. On discharge, children are followed up in the paediatric cardiology clinic where they continue to receive medical management for the underlying heart disease. Opportunities for surgical management are usually available outside the country and usually made possible by sponsors – non- governmental organizations (NGO), well-meaning Nigerians and the government.

For the current review, case records of children with a clinical diagnosis of IE were retrieved. The patients' demographic characteristics such as age at presentation with IE and gender were obtained and recorded on a proforma. Other data obtained include year of diagnosis, duration of hospital admission, underlying cardiac pathology

if any, previous history of heart surgery, clinical features at presentation, possible sources of bacteremia (based on the history and clinical features at presentation or during the course of admission) and clinical outcome (death or discharge).

Blood cultures performed at the time of admission were also reviewed and the isolates from positive cultures documented. The presence or absence of vegetations at echocardiography was noted and the diagnosis of IE - either 'definite', 'probable' or 'no' IE, verified [8]. Children verified as having 'no' IE were excluded from further analysis.

2.4 Ethics

This study was approved by the Research Ethics Committee of the Jos University Teaching Hospital.

2.5 Statistics

Data was imputed in and analyzed using Epi info version 7. Frequency tables and bar charts were used to display non-parametric tests. Chi square was used to test for significance between variables and gender. P values of <0.05 were considered statistically significant.

3. RESULTS

3.1 Descriptive Characteristics of the Subjects

Over the 7 year period under review, a total of 33 children were admitted and investigated for IE, of which two case records were missing and one was verified to have 'no' IE. The remaining 30 children treated for IE ranged from 3 months to 17 years in age with a mean of 9.5 years [95% Confidence Interval 7.3 – 11.7 years] and a male to female ratio of 0.7:1. Fifteen (50.0%) children had underlying RHD only, 13 (43.3%) congenital heart disease (CHD) only, one (3.3%) had both RHD and CHD (a ventricular septal defect, VSD) and one (3.3%) child, the youngest in the study, had no underlying heart condition – Table 1.

The commonest underlying CHD was VSD only which was present in 4 (30.8%) of 13 children with CHD only followed by Patent Ductus Arteriosus (PDA) only in 3 (23.1%) of them. Two (15.4%) children had both a VSD and a PDA while one child each had atrioventricular septal defect (AVSD), congenital mitral incompetence (MI), tetralogy of Fallot (TOF) and a complex cyanotic congenital heart disease (CCHD). A diagnosis of definite IE was made in 16 (53.3%) children and probable IE in the remaining 14 (46.7%) – Table 1. None of the children with infective endocarditis had undergone cardiac surgery.

The yearly distribution of children with infective endocarditis showed that the highest number of children with IE were managed in 2016, when 10 (33.3%) cases were admitted and the lowest in 2011 when only one boy was admitted – Fig. 1.

3.2 Possible Sources of Bacteremia

The possible source of bacteremia was identified in 18 (60.0%) children, with respiratory tract infections being the most common occurring in 8 (26.7%) of the 30 children, of which three (3) were throat infections and the remaining five, pneumonias. Urinary tract infections were the likely source of bacteremia in 5 (16.7%) children and were significantly more common in females (P = 0.02) Three (10.0%) children had dental carries while only one child had a dental procedure prior to development of IE – Table 2. One of the children with dental carries also had a throat infection.

3.3 Clinical Features of Infective Endocarditis

Majority of the clinical features were non-specific and included fever (70.0%), anorexia (63.3%), vomiting (40.0%) and malaise (30.0%). Fever was significantly more common in males with up to 92.3% of them presenting with fever as opposed to 52.9% of females – P = 0.01. Almost two-thirds had congestive cardiac failure while splenomegaly was found in 6 (20.0%) children and a changing murmur in 3 (10.0%). Neurological features were present in 6 (20.0%) children and included hemiparesis alone in 2 (13.3%), expressive aphasia alone in 1 (3.3%), and upper motor neuron facial nerve palsy alone in 1 (3.3%) child. One child had hemiparesis with upper motor neuron facial nerve palsy while another had hemiparesis with expressive aphasia – Table 3.

3.4 Blood Culture Results

A positive blood culture was obtained in 11 (36.7%) children with infective endocarditis and *Staphylococcus aureus* was the most common isolate, detected in 5 (45.5%) of the children with

positive blood cultures. Other isolates were Klebsiella species in 3 (27.3%), *Pseudomonas aeruginosa* in 2 (18.2%) and *Acinetobacter baumami* in 1 (9.1%) child – Table 4. The child with no underlying cardiac defect had a positive blood culture that grew *Staphylococcus aureus*. *Streptococcus viridans* was not isolated in any blood culture sample obtained from the children.

Table 1. Descriptive characteristics of 30 children with infective endocarditis

Variable	Total 30(100.0%)	Male 13(43.3%)	Female 17(56.7%)	*P* value
Age group (Years)				
<1	4(13.3)	3(23.1)	1(25.0)	
1-4	4(13.3)	1(7.7)	3(17.6)	
5-9	3(10.0)	1(7.7)	2(11.8)	
10-14	11(36.7)	6(46.2)	5(29.4)	
15-19	8(26.7)	2(25.0)	6(35.3)	0.41
Underlying heart disease				
Congenital Heart Disease (CHD) only	13(43.3)	8(53.8)	5(29.4)	
Rheumatic Heart Disease (RHD) only	15(50.0)	4(30.8)	11(64.7)	
Both CHD (VSD) and RHD	1(3.3)	0(0.0)	1(5.9)	
None	1(3.3)	1(7.7)	0(0.0)	0.10
Type of infective endocarditis				
Definite	16(53.3)	7(53.8)	9(52.9)	
Possible	14(46.7)	6(46.2)	8(47.1)	0.48

CHD – Ventricular septal Defect (VSD) alone – 4 (30.8%), Patent ductus arteriosus (PDA) alone – 3 (23.1%), VSD+PDA – 2 (15.4%), Atrioventricular septal defect (AVSD) – 1 (7.7%), Congenital mitral incompetence 1 (7.7%), Tetralogy of Fallot (TOF) – 1 (7.7%), Complex Cyanotic Congenital Heart Disease (CCHDx) – 1(7.7%)

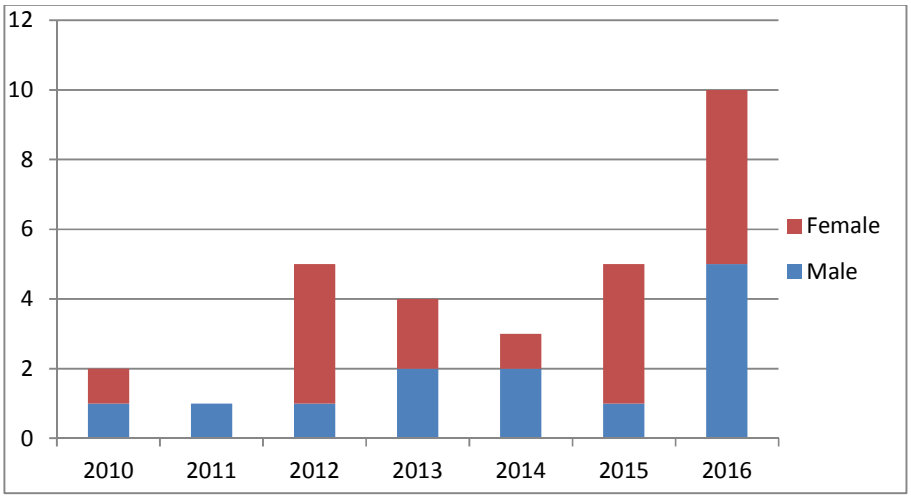

Fig. 1. Yearly distribution of children admitted with infective endocarditis

Table 2. Possible source of bacteremia in 18 subjects

Predisposing factors	Total 30(100.0)	Male 13(43.3)	Female 17(56.7)	*P* value
Respiratory tract infection †	8(26.7)	4(30.8)	4(23.5)	0.34
Skin infection	1(3.3)	0(0.0)	1(5.9)	0.28
Urinary tract infection	5(16.7)	0(0.0)	5(29.4)	0.02*
Dental carries	3(10.0)	0(0.0)	3(17.6)	0.08
Dental procedures	1(3.3)	0(0.0)	1(5.9)	0.28

**statistically significant*
† had throat infection and 5 had pneumonia

Table 3. Clinical features in children with infective endocarditis

Variables	Total 30(100.0)	Male 13(43.3)	Female 17(56.7)	*P* value
Clinical features				
Fever	21(70.0)	12(92.3)	9(52.9)	0.01*
Congestive cardiac failure	19(63.3)	7(53.8)	12(70.6)	0.19
Anorexia	19(63.3)	7(53.8)	12(70.6)	0.19
Vomiting	12(40.0)	6(46.2)	6(35.2)	0.29
Malaise	8(30.0)	1(7.7)	8(17.1)	0.37
Splenomegaly	6(20.0)	3(25.0)	3(17.6)	0.37
Hemiparesis	4(13.3)	2(15.4)	2(11.8)	0.40
New/ changing murmur	3(10.0)	2(15.4)	1(5.9)	0.23
Loin tenderness	3(10.0)	1(7.7)	3(17.6)	0.25
Expressive aphasia	3(10.0)	1(7.7)	2(11.8)	0.39
Subnormal temperature	3(10.0)	1(7.7)	2(11.8)	0.39
Others ‡	9(30.0)	6(46.1)	3(17.6)	0.10

Statistically significant

‡ Two children each presented with headache, weight loss, Osler's nodes and facial nerve palsy and one case of macroscopic hematuria

Urine culture was positive in three girls; *Escherichia coli* was the isolate in two of them and Klebsiella species in the third. Organisms isolated from their throat included *Streptococcus pneumonia* in two children and *Streptococcus pyogenes* in a third.

3.5 Presence of Vegetations and Outcome

Vegetations were detected in 12 (40.0%) children using transthoracic echocardiography and over half of these (58.3%) were found on the mitral valve, followed by the pulmonary valve and ventricular septum in 2 (16.7%) cases each, while the aortic valve affected in only one (8.3%) child. Eight (26.7%) children died during the course management of infective endocarditis and a significantly higher number were males (*P* = 0.02) – Table 4.

4. DISCUSSION

This study was carried out to describe the profile of IE in children in Jos, which is located in the North-central part of Nigeria, and to identify the peculiarities of the disease in our environment with its high prevalence of rheumatic heart disease (RHD) [2,3,9]. A total of 30 children were managed for infective endocarditis over a 7 year period, similar to that reported as far back as 1991 in a neighbouring state in Northern Nigeria where 32 cases were detected over an 8 year period [4]. In contrast, Johnson et al. [10] recorded only 47 cases over a 60 year period in Mayo clinic in the United States. This difference highlights the marked decline in the incidence of IE in developed countries which is probably related to their improved standards of living and health care delivery including the decline in the prevalence of RHD [10].

The mean age at diagnosis of infective endocarditis in this study (9.5 years) is higher than that reported by Ahmadi and Daryushi [11] who reported a mean age of 6.31 years in their study of 24 children with IE over a six year period in Iran. The difference might be related to the fact that majority of their patients had underlying CHD as opposed to RHD which was the more common underlying cardiac abnormality in the present report. Half of the IE patients in a Brazilian study were newborns and infants with CHD compared with only four (13%) infants in the present series [12]. One case of neonatal IE due to *Candida albicans* was reported from a neonatal unit in southwestern Nigeria in 1989. [13].

Our youngest patient was a three month old with no underlying heart disease but a blood culture isolate of *Staphylococcus aureus.* Six percent of patients in the previous northern Nigerian study of IE in children also had no underlying structural heart disease, as do up to 35% in Taiwan [4,14]. *Staphylococcus aureus* endocarditis, a severe acute illness with high mortality, often affects anatomically normal hearts as a complication of *Staphylococcus aureus* septicaemia in young children [15].

Table 4. Blood culture, echocardiographic findings and outcome in patients with infective endocarditis

Variables	Total 30(100.0)	Male 13(43.3)	Female 17(56.7)	*P* value
Positive blood culture				
Yes	11(36.7)	4(30.8)	7(41.2)	
No	19(63.3)	9(69.2)	10(58.8)	0.29
Organism isolated	1136.7)	4(30.8)	7(41.2)	
Staphylococcus aureus	5(45.5)	3(75.0)	2(28.6)	
Klebsiella species	3(27.3)	0(0.0)	3(42.9)	
Pseudomonas aeruginosa	2(18.2)	0(0.0)	2(28.6)	
Acinetobacter baumami	1(9.1)	1(25.0)	0(0.0)	0.12
Presence of vegetations				
Yes	12(40.0)	6(46.2)	6(35.3)	
No	18(60.0)	7(53.8)	10(64.7)	0.29
Location	12(40.0)	6(46.2)	6(35.3)	
Mitral valve	7(58.3)	3(50.0)	4(66.1)	
Aortic valve	1(8.3)	1(6.7)	0(0.0)	
Pulmonary valve	2(16.7)	1(6.7)	1(16.7)	0.35
Outcome				
Discharged	22(73.3)	6(50.0)	14(87.5)	
Died	8(26.7)	6(50.0)	2(12.5)	0.02*

**statistically significant*

4.1 Presence of Underlying Heart Conditions

The finding of ventricular septal defect (VSD) as the most common CHD in this study, present in 30.8% of children followed by Patent ductus ateriosus (PDA) in 23.1% is similar to the report by Roodpeyma et al. [16] who reported rates of 28.6% each for VSD and PDA. Ahmadi et al. [11] however found 41.2% of children with IE to have underlying VSD, followed by aortic stenosis in 23.6%. Previous studies have shown that children with cyanotic heart diseases, left sided cardiac lesions and those within six months post cardiac surgery have the highest risk of IE [17,18]. The underlying cardiac pathology will vary from place to place and depends on the prevailing structural heart diseases in the region including the availability of cardiac surgery which is not yet available in our center.

4.2 Possible Sources of Bacteremia

This study identified that respiratory tract infections and urinary tract infections were the most common possible sources of bacteremia in children which was in contrast to what was observed by Strom et al. [19] in a study carried out in Philadelphia in the late 1980s where prior skin infection was the commonest possible source of bacteremia and no case of infective endocarditis followed a urinary tract infection. They also observed that most cases had a prior history of pneumonia however they considered this more of an early manifestation of infective endocarditis than a predisposition which is also a possibility in the present study.

There was an apparent paucity of dental carries and procedures as likely predisposing factors to IE in this study could possibly explain why *Streptococcus viridans* which is normally found in the oral cavity but can cause invasive disease, was not isolated in any of the blood cultures [20]. Early treatment of infections, educating children and caregivers on prevention of urinary tract infections, dental carries and prophylaxis against IE will help to reduce the burden of this disease.

4.3 Clinical Features and Causative Organisms

Most of the clinical features in children diagnosed and managed for IE in this study were nonspecific and similar to reports in several other studies [21,22]. This buttresses the fact that a high index of suspicion is required for the diagnosis of infective endocarditis in children because the common clinical features of the disease are non-specific.

The commonest causative agent being *Staphylococcus aureus* (45.5%) in this study is consistent with several other studies where *Staphylococcus aureus* was identified in 36-68%

of cases of IE with positive blood culture results in developing countries and in studies carried out in intensive care units in developed countries [4,23-25]. Other infectious agents seem to differ from one region to the other. While the earlier northern Nigerian study documented similar organisms and frequency of occurrence as the present study, they also found three children each with Salmonella species and alpha hemolytic Streptococcus [4].

The finding of culture negative IE is not unusual and has been reported to range from 8% to 36% in past studies [26,27]. The blood culture was negative in 63% of children in the present study, compared with 42% in the previous study from northern Nigerian study [4]. Antibiotic use/misuse which is one of the causes of culture negative IE is known to be very prevalent in our environment where many patients use over-the-counter medications including antibiotics before presenting to a hospital [28]. Culture negative IE could also be attributable to infection caused by fastidious organisms such as *Streptococcus pneumoniae*, *Abiotrophia* and *Granulicatella* species or HACEK organisms which grow poorly in vitro and have less standardized methods of culture. The diagnosis of fungal IE is limited by lower sensitivity of blood cultures for yeast and virtually no sensitivity for filamentous fungi. Also, children with PDA are more likely to have the organisms are filtered by the lungs, since the vegetation would commonly occur on the right side of the heart and therefore no isolates may be detected when blood culture is done [29].

4.4 Vegetations

Our finding of vegetations in only 40% of our IE cases could be attributable to the relatively lower sensitivity (43-70%) of trans-thoracic echocardiography as opposed to trans-esophageal echocardiography (up to 90%) [30]. The mitral valve as the commonest site for vegetations (in 58.3% of our patients with vegetations) is consistent with the report by Niwa et al. [31] who also observed that the mitral valve was the commonest site for vegetations though their incidence was lower at 25.1%. The fact that RHD which commonly affects the mitral valve was the major underlying cardiac condition in our study unlike that of Niwa et al. [31] which did not include any case of RHD, might explain the difference.

4.5 Outcome

Our mortality rate of 28.6% is similar to reports from developed countries about 5 – 10 years ago, when mortality rates reached up to 30% [32,33], but is much lower than the 70% reported by Falase et al. [34] in Southern Nigeria in the 1970's and 47% in the earlier Northern Nigerian study [4]. The study in Southern Nigeria was however carried out in the era before echocardiography became readily available and there was a narrow choice of antibiotics for treatment. Other studies in Iran and Spain have reported lower mortality rates of 5% and 19% respectively [11,35].

5. CONCLUSION

A high index of suspicion remains essential in making a diagnosis of IE, more so as many of our patients presented with non-specific symptoms and signs. Decreasing the likelihood of bacteremia by prompt treatment of other infections, prevention of urinary tract infection in females and regular checks for good oral hygiene and the absence or presence of dental carries should help to reduce the occurrence of IE especially in children with underlying structural heart disease.

CONSENT

It is not applicable.

ETHICAL APPROVAL

The study was approved by the Ethical Review Board of the Jos University Teaching Hospital, Jos, Plateau State.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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