Infective Endocarditis in children: A 23-year experience at a Southern African tertiary institution

A Research Report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of

Master of Medicine in Paediatrics

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DECLARATION

I, Meera Ooka, declare that this research report is my own work. This research report is being submitted for the degree of Masters of Medicine in the branch of Paediatrics at the University of the Witwatersrand, Johannesburg. It has not been submitted prior for any other degree or to any other University.

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Dr. Meera C.N. Ooka Date

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LIST OF ABBREVIATIONS

IE: infective endocarditis

CHBAH: Chris Hani Baragwanath Academic Hospital

CHD: congenital heart disease

RHD: rheumatic heart disease

BC: blood culture

CF: cardiac failure

CVC: central venous catheter

HIV: human immunodeficiency virus

PMTCT: prevention of mother to child transmission

WHO: World Health Organisation

IMCI: Integrated management of childhood illness

HACEK: Acronym for *Haemophilus* species, *Aggregatibacter* species, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* species

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Infective Endocarditis in children: A 23-year experience at a Southern African tertiary institution

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Abbreviations:

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CONTRIBUTOR'S STATEMENT

Dr. Ooka conceptualized and designed the study, collected data, analyzed the data, drafted the initial manuscript, revised the manuscript and approved the final manuscript submitted.

Professor Cilliers conceptualized and designed the study, assisted with data analysis and interpretation, reviewed and revised the manuscript providing critical feedback and approved the final manuscript for submission.

Abstract

Background: There is a paucity of data regarding infective endocarditis (IE) in children particularly in low-to-middle income settings with no recent data from Sub-Saharan Africa.

Objectives: To determine the demographic and clinical profiles of paediatric patients diagnosed with IE at the Chris Hani Baragwanath Academic Hospital (CHBAH), Johannesburg, South Africa.

Methods: A retrospective descriptive study of all paediatric patients diagnosed with IE between 1993 and 2015 and captured on the Paediatric cardiology electronic database. Demographic data, the presence of congenital or acquired structural heart disease and other risk factors, blood culture results and complications were recorded and analysed using basic statistical methods.

Results: A total of 183 patients were included in the study. The median age was 31.2 months with a male: female ratio of 1.1:1. Ninety-seven patients (53%) had underlying congenital heart disease (CHD), 26 had rheumatic heart disease (14.2%), and 45 (24%) were identified with structurally normal hearts. Underlying sepsis (37.8%), central venous catheters (31.2%), prematurity (15.6%) and HIV (13.3%) were found to be risk factors in the group with normal hearts. *Staphylococcus Aureus* and *Streptococcus Viridans* were found to be the most common offending pathogens. Complications were documented in 103 (56.3%) patients. These included cardiac failure, worsening valve lesions, vascular complications (embolization and mycotic aneurysm formation), other manifestations of sepsis, surgery required to treat complications and death. The overall mortality rate was 23.5%. Cardiac failure and vascular complications were associated with a high risk of mortality.

Conclusion: CHD is the most common association with IE followed by structurally normal hearts in premature infants and patients with central venous catheters. More than half the patients suffered complications and almost a quarter died highlighting the devastating outcomes that IE poses.

Introduction

Infective endocarditis (IE) is a relatively rare but important clinical entity in children because of its significant association with morbidity and mortality (1-4). It is characterized by infection of the endocardial surface of the heart which may include one or more heart valves, the mural endocardium, or a septal defect (5). The clinical course of IE is often complicated and adverse sequelae include valvular dysfunction, cardiac failure, intracardiac extension of the infection, neurologic sequelae due to septic emboli or mycotic aneurysms, as well as renal injury resulting from immune mediated or embolic phenomena or sepsis (6). The average mortality rate globally varies between 16 and 25%, but is higher in some parts of Africa with a mortality rate of 47% reported in a Nigerian publication in the 1990s (7). Various factors such as late diagnosis, resistant infecting organisms and the development of complications contribute to mortality risk (5). Poor prognostic variables include advanced HIV disease, cardiac failure, *Staphylococcus Aureus* infective endocarditis and peri- annular abscess formation which may require surgical intervention (6). There is no recent data within Sub-Saharan Africa regarding outcomes of IE in children.

According to data published by the American Heart Association, IE accounts for 1 in 1280 paediatric admissions per year (2). Despite the use of prophylactic antibiotics in certain predisposed individuals, the prevalence has not decreased (8), and according to some reports may be on the rise (9-11). The persistence of IE as an important cause of childhood illness has occurred despite the marked decline of rheumatic heart disease (RHD), and can be partly attributed to the increased survival rates of children with congenital heart disease (CHD) due to advances in corrective and palliative cardiac surgical procedures in some parts of the world (2). RHD on the African continent, however, is frequently associated with IE in children. A study done at a tertiary hospital in Addis Ababa, Ethiopia, between 2008 and 2013 in children between 7 months and 14 years, showed that 49% of their study cohort of 40 patients with IE had RHD and 51% had CHD (12). In contrast, an earlier study done at the Ahmadu Bello University teaching hospital in Nigeria in 1991, showed that the majority of children in their study cohort of 32 patients (66%) had RHD while 28% had underlying CHD (14). The only similar study from Sub-Saharan Africa consisted of a very small sample population, undertaken in Cape Town over a 10-year period in the 1980s. Seventy percent of the 29

children enrolled in the study had CHD, and the minority (16%) had underlying RHD. Studies from other low to middle income countries outside of Africa, also show a high association between RHD and IE, such as the study published from Pakistan in 2001 (13). A dramatic decline in the number of children presenting with acute rheumatic fever and RHD at the CHBAH has been documented over the last two decades (14). It is likely that the IE associated with RHD may also have declined over the same period. Etiological patterns of IE have yet to be delineated within the Southern African paediatric population in the face of a possible evolving epidemiological profile.

Another key factor in the evolving epidemiology in developed countries is an increase in catheter associated IE due to management of neonates and children in intensive and high care settings (2, 10). Prolonged use of indwelling central venous catheters (CVC), and prolonged hospitalization with frequent interventional therapies, have led to an increase in the incidence of IE (5). However, even within our very limited resourced setting, there has been a gradual shift towards expansion of intensive care to very low birth weight babies at our institution, as well as frequent use of indwelling CVCs in our paediatric intensive care and oncological units. CHBAH has both the largest neonatal as well as paediatric oncology referral units within South Africa. Other risk factors for IE such as intravenous drug use and degenerative heart disease are less important in the paediatric population (2).

Bacteriologic diagnosis is critical to management of IE, however, one third of patients present with culture negative IE. The most common reason for this is inappropriate antibiotic administration without proper bacteriological identification, which poses a serious challenge to the management. Other reasons are unusual organisms such as fungi or certain fastidious intracellular bacteria that require specialized laboratory identification techniques (6). It is imperative to profile common offending organisms and drug sensitivities within each setting, in order to direct empiric antibiotic treatment guidelines on a background of increasing antibiotic resistance and the creation of superbugs. A study published in Cape Town in 2016 attributed 50-75% of native cardiac valve infective endocarditis to *Streptococcus Viridans* and 25% to *Staphylococcus Aureus.* *Staphylococcus Epidermidis* and *Staphylococcus Aureus* were

shown to be the predominant offending organisms in endocarditis associated with prosthetic valves. Profiling infecting organisms not only directs therapy but allows the physician to prognosticate depending on the offending organism.(6)

The Chris Hani Baragwanath Academic Hospital (CHBAH) is the third largest hospital in the world and is a major tertiary referral center within Gauteng's Health System (15). It serves mainly indigent patients from the community of Soweto, which purportedly has a population of more than 1.2 million people (16), as well as being a major referral center for secondary care hospitals in the region, neighboring provinces, and frequently patients from beyond our country's borders. The Paediatric Cardiology unit consults an average of 60 to 100 patients per week (both inpatients and outpatients). All patient details are captured onto an electronic database which was started in 1993. The hospital serves as an ideal setting to analyze and profile IE in children within a Southern African Tertiary setting located in a low-to-middle income country.

Objectives

To determine the demographic and clinical profiles of paediatric patients diagnosed with IE between 1993 and 2015 at the CHBAH, a Southern African Tertiary care centre. Epidemiological profiles over time, complications, mortality rate and associated risk factors, aetiological organism profile and vegetation characteristics were analysed.

Methods

Study design and data collection

All paediatric patients diagnosed with IE based on echocardiographic confirmation of a vegetation, at the CHBAH between January 1993 and December 2015 were included in the study. Patients were identified using the CHBAH Paediatric Cardiology computerized database on which all patients with a cardiac diagnosis at the CHBAH are captured. Demographic data obtained included age at presentation, gender and place of origin. Other information collected included: year at presentation, underlying cardiac lesions, possible risk factors, associated co-

morbidities, complications including death, surgery undertaken for IE, vegetation site and size and blood culture (BC) results. The size of the vegetations were designated as either ≥ 10mm or <10mm in terms of widest diameter. The vegetation sites were documented as present within the right or left side of heart or both. BC results from the year 2002 onward were obtainable from the National Health Laboratory Service (NHLS) Corporate Data Warehouse, with their permission. Some BC results done before 2002 were retrieved from the cardiology database, if recorded. BC results closest to the time of diagnosis of IE, within 14 days, were captured for the study. When more than 2 organisms were isolated on the blood culture, samples were excluded due to a higher likelihood of contaminated specimens. Microbial pathogen antibiotic sensitivity profiles were not available in the majority of cases and not used in the study, with the exception of Methicillin Resistant *Staphylococcus Aureus.* Patient medical records were sourced for data not available on the electronic database. Missing data has been highlighted throughout the study and taken into account for the final analysis.

Ethical consideration

Permission to access the study data and to undertake the study was approved by the University of the Witwatersrand (Wits) Faculty Graduate Studies Committee, the Wits Human Research Ethics Committee (clearance certificate number M160860) and the relevant medical authorities at the CHBAH.

Data analysis

The data was captured on a Microsoft excel spreadsheet and analysed according to standard statistical methods using STATA 13.0 and R. Continuous variables were presented as medians and interquartile ranges due to the non-normal nature of distribution. Categorical variables were described using frequencies and percentages, and compared using Pearson Chi-square test or Fisher's exact test in univariate analysis. Associations between multiple variables and the development of complications of IE as well as death, were determined using logistic regression. A two-tailed p value < 0.05 was considered as statistically significant.

Results

Distribution of IE

A total of 183 patients presenting to the CHBAH between 1993 and 2015, were diagnosed with IE. This constituted 0.8% of the 22 094 patients seen by the Paediatric cardiology unit during this period. There is a fluctuation in distribution of IE cases across the study period, with no significant increase or decline in the overall incidence *(Figure 1)*.

Demographic characteristics

Ninety-seven patients were male (53%) and 86 (47%) were female. The median age at diagnosis was 31.2 months (IQR, 1.8-115.2 months). The largest proportion of patients were found to be above the age of five years (41%), and between 28 days and one year (21.9%) *(Table 1)*. Most patients gave addresses within the Gauteng region, followed by close to a third from outside Gauteng but within South Africa, and a very small number originating from neighbouring states outside South Africa.

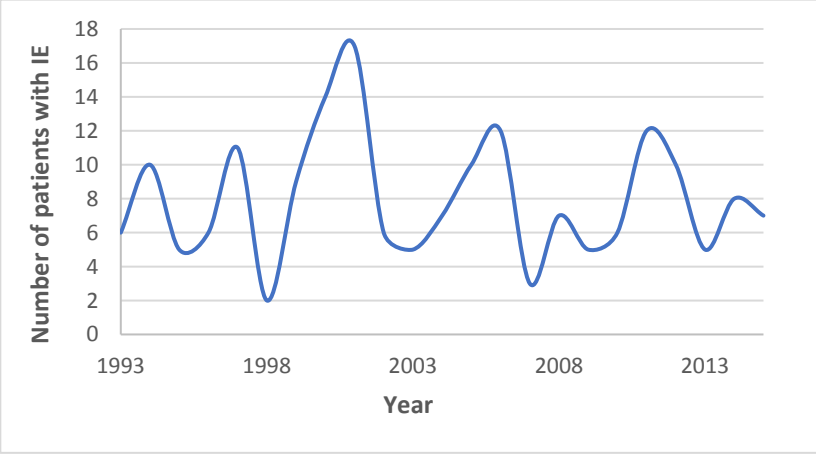

Figure 1. Distribution of IE from 1993 to 2015

Table 1. Demographic characteristics of 183 children with IE at the CHBAH (1993-2015)

Demographic characteristics		**Total number (% total study population)**
Age		
	0-28 days	28 (15.3)
	28 days-1year	40 (21.9)
	1year-5years	39 (21.3)
	> 5years	75 (41.0)
	Not Recorded	1 (0.5)
Median age (IQR): 31.2 (1.8-115.2)		
Sex		
	Male	97 (53.0)
	Female	86 (47.0)
Place of Origin		
	Gauteng	130 (71.0)
	Outside Gauteng (within SA)	50 (27.3)
	Outside SA	3(1.6)

(IQR= interquartile range; SA= South Africa)

Structural heart disease as a risk factor

Ninety-seven patients (53%) had underlying CHD with 62 (63.9%) having acyanotic cardiac lesions and 35 (36.1%), having cyanotic lesions *(Table 2).* RHD was present in 26 patients, 6 of whom presented with acute rheumatic heart disease. The RHD group constituted only 14.2% of the study population with 22 of the 26 patients with RHD (84.6%) presenting in the early part of the study period between 1993 and 2003. *Figure 2* shows CHD, as a risk factor for IE, was more frequent compared to RHD over the study period. Of note is the marked reduction in frequency of IE associated with RHD, with only one such patient being diagnosed since 2008.

Table 2. Underlying cardiac disease in children with IE at the CHBAH

Variable		**Total Number (% total study population)**
CHD		97 (53.0)
	Acyanotic	62 (33.9)
	Cyanotic	35 (19.1)
RHD		26 (14.2)
	Acute RHD	6 (3.3)
	Chronic RHD	20 (10.9)
Other cardiac pathology		15 (8.2)
Structurally normal heart		45 (24.6)

(CHD= congenital heart disease; RHD= rheumatic heart disease)

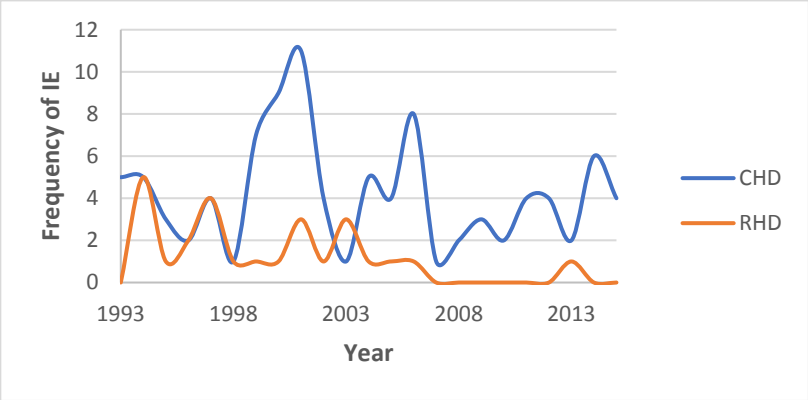

Figure 2. Distribution of IE in patients with underlying congenital vs. rheumatic heart disease over time

Other Risk Factors and Associations with IE

Fifteen patients (8.2%), had other cardiac pathology such as dilated cardiomyopathies, left ventricular hypertrophy, cor-pulmonale and pericardial effusions; one patient had congenital heart block. Of these, 86.7% had one or more predisposing risk factors for IE. These included underlying sepsis (three with *Staphylococcus Aureus* sepsis), HIV positive status, prematurity, underlying malignancies (Wilms Tumours and Non- Hodgkins lymphoma) and central venous catheters (CVC). Patients with malignancies in this group all had central venous lines. Two patients, one with congenital heart block and the other with a dilated cardiomyopathy, were not documented to have risk factors for IE.

Twenty-two patients in the CHD group had undergone cardiac surgery preceding the diagnosis of IE, namely repair of congenital cardiac and valve lesions, and palliative surgery consisting of systemic-pulmonary shunts or pulmonary artery banding. Most of these patients (13/22) developed IE within 6 months following cardiac surgery. The remainder (9/22) did not have the time period documented. More patients in the CHD group had other associations documented than the RHD group. There were 18 syndromic patients, 16 of whom had CHD. The syndromes included trisomy 21, DiGeorge syndrome, Noonan Syndrome, fetal alcohol syndrome, Pierre Robin Syndrome, Fanconi Anaemia and Diamond Blackfan syndrome.

Table 3. Other Risk Factors and Associations with IE

Risk factors/Associations	Total Number (% total population)	CHD (% patients with CHD)	RHD (% patients with RHD)	Other Cardiac Pathology (% other cardiac pathology)	Structurally Normal heart (% normal hearts)
Underlying sepsis	63 (34.4)	27 (27.8)	10 (38.5)	9 (60)	17 (37.8)
Central venous catheter	26 (14.2)	8 (8.2)	-	4 (26.7)	14 (31.1)
Prematurity (Gestational age < 37 weeks at diagnosis)	22 (12.02)	13 (13.4)	-	2 (13.3)	7 (15.6)
HIV positivity	15 (8.2)	5 (5.2)	-	4 (26.7)	6 (13.3)
Cardiac Surgery preceding IE	22 (12.0)	22 (22.7)	-	-	-
Previous episode of IE	2 (1.1)	1 (1.0)	-	-	1 (2.2)
Malignancy	15 (8.2)	1 (1.0)	-	3 (20)	11 (24.4)
Autoimmune Disease	5 (2.7)	-	-	2 (13.3)	3 (6.7)
Underlying Syndrome	18 (9.8)	16 (16.5)	-	-	2 (4.4)

(CHD= congenital heart disease; RHD= rheumatic heart disease; HIV= Human Immunodeficiency Virus; IE= infective endocarditis)

Normal hearts and IE

Close to a quarter of the patients with IE (24.6%), had structurally normal hearts (*Figure 3*). A large number (17/45) of this group (37.8%), had sepsis including staphylococcal, streptococcal, enterococcal, fungal and gram-negative sepsis, or skin abscesses, septic arthritis, osteomyelitis and pneumococcal meningitis. Risk factors for sepsis included CVCs in 14 patients (31.1%), 7 (15.6%) were premature with gestational age < 37 weeks and 6 (13.3%) had HIV. The malignancies were mainly haematological and 5/11 had CVCs. Four patients with malignancies did not have any other risk factors of note. Fifteen (33.3%) patients had more than one association.

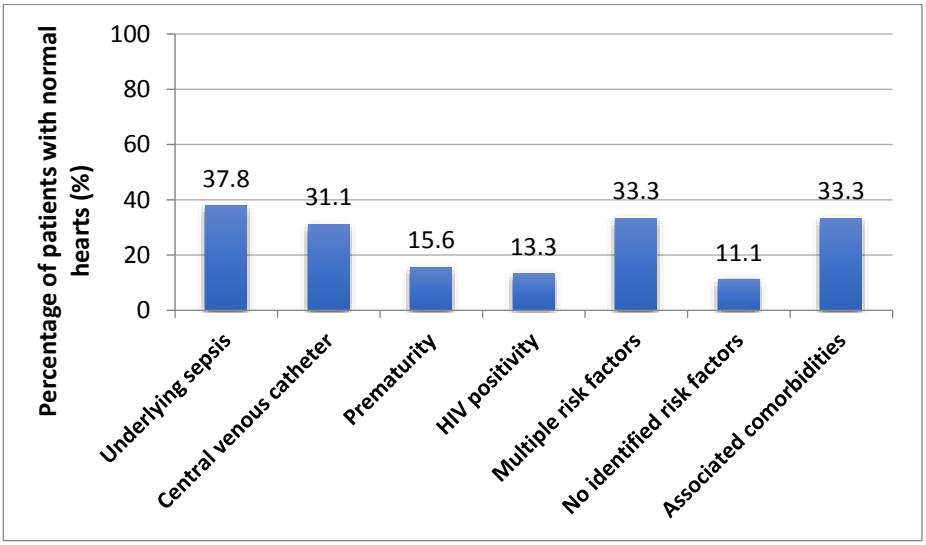

Figure 3. Normal hearts and associations

(HIV- Human Immunodeficiency Virus)

Complications

A total of 103 patients suffered complications related to endocarditis (56.3%) *(Table 4).*

The most common complication was worsening of valve lesions in 43 cases (23.5%), followed by vascular complications in 41 cases (22.4%). Cardiac failure was present in 25 patients (13.7%). Further septic complications were diagnosed in 14 patients (7.7%). These consisted of osteomyelitis, septic arthritis, an empyema, lung and intracranial abscesses, meningitis and a tricuspid valve abscess.

PERIPHERAL VASCULAR COMPLICATIONS

Peripheral vascular complications occurred in 3 patients who developed gangrene of the limbs. Two developed *Staphylococcus Aureus* endocarditis within 3 months post-surgical repair of congenital cardiac lesions (Tetralogy of Fallot and atrioventricular septal defect respectively). Both were found to have right ventricular outflow tract vegetations. The first patient developed gangrene of both feet and the second, gangrene of the fingertips. The third patient, with RHD

and vegetations on both the aortic and mitral valves had gangrene of the right leg necessitating a below-knee amputation. 'Other' systemic embolization refers to a single patient in whom a vegetation embolized to the descending aorta. *(Table 4)*

CNS COMPLICATIONS

Central nervous system (CNS) complications included cerebral embolic ischaemic infarcts in 21 cases (11.5%), 2 patients developed meningitis and one had a brain abscess. The latter 3 patients are documented under "septic complications" *(Table 4).*

ANEURYSMS

The ten patients who developed cardiac and systemic vascular aneurysms comprised 8 patients with CHD and 2 with RHD *(Table 4).* Those with CHD mostly had right ventricular outflow tract and branch pulmonary artery aneurysms following the development of vegetations within the right side of the heart. The two patients with RHD had mitral valve vegetations and developed intracardiac aneurysms. One patient developed a subaortic aneurysm and the other both subaortic and submitral valve aneurysms. A large cerebral mycotic aneurysm was diagnosed in a 3-year-old child who demised following rupture of the aneurysm, resulting in fatal intracerebral haemorrhage.

SURGERY FOR COMPLICATIONS

Thirty-six patients (19.7%) required surgery related to complications of IE. These operations included removal of vegetations, valve repair or replacement, repair of ruptured chordae, revision of a VSD patch, a subaortic aneurysm repair and a below-knee amputation for gangrene.

MULTIPLE COMPLICATIONS

Sixty-one patients (33.3%) had more than one complication documented. Some patients suffered several complications, one of whom was a 10-year-old child who had RHD and IE with a large vegetation on the mitral valve. She developed a subaortic aneurysm and had worsening aortic, mitral and tricuspid valve insufficiency necessitating repair of her mitral valve and subaortic aneurysm, but presented in severe cardiac failure following surgery and demised shortly thereafter.

Table 4. Complications in patients with IE at the CHBAH 1993-2015

Complication	**Number (% total sample population)**	**CHD Number (% of specific complication)**	**RHD Number (% of specific complication)**	**Structurally normal heart Number (% of specific complication)**
Worsening heart valve lesions	43 (23.5)	25 (58.1)	11 (25.6)	6 (14.0)
Vascular complications	41 (22.4)	25 (61.0)	11 (26.8)	5 (12.2)
Pulmonary embolization	8 (4.4)	5 (62.5)	1 (12.5)	2 (25.0)
Systemic embolization	26 (14.2)	13 (50.0)	9 (34.6)	3 (11.5)
Cerebral	21 (11.5)	11 (52.4)	8 (38.1)	2 (9.5)
Renal/splenic	1 (0.5)	0	1 (100)	0
Peripheral vascular	3 (1.6)	2 (66.7)	1 (33.3)	0
Other	1 (0.5)	0	0	1 (100)
Aneurysms (intracardiac and systemic)	10 (5.5)	8 (80.0)	2 (20.0)	0
Mycotic aneurysms	1 (0.5)	1 (100)	0	0
Cardiac failure	25 (13.7)	12 (48.0)	7 (28.0)	3 (12.0)
Septic Complication/s	14 (7.7)	6 (42.9)	1(7.1)	5 (35.7)
Osteomyelitis	5 (2.7)	2 (40.0)	0	2 (40.0)
Septic Arthritis	2 (1.1)	0	0	1 (50.0)
Empyema/lung abscess	2 (1.1)	1 (50.0)	0	1 (50.0)
Brain abscess	1 (0.5)	0	0	1 (100)
Meningitis	2 (1.1)	2 (100)	0	0
Valvular/intracardiac abscess	2 (1.1)	1 (50.0)	1(50.0)	0
Death - IE related	32 (17.5)	22 (68.8)	3 (9.4)	7 (21.9)
Death – Other/cause not clear	11 (6)	7 (63.6)	0	3 (27.3)
Surgery required for IE	36 (19.7)	18 (50.0)	15 (41.7)	2 (5.6)
Multiple complications	61 (33.3)	36 (59.0)	15 (24.6)	8 (13.1)
Total no of patients with complications	**103 (56.3)**	**55 (53.4)**	**20 (19.4)**	**22 (21.4)**

(IE= infective endocarditis; CHD= congenital heart disease; RHD= rheumatic heart disease)

Complication Risk

Table 5 shows that RHD, HIV positivity, gender, *Staphylococcus Aureus* sepsis, fungal sepsis, and vegetation site, are significantly associated with the development of complications (p value< 0.05). CHD, prematurity, cardiac surgery preceding IE and vegetation size are not significantly associated (p value >0.05).

Mortality

All cause in-hospital mortality included 43 cases with a total mortality rate of 23.5%. Variables significantly associated with mortality ($p < 0.05$) using simple logistic regression are RHD, HIV, prematurity, the presence of underlying sepsis (particularly *Staphylococcus Aureus* and fungal sepsis), cardiac surgery preceding the diagnosis of IE, cardiac failure, vascular complications and CNS complications. Conversely, gender, vegetation site and size, the presence of worsening valve lesions, septic complications and surgery required for IE and its complications did not have significant associations with mortality *(Table 6).*

Table 5. Bivariate logistic regression for variables listed and presence of complications

Variable	**Chi square**	**P-value**	**Odds ratio (95 % C.I)**
CHD	0.84526	0.3579	1.49 (0.64,3.47)
RHD	20.573	5.735e-06	*
Cardiac surgery preceding IE	2.7478	0.09739	2.27(0.84,6.09)
HIV positivity	9.7499	0.001793	4.11 (1.61,10.48)
Prematurity	1.1421	0.2852	1.48 (0.72,3.05)
Gender	3.8785	0.04891	0.55 (0.31,1)
Staphylococcus Aureus sepsis	114	2.2e-16	*
Fungal sepsis	114	2.2e-16	*
Vegetation site	6.2756	0.01224	0.44 (0.23,0.84)
Vegetation size	0.0034	0.9536	0.97 (0.39,2.42)

(CHD= congenital heart disease; RHD= rheumatic heart disease; IE= infective endocarditis; HIV= Human Immunodeficiency Virus)

*Odds ratio for RHD, Staphylococcus Aureus sepsis and fungal sepsis would reflect as either infinity or zero as some expected frequencies in respective categories consist of values <5 hence chi-square distribution does not reliably approximate the distribution of all possible chi-square values under this circumstance.

Table 6. Bivariate logistic regression for variables listed and mortality

Variable	**Chi square**	**P-value**	**Odds ratio (95% C.I)**
CHD	0.061293	0.8045	1.12 (0.46,2.76)
RHD	30.687	3.032e-08	12.29 (4.35,34.73)
HIV	20.42	6.219e-06	5.55 (2.52,12.22)
Prematurity	16.826	4.097e-05	4.29 (2.08,8.84)
Underlying sepsis	13.114	0.0002932	3.18 (1.68,6.03)
Gender	0.17798	0.6731	1.16 (0.58,2.30)
Staphylococcus Aureus sepsis	114	2.2e-16	*
Fungal sepsis	114	2.2e-16	*
Vegetation site (left versus right)	1.2342	0.2666	1.56 (0.71,3.41)
Vegetation size (<10mm versus ≥ 10mm)	0.64	0.4237	0.66 (0.24,1.84)
Cardiac surgery preceding IE	11.564	0.0006725	*
Cardiac failure	9.6709	0.001872	3.78 (1.57,9.09)
Worsening valve lesion/s	0.13581	0.7125	1.16 (0.53,2.56)
Septic complications	3.1608	0.07542	2.68 (0.87,8.20)
CNS complications	4.3868	0.03622	2.53 (1.04,6.13)
Vascular complications	5.0351	0.02484	2.35 (1.10,5.01)
Surgery for IE and its complications	1.1632	0.2808	0.59 (0.23,1.54)

(CHD= congenital heart disease; RHD= rheumatic heart disease; HIV= Human Immunodeficiency Virus; IE= infective endocarditis; CNS= central nervous system)

*Odds ratio for *Staphylococcus Aureus* sepsis, fungal sepsis and cardiac surgery preceding IE would reflect as either infinity or zero as some expected frequencies in respective categories consist of values <5 hence chi-square distribution does not reliably approximate the distribution of all possible chi-square values under this circumstance.

A multivariate regression analysis *(Table 7)* shows a significant relationship between cardiac failure (CF), vascular complications and death. The odds of dying with CF are 6 times the odds of participants without CF, while the odds of dying in the presence of vascular complications (including CNS vascular sequela) are 3.4 times the odds of patients without.

Table 7. Multivariate logistic regression for variables listed and mortality

Variable	Estimate	Standard Error	Z value	P value
Intercept	-2.200582	0.624375	-3.524	0.000424
CHD (Acyanotic)	0.505309	0.546158	0.925	0.354858
CHD (Cyanotic)	0.608802	0.643377	0.946	0.344016
RHD	-0.951609	0.912691	-1.043	0.297114
HIV positivity	-0.009069	0.785985	-0.012	0.990794
Prematurity	-0.677516	0.849830	-0.797	0.425313
Underlying sepsis	0.386669	0.458325	0.844	0.398860
Gender	-0.180307	0.432670	-0.417	0.676875
CF	1.907556	0.579231	3.293	0.000990
Worsening valve lesions	0.019372	0.523753	0.037	0.970495
Septic complications	1.258482	0.686347	1.834	0.066714
Vascular complications	1.229647	0.499649	2.461	0.013854
Vegetation site	0.097853	0.500554	0.195	0.845009
Surgery required for complication of IE	-0.683883	0.642888	-1.064	0.287435

(CHD= congenital heart disease; RHD= rheumatic heart disease; HIV= Human Immunodeficiency Virus; CF= cardiac failure; IE= infective endocarditis)

Microbiology

A total of 114 (62.3%) blood cultures were accessible between 1993-2015 *(Table 8)*. Of these the majority, 87 (76.3%), were from patients with a diagnosis of IE from 2002 onward. The remaining 27 patients (23.7% of available BC) were diagnosed with IE prior to 2002. *Figure 4* shows the distribution of the etiologic pathogens with Staphylococcal species being the commonest in 43 (37.8%) patients. Of these, 16 (14%) were sensitive *Staphylococcus Aureus* species and 11 (9.6%) were methicillin resistant *Staphylococcus Aureus* species. The remainder within this group consisted of *Staphylococcus Epidermidis* and Coagulase-negative *Staphylococcus Aureus* (CoNS). Seventeen patients cultured *Streptococcus Viridans* (14.9%) which was the second most common organism after *Staphylococcus Aureus.* Fungal growth on BC was present in 10 patients (8.8%), 9 of whom cultured candida species (including *Candida Albicans, Candida Parapsilosis, Candida Tropicalis*) and one with an Aspergillus species. No HACEK organisms were cultured and 22 (19.3%) blood cultures had no microbial growth.

Table 8. Microbial pathogens grown on blood cultures

Microorganism cultured	**Number (% of total available BC)**	**CHD Number (% of specific organism grown)**	**RHD Number (% of specific organism grown)**	**Structurally normal heart Number (% of specific organism grown)**
Staphylococcus species	43 (37.8)	18 (41.9)	3 (7.0)	15 (34.9)
Staphylococcus Aureus	16 (14.0)	6 (37.5)	1 (6.3)	5 (31.3)
Staphylococcus Epidermidis	4 (3.5)	1 (25.0)	1 (25.0)	2 (50.0)
*MRSA	11 (9.6)	6 (54.5)	1 (9.1)	3 (27.3)
*CoNS	12 (10.5)	5 (41.7)	-	5 (41.7)
Streptococcus species	20 (17.5)	9 (45.0)	9 (45.0)	2 (10.0)
Streptococcus Viridans	17 (14.9)	7 (41.2)	8 (47.1)	2 (11.8)
Streptococcus Pneumoniae	2 (1.8)	1 (50.0)	1 (50.0)	-
Streptococcus Milleri	1 (0.9)	1 (100.0)	-	-
Gram negative organisms	19 (16.7)	12 (63.2)	0	7 (36.8)
Klebsiella Pneumoniae	8 (7.0)	4 (50.0)	-	4 (50.0)
Klebsiella Oxytoca	1 (0.9)	-	-	1 (100)
Enterobacter Cloacae	1 (0.9)	-	-	1 (100)
Escherichia Coli	1 (0.9)	1 (100)	-	-
Salmonella species	3 (2.6)	3 (100)	-	-
Pseudomonas Aeruginosa	2 (1.8)	1 (50.0)	-	1 (50.0)
Acinetobacter Baumannii	3 (2.6)	3 (100)	-	-
Enterococcus species	2 (1.8)	1 (50.0)	-	-
Corynebacterium	3 (2.6)	1 (33.3)	-	-
Fungal organisms	10 (8.8)	4 (40.0)	1 (10.0)	4 (40.0)
Candida species	9 (7.9)	4 (44.4)	0	4 (44.4)
Aspergillus	1 (0.9)	-	1 (100)	-
***HACEK**	0	-	-	-
Culture negative	22 (19.3)	12 (54.5)	2 (9.1)	6 (27.3)
Polymicrobial	4 (3.5)	3 (75.0)	-	1 (25.0)
Total	*114	57 (50.0)	15 (26.3)	34 (29.8)

(MRSA=Methicillin Resistant *Staphylococcus Aureus*; CoNS= Coagulase Negative *Staphylococcus Aureus*; HACEK= group of fastidious gram-negative coccobacillary organisms *Haemophilus* species*, Aggregatibacter* species*, Cardiobacterium hominis, Eikenella corrodens and Kingella* species)

*Note that the total number of blood cultures available were 114, however 4 patients had more than one pathogen on BC giving a total of 119 results

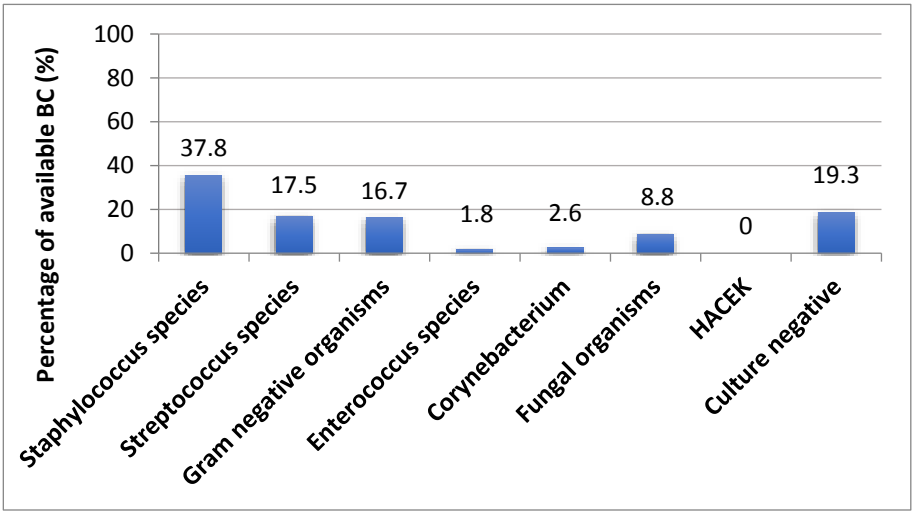

Figure 4. Distribution of etiologic microorganisms grown on BC

(HACEK- group of fastidious gram-negative coccobacillary organisms Haemophilus species, Aggregatibacter species, Cardiobacterium hominis, Eikenella corrodens and Kingella species)

Congenital Heart Lesions

The commonest cardiac lesions associated with IE were the acyanotic group of CHD with patent ductus arteriosus and ventricular septal defect being the most common, constituting 56.5% of those affected. Tetralogy of Fallot was the most common cyanotic congenital cardiac lesion and made up 74.3% of the cyanotic CHD group. There was no significant association with complications in the cyanotic group when compared to the acyanotic group, p-value 0.4 (RR =0.8; 95% CI, 0.6-1.2).

Table 9. Frequency of specific cardiac lesions in patients with IE and CHD with frequency of resultant complications

CHD	Number	Complications
ACYANOTIC CHD	**62**	**33 (53.2%)**
PDA	18	7
VSD	17	10
AVSD	9	5
ASD	4	2
Mitral valve insufficiency (cleft/prolapse/shortened chordae)	4	3
Pulmonary stenosis	4	0
Aortic stenosis	3	3
Interrupted Aortic Arch	1	1
Coarctation of the Aorta	1	1
Hypertrophic cardiomyopathy	1	1
CYANOTIC CHD	**35**	**22 (62.9%)**
TOF	26	15
TGV	4	3
Double outlet right ventricle	2	2
Pulmonary atresia	1	1
Total anomalous pulmonary venous drainage	1	1
Truncus arteriosus	1	0

(CHD= congenital heart disease; PDA= patent ductus arteriosus; VSD= ventricular septal defect; AVSD= atrioventricular septal defect; ASD= atrial septal defect; TOF= Tetralogy of Fallot; TGV= Transposition of the great vessels)

Vegetation Site

Table 10. Sites of vegetation/s amongst various groups

	Total number (% study population)	**CHD**	**RHD**	**Structurally normal heart**	**Other cardiac disease**
Left-sided vegetation	65 (35.5%)	18	25	15	7
Right-sided vegetation	108 (59.0%)	71	1	28	8
Both left-and right-sided vegetations	9 (4.9%)	7	0	1	1

**Note that one patient did not have vegetation site documented and percentages are calculated accordingly*

The majority of patients (59%) had vegetations located in the right side of the heart. Most of these patients (65.7%) had underlying CHD, followed by normal hearts (25.9%). Left sided

vegetations were present in 35.5% of patients. The highest proportion in this group had underlying RHD (38.5%). There was, however, a spread of left-sided lesions amongst all groups. Nine patients had bilateral vegetations, most of whom had CHD. Those with left-sided lesions were significantly more at risk for systemic embolization of vegetations, p-value 0.007 (RR=2.9; 95% CI, 1.3- 6.6).

Vegetation size and complications

The vegetation size was recorded in 80 out of the 183 participants. Of these, 50 patients had vegetations <10mm in widest diameter, while 30 patients had vegetations ≥10mm. These were compared against specific and overall complications. No significant associations were found such as an increased risk of heart failure or need for surgery in patients with large vegetations *(Table 11).*

Table 11. Vegetation size and complications

	Vegetation size ≥ 10mm	**Vegetation size < 10mm**	**P value**	**Odds ratio (95% CI)**
Complications	17	28	0.9	1.0 (0.7-1.5)
CF	5	6	0.74	1.4 (0.8-4.1)
Worsening valve lesion	9	9	0.21	1.7 (0.7-3.8)
CNS	7	6	0.18	1.9 (0.7-5.2)
Embolization	6	8	0.70	1.2 (0.46-3.2)
Septic complications	3	4	1.0	1.3 (0.3-5.2)
Need for surgery for IE	8	6	0.09	2.2 (0.9-5.8)
Death	9	11	0.42	1.4 (0.6- 2.9)

(CF= cardiac failure; CNS= central nervous system; IE= infective endocarditis)

Discussion

FREQUENCY OF IE

The frequency of IE has remained relatively constant over the last 2 decades. This is consistent with a large study carried out by Gupta et al who also showed a static incidence of IE despite guideline changes for the administration of prophylactic antibiotics to the highest risk patients introduced by the American Heart Association (AHA*)* in 2007 and National Institute of Health and Clinical Excellence (NICE) in 2008 (10). This was a study assessing trends and outcomes of 3840 children diagnosed with IE in the United States between 2000 and 2010 (10). Some centres, however, have shown an increase in incidence thought to be due to the availability of more sensitive diagnostic techniques, increased survival of patients with CHD, expansion of care of premature babies and the increased use of central venous catheters (1, 2, 4, 10, 17, 18). Bates et al showed a slight increase in IE of 0.13 cases/10 000 hospitalizations per semi-annual period in the US, reviewing 841 children from more than 40 paediatric centres between 2003 and 2014. The secondary analysis did not show any significant change in IE frequency after the revision of the AHA antibiotic prophylaxis guidelines (19). The spike of increased IE cases in our cohort in the early 2000s could have possibly been driven by socio-political factors. A massive influx of economic and political refugees from surrounding countries, especially young women and children into South Africa, many of whom sought dwelling in informal settlements in Gauteng occurred at that time (14).

DEMOGRAPHY

There is no significant gender predilection of IE amongst our patient population (male: female ratio of 1.1:1) which is consistent with published literature (5, 17). There is a bimodal age distribution of patients presenting most commonly in the neonatal period and infancy (37.2%) or after the age of 5 years (41.0%). This bimodal spread was also documented by Day et al. in a large study published in 2009, however their second peak was present in late adolescence (17). Immunological immaturity as well as complexities in management of very ill neonates and infants, may be contributory factors to the high incidence in the younger group. This includes frequent transient episodes of bacteraemia from trauma to the skin and mucous membranes through phlebotomy procedures, peripheral and central vascular cannulation, frequent

endotracheal suctioning and parenteral hyperalimentation (2). Surgical correction and palliative procedures in patients with CHD with resultant increase in life expectancy may be a consideration in older patients with an ongoing risk for IE.

EPIDEMIOLOGY

The epidemiological patterns of IE in children is evolving. A large proportion of patients have underlying CHD (53%) consistent with trends in both resource replete and resource challenged countries (2-4, 18). There are very few publications regarding IE in African paediatric patients. The last published data from Sub Saharan Africa was a small study in Cape Town in 1989 which showed that most patients (70%) had underlying CHD (20). However, patient numbers were small (29 children over a 10-year period) from one area in South Africa and is therefore not necessarily reflective of the South African population at large. The most common congenital cardiac lesions in this study were TOF, PDA and VSD in decreasing order of frequency. TOF and VSD were also found to be the predominant underlying congenital heart lesions in a large multicentre American study published by Day et al. in 2009, corroborating demographic and clinical characteristics of 1588 children with a diagnosis of IE (17). The Cape Town study noted that 14.2% of patients in their study had underlying RHD, which is similar to our study cohort. In contrast, other publications from Africa (Morocco and Nigeria) have documented RHD as the predominant underlying cardiac disease in paediatric patients with IE (7, 21). Moges et al also showed a high frequency of IE in children with RHD in an Ethiopian study published in 2015 (49%), but with an almost equal number of patients with CHD (51%) (12). The pattern of frequency of IE in patients with RHD has changed dramatically over time. The levels have dropped in relation to the steady decline in the incidence of ARF and RHD, which has been documented at our institution (14). Only one patient with IE and RHD was documented between 2007 and 2015. The frequency of CHD and IE however, remains fairly constant.

A significant proportion of the study cohort had structurally normal hearts (24.6%) of which a large proportion had underlying sepsis. Of these, 41.2% had *Staphylococcus Aureus* sepsis which was equally prevalent between children in the first year of life and older than 5 years of age. Important risk factors that can lead to IE in patients with normal hearts include central

venous catheters, prematurity and HIV positivity in decreasing order of frequency. An increase in survival of premature babies with the expansion of intensive and high care particularly in low and extremely low birth weight babies (2, 17, 18, 22), along with the HIV pandemic in Sub Saharan Africa (23), are some possible contributory factors to the high incidence of IE in patients with normal hearts. The estimated prevalence of HIV in the South African population in 2016 remains high at 12.7% (24). Most of the HIV positive patients in the study cohort presented in the post millennial era (86.7%) and one third presented prior to the government roll-out of anti-retroviral treatment in 2003. However, a small proportion of patients with IE were HIV positive (8.2%). This may be due to a decrease in infectious complications in HIV patients following the increased roll-out of anti-retroviral therapy (25), as well as decreased vertical transmission of the virus, due to advances in strategies and implementation of prevention of mother to child transmission (PMTCT) programs.

COMPLICATIONS

More than half of the study population developed complications. The patients with CHD formed a significantly higher proportion of patients compared to other patient groups and therefore had a higher proportion of complications compared to the other groups. Worsening of valve lesions was the most common, followed by vascular complications and heart failure in both the CHD and RHD groups. Nineteen patients of the 43 who developed worsening valve lesions underwent either valve repair or replacement of affected valves (44.2%).

Septic emboli in children with IE are a common phenomenon often resulting in extracardiac infection (26). Other septic manifestations which may have resulted from septic emboli were documented in 14 patients (7.7%) the nature of which have been previously discussed. Sixty-one patients suffered more than one complication and, in some cases, up to 5 complications, which underlines the extent of adverse outcomes that IE may pose in children. Associated RHD, HIV positivity, gender, *Staphylococcus Aureus* sepsis, fungal sepsis, and vegetation site had significant associations with the development of complications. Staphylococcal and fungal IE, and left sided vegetations are the most common associations with complications in the study cohort which are similar to other publications (26). A significant proportion of patients suffered central nervous system complications (13.1%). The most devastating cerebral complication was

documented in a 3-year-old HIV positive female who died following rupture of a large cerebral mycotic aneurysm resulting in a massive intracerebral haemorrhage demonstrated at autopsy. She had a ventricular septal defect and presented to the outpatient department with what was thought to be a bronchopneumonia and was discharged on oral antibiotics. She was re-admitted a few days later with a decreased level of consciousness and found to have large vegetations on the mitral valve. Treatment for IE was commenced immediately, however, she demised suddenly shortly after admission to hospital.

SITE OF VEGETATIONS

CNS complications were more frequent in patients with RHD (30.8%) compared to 14.4% with CHD, and only 6.7% in patients with normal hearts. This may be because most vegetations were present in the left side of the heart in patients with RHD compared to the other 2 groups and therefore more likely to embolize systemically into the cerebral vasculature. Patients with vegetations in the left side of the heart were 2.9 times more likely at risk for systemic embolization than those with right sided lesions ($p=0.007$). The majority of patients (80.4%) with CHD had right heart vegetations. The terminal point of the left to right shunts in patients with CHD is within the right heart causing injury to the endothelium at the distal end of the jet created by the shunt. The denudation of the endothelium results in overlying platelet plug formation and microbial and fibrin deposition to form vegetations (2). Patients with CHD therefore have a higher frequency of right-sided vegetations. Eight patients with right sided lesions had vegetations associated with systemic embolic complications. Seven patients with acyanotic CHD had vegetations in both the left and right heart. This infrequent finding may occur occasionally in patients with right-to-left shunts which is not the case in our cohort, all of whom had left-to-right shunts. Bilateral heart vegetations have also been described in patients with pulmonary arteriovenous malformations (27).

VEGETATION SIZE

Vegetation size ≥10mm has been shown to be a predictor of embolization and complications (1, 2), but this was not confirmed in the study. However, the vegetation size was not recorded in more than half of the sample population, therefore limiting this part of the analysis. Fungal endocarditis is said to often be associated with large, friable vegetations with a high risk of systemic embolization (28). Due to the limited availability of blood cultures on the laboratory database after 2002, only 17 BC results (65.4%) were retrievable in patients with systemic embolization. Two patients (11.8%) cultured Candida species, 6 (35.3%) cultured *Streptococcus Viridans* and 4 (23.5%) were found to have *Staphylococcus Aureus.*

MORTALITY

The overall in hospital mortality rate of the study cohort was 23.5%, which is significantly higher than the average mortality of about 5% from mostly developed countries, reported in an UpToDate review of paediatric IE in June 2017 (26). Similarly, an American survey of 3840 children with IE between 2000 and 2010, using the Nationwide Inpatient Sample (NIS) database, showed an overall 2.8% mortality rate (10). In contrast, a much higher hospital mortality of 47% was reported in a publication from the Guinea Savannah of Nigeria (7). Multiple factors in the study patients were shown to have significant associations with mortality, using simple regression analysis. These included RHD, HIV positivity, prematurity, *Staphylococcus Aureus* and fungal sepsis, preceding cardiac surgery and cardiac failure, CNS and vascular complications. A multi regression analysis showed that cardiac failure ($p= 0.0009$) and vascular complications (including peripheral vascular and cerebral vascular complications) were shown to have the most significant relationship with mortality ($p=0.01$). Factors associated with an increased risk of mortality reported in the literature include *Staphylococcus Aureus* endocarditis, cyanotic CHD and prematurity (26). A search of African literature showed CNS complications to be significantly associated with risk of death, in a study cohort of 73 children from 3 Tunisian tertiary care centres in 2016 (29).

SURGERY

A large number of study patients (19.7%) required surgery as a result of IE and its complications. These surgeries consisted predominantly of removal of intracardiac vegetations, valve repairs and replacements, aneurysm repairs and limb amputations due to gangrene caused by peripheral vascular embolization of vegetations. There was a mortality of 16.7% in patients that underwent surgery for complications of IE compared to 25.2% in the group who did not undergo surgery, but surgery itself, compared to other high-risk variables, was not shown to have a significant association with mortality (p= 0.29). There is very little data analysing surgical outcomes in paediatric populations from resource limited settings. A study carried out at the Texas Children's Hospital, analysed a paediatric sub cohort of 46 patients with IE who underwent surgery for complications, among a total sample population of 76 patients between 1996 and 2010. There was no statistical significance between the mortality rate of 6.5% in the group of 46 patients that underwent surgery, compared to the mortality rate of 10% among patients who did not. Indications for surgical intervention among this cohort included severe valvular insufficiency often associated with concomitant ventricular dysfunction, septic embolization and persistent vegetations despite adequate medical therapy (30). With regard to African data, the only study found was a Tunisian cohort of 73 patients with IE of which 50.7% underwent surgery. The 6-month mortality rate was 21.6% amongst the surgical group and 11.1% amongst those who did not require surgery (29), which was not statistically significant (p= 0.36).

MICROBIOLOGY

The most commonly cultured pathogen on BC was *Staphylococcus Aureus* which comprised 23.6% of all BC results available. The majority presented in patients with either CHD or structurally normal hearts. *Streptococcus Viridans* was the second most common pathogen, mostly present in patients with underlying structural heart disease, with equal numbers in both CHD and RHD groups. A similar pattern is seen in patients with structural heart defects in other publications (2-4, 10, 18, 26). A new trend is the observation that hospital acquired pathogens such as gram-negative bacilli, fungal species and CoNS are on the rise (1, 18). The blood cultures from the study cohort that were available from 2002 also showed a high percentage

(43.7%) of hospital acquired organisms. The majority (57.9%) were cultured after 2009. The HACEK group of coccobacilli which are reportedly more commonly found in neonates and immunocompromised children (5,25), were not cultured in the study cohort. Antimicrobial sensitivity profiles for pathogens cultured were mostly not accessible, apart from *Staphylococcus Aureus* and therefore have not been included in the study.

A significant proportion of BCs were negative (19.3%), which exceeds the 5-7% negative BC rate reported recently (26). Possible reasons for the high percentage of negative BCs include: 1) the administration of antibiotics at a referring centre or primary health care facility, in accordance with the WHO guidelines for children; 2) Insufficient volumes of blood taken for culture, especially in infants and premature neonates (26); 3) Inappropriate blood culture techniques for fastidious microorganisms, including those belonging to the HACEK group (2).

Conclusion

IE in children remains an important clinical entity with a very high morbidity and mortality rate particularly in patients developing cardiac failure and vascular complications. Although *Staphylococcus Aureus* and *Streptococcus Viridans* remain the most common organisms in paediatric IE, hospital-acquired pathogens are emerging as important causes of IE. Most patients have underlying acyanotic congenital heart disease. There is a substantial portion of patients with anatomically normal hearts that are diagnosed with IE, mostly related to prematurity and use of central venous catheters in young children. There should be increased awareness about the critical need for aseptic techniques when placing central venous catheters in children. Other preventative measures, such as good dental hygiene in patients with structural heart disease, should be emphasized, as well as enforcing antimicrobial prophylaxis for highest risk patients according to the 2007 American Heart Association (AHA) guidelines. Although the current study has shown similarities with publications from both resource-replete and resource-limited countries, a continued survey is required in our setting to allow a better understanding of the patient and pathogen profile, for the purposes of better patient care and management and appropriate empiric antibiotic use.

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APPENDIX A:

AUTHOR GUIDELINES FOR THE CARDIOVASCULAR JOURNAL OF AFRICA

INFORMATION FOR AUTHORS

The Cardiovascular Journal of Africa is pleased to consider original articles, reviews, discussions on topical issues, case studies, meeting reports and other contributions relevant to the understanding, treatment and care of vascular disease.

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  Paid on Submission of Manuscript.

- **Article Processing/Publishing Fee:** South African and International Authors: ZAR 6000.
  Paid on Article Acceptance for Publication in the CVJA.

This is normal for most, if not all, journals. We so far have been able to survive without charging authors for submissions and processing but can no longer do so. We regret that we have to implement this as from the 13 of December 2016. Payment will need to be made online and once payment has been received, the manuscript will be further processed for possible publication.

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The Cardiovascular Journal of Africa (CVJA), which incorporates the Cardiovascular Journal of South Africa, is particularly concerned with publication of scientific articles related to Cardiac and Vascular conditions and situations, concerning adults and children, in Sub Saharan Africa. But will accept articles from all parts of the world.

Basic Science publications related to clinical aspects either for elucidation, in-depth understanding or therapeutic approaches are accommodated. The Journal functions as official medium for other related societies which do not as yet have own Journals such as, Hypertension, Stroke, Nuclear Medicine and Magnetic Resonance in Cardiology, Paediatrics, Molecular and Cellular Cardiology, and Vascular disease in Diabetes and Obesity.

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Title page as above. Abstract (150 words) setting out the scope, key messages and conclusions of the review. Body of text liberally partitioned with headings and subheadings leading to a synopsis with conclusions at the end. Key messages in a separate box itemising two to five short principal statements. Acknowledgements, references, tables and figures as above.

Other articles should adopt a concise style consistent with similar articles previously published in the journal. Manuscripts should include a title page, and appropriate subheadings for text. Style of tables, figures and references as above.

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APPENDIX B: RESEARCH PROTOCOL:

AN ANALYSIS OF PAEDIATRIC PATIENTS WITH INFECTIVE ENDOCARDITIS AT THE CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL (OVER A 22 YEAR PERIOD)

Meera Ooka (MBBCh WITS)

Student Number: 0601674N

Degree: Masters of Medicine in the Discipline of Paediatrics

Research Protocol 2016

Supervisor: Professor Antoinette Cilliers (Principal Paediatric Cardiologist, Chris Hani Baragwanath Academic Hospital)

Contents

1. Introduction

1.1 Background

Infective endocarditis is a relatively rare but important clinical entity in children, as it is associated with significant morbidity and mortality (1,2,3). It is characterized by infection of the endocardial surface of the heart which may include one or more heart valves, the mural endocardium, or a septal defect (4). Mortality rates are much lower than that within the pre-antibiotic era however it remains a life threatening disease which may confer serious complications (2,3). The clinical course of infective endocarditis is often complicated and adverse sequelae include valvular dysfunction and cardiac failure, local intracardiac extension of the infection- including abscesses, fistulae and pseudoaneurysms, neurologic sequelae due to septic emboli or mycotic aneurysms as well as renal injury resultant from immune mediated or embolic phenomena or sepsis and haemodynamic instability (5). The average mortality rate globally is said to be between 16-25% with contributory factors including late diagnosis or resistant infecting organisms and the development of complications (4). Poor prognostic variables include patients with cardiac failure, periannular complications delineated on echocardiography and *Staphylococcus Aureus* associated infective endocarditis – often necessitating surgical intervention or conferring a higher risk of death (5). Within Sub-Saharan Africa mortality is reported as high as 26% (6). Another factor associated with an increased risk of mortality is advanced HIV disease (5), which must be explored in the setting of a high HIV burden in Sub Saharan Africa.

According to data published by the American Heart Association, infective endocarditis accounts for 1 in 1280 paediatric admissions per year (1). No racial or sexual predilection has been noted in published literature (4). Despite the use

of prophylactic antibiotics in certain predisposed individuals, the number of patients hospitalized for infective endocarditis has not shown a significant decrease (7) and factors contributing to this will be further discussed. There is a lack recent literature pertaining to infective endocarditis in the paediatric population in Africa. Research efforts should be directed in exploring this disease within an African context in the face of an evolving epidemiological profile.

Infective endocarditis remains both a diagnostic and therapeutic challenge. The clinical presentation is varied ranging from nonspecific signs and symptoms to cardiac valvular dysfunction, heart failure or symptoms resultant from peripheral embolization (5). The modified Duke diagnostic criteria are generally used to make a diagnosis of infective endocarditis. These criteria combine clinical, microbiological, pathological and echocardiographic characteristics of infective endocarditis. The need for standardization of diagnostic criteria globally is pertinent to facilitating collaborative epidemiological investigation (8).

The epidemiology of paediatric infective endocarditis has changed in the modern era due to the increased survival rates of children with congenital cardiac disease and a decline of rheumatic heart disease (1). Current data shows that children diagnosed in the current era are more likely to have underlying congenital heart disease or post- operative infective endocarditis (8,9). An increasing proportion of children with infective endocarditis have had prior corrective or palliative surgery for congenital heart disease. Approximately 50% with infective endocarditis complicating congenital heart disease have had surgical intervention particularly, complex intracardiac repairs or palliative shunts (1). Existing literature pertaining to infective endocarditis within the paediatric population in Africa still attributes a large proportion to underlying rheumatic heart disease. Determinants of persistence of rheumatic fever and rheumatic heart disease include poverty,

overcrowding, malnutrition, low level of disease awareness in communities, shortage of resources allowing provision of quality care, and potentially more virulent group A streptococci. These socio-economic, environmental and health system related factors potentially favor transmission, inadequate diagnosis and management of streptococcal pharyngitis and poor adherence to secondary prevention measures (10). A study done in a tertiary hospital in Addis Ababa, Ethiopia between 2008 and 2013 including 40 patients with a diagnosis of infective endocarditis, showed a 49% association with rheumatic heart disease and similar proportion of 51% having underlying congenital heart disease. This study is reflective of a persisting significant proportion of paediatric infective endocarditis being associated with rheumatic heart lesions. A study published in Pakistan conducted at a Cardiology Unit at a children's hospital in 2001 established often late referral, low yield of positive blood cultures and still a strong association with underlying rheumatic heart disease within a developing setting (11).

In the face of an evolving epidemiology, a more widespread and longitudinal analysis needs to be conducted within our African context in attempt to profile the disease within a developing setting. A small study published in the Journal of Tropical Paediatrics evaluating the profile of 29 children diagnosed with infective endocarditis over a 10-year period showed a 70% association with underlying congenital heart disease, 16% with rheumatic heart disease and the remaining 14% with structurally normal hearts. 41% had undergone cardiac surgery prior to the development of endocarditis (8).

Another key factor in the evolving epidemiology of paediatric infective endocarditis is an increase in catheter associated infective endocarditis due to complexities in management of neonates and children in intensive care and high care settings (1). Both prolonged use of indwelling catheters and prolonged

hospitalization with frequent interventional therapies has led to an increase in incidence (4). Current published data shows evidence of this largely in developed countries. Bacterial endocarditis in the neonate is an uncommon occurrence however is documented to be on the rise in view of the above. Signs and symptoms in the neonate may be indistinguishable from a presentation of septicemia or congenital heart disease and thus demands a high index of suspicion for diagnosis to be made (12). A stronger association is thought to occur with placement of intracardiac venous catheters as opposed to central venous catheters and umbilical arterial catheters (12). Risk factors such as intravenous drug use and degenerative heart disease are much less substantial within the paediatric population with infective endocarditis (1).

With regards to infecting organisms, one third of patients present as culture negative infective endocarditis. The most common reason for this is prior antibiotic administration without appropriate blood cultures being taken at the time, further posing a challenge to diagnosis. Another reason for negative cultures may be unusual offending organisms such as fungi or certain intracellular bacteria (5). It is imperative to profile common offending agents and drug sensitivities within our setting to direct empiric antibiotic treatment guidelines on a background of increasing antibiotic resistance and the creation of superbugs. A study published in Cape Town earlier this year (2016) attributed 50-75% of native valve infective endocarditis to *Streptococcus Viridans* and 25% to *Staphylococcus Aureus.* *Staphylococcus Epidermidis* and *Staphylococcus Aureus* were shown to be the predominant offending organisms in endocarditis associated with prosthetic valves. Profiling infecting organisms not only directs therapy but also provides a degree of prognostic information within this complex disease. (5)

1.2 Rationale

The Chris Hani Baragwanath Academic Hospital is the third largest Hospital in the world with approximately 3200 beds located in the south of Johannesburg. It is one of the 40 Gauteng provincial hospitals, being a major tertiary referral center within Gauteng's Health System (13). It is the largest of the four teaching hospitals incorporated into the Academic and practical forum of health science students of the University of the Witwatersrand. It serves the community of Soweto alone constituting a population of more than 1,2 million people as well as surrounding areas. It also serves as a referral center for surrounding provinces and frequently encounters patients from neighboring states. Within the paediatric department, there are approximately 164 general paediatric beds, 10 beds within the admission unit, 43 within the specialist hematology- oncology wards, 40 short stay beds, >100 neonatal beds, 12 neonatal ICU beds with additional beds in the paediatric intensive care unit (13). The Paediatric Cardiology unit sees on average 22 new and 60 to 100 patients in total per week and all patient details are captured onto a cardiology database which has been established since 1993. In view of all of the above, the Chris Hani Baragwanath Hospital serves as a conducive setting for the analysis of infective endocarditis within the paediatric population within an African setting, in a low income country with limited resources. Minimal existing literature in this milieu and the importance of this disease in view of its conferring significant morbidity and mortality, in the face of a changing epidemiology and possibly disease profile merits further investigation and profiling.

2.Study Aims and Objectives:

2.1 Principal Aim

To determine the profile of paediatric patients diagnosed with infective endocarditis presenting to the Chris Hani Baragwanath Academic Hospital between 1993 and 2015.

2.2 Study Objectives

i. To determine the number and describe the demographics of patients diagnosed with infective endocarditis at a tertiary hospital in South Africa over a twenty- two-year period

ii. To determine the proportion with underlying congenital or acquired structural heart disease versus that in patients with normal hearts

iii. To delineate other underlying risk factors or associated comorbidities

iv. To compare the epidemiology of infective endocarditis between two eras (former versus latter period of the overall twenty two year study period)

v. To determine the prevalence of major complications associated with this disease

vi. To profile the infecting organisms encountered in our setting

3. Methodology

3.1 Study Design

A retrospective descriptive study of paediatric patients diagnosed with infective endocarditis at the Chris Hani Baragwanath Academic Hospital between 1 January 1993 and 31 December 2015

3.2 Study Population and Sampling

i. Inclusion Criteria

-All children presenting to the Chris Hani Baragwanath Academic Hospital and diagnosed with infective endocarditis between 1 January 1993 and 31 December 2015

-Approximately 187 patients will be enrolled for the study

ii. Exclusion Criteria

There are no exclusion criteria as all patients with infective endocarditis diagnosed during the study period are included on the Paediatric Cardiology Database.

3.3 Procedures

Data will be obtained from the CHBAH Paediatric Cardiology Computer database. Permission will be obtained from the required hospital authorities including the Department of Paediatrics and Paediatric Cardiology at the Chris Hani Baragwanath Academic Hospital.

3.4 Data collection and Handling

Data will be collected directly from the paediatric cardiology database and entered onto a prepared data collection sheet (see appendix A). The information captured would include patient's study number, year at presentation, age at presentation, sex,

cardiac diagnosis, associated comorbidities, site of vegetation or echocardiographic findings, organism/s grown on blood culture, surgery undertaken for infective endocarditis, surgery undergone for other and lastly documented complications including mortality.

3.5 Data analysis

Data will be captured onto a Microsoft excel spreadsheet. This study encompasses the analysis of largely categorical variables for which proportions and percentages will be enumerated. A sample range will be determined based on age at presentation and mean, median, standard deviation and or interquartile percentages will be used based on the nature of distribution. The proportions of underlying cardiac structural lesions posing a risk for infective endocarditis namely, congenital cardiac versus rheumatic cardiac lesions, will be determined and a resultant comparison of the underlying etiology between two divided eras within the study period will be carried out to test the alternative hypothesis of a changing etiological profile in current literature. A critical level or p value <0.05 will be considered statistically significant for this study. Comparisons will be carried out with the aid of chi square tables for categorical variables and Student t-test for continuous variables. The prevalence of various complications as well as a case fatality rate will be determined. Data analysis will be done the aid of software package Statistica. A statistician will be consulted if any further assistance may be required.

3.6 Confidentiality and ethical considerations

Personal patient details will not be included in the study maintaining patient confidentiality. Furthermore, in view of it being a retrospective descriptive study with data obtained from existing records and the maintenance of patient confidentiality, it will not be expected to gain consent from involved patients, parents or primary caregivers.

Application for the study will be made to:

-The University of Witwatersrand Faculty Graduate Studies Committee

-The Human Research Ethics Committee of the University of the Witwatersrand

-Relevant medical authorities at the Chris Hani Baragwanath Academic Hospital including the Medical Advisory Committee, Department of Paediatrics and Paediatric Cardiology.

4. Limitations

In view of this study being a retrospective audit, it relies on existing records captured during the period of analysis. Incomplete records may render an element that may weaken the study.

5. Timeline

	Jun 2016	Jul 2016	Aug 2016	Sep 2016	Oct 2016	Nov 2016	Dec 2016	Jan 2017	Feb 2017	Mar 2017	April 2017	May 2017	June 2017	Jul 2017	Aug 2017
Literature															
Preparation of Protocol															
Protocol Assessment															
Ethics Approval															
Post Graduate															
Data collection															
Data analysis															
Writing up of research															
Supervisor															
Writing up of paper															

6. Cost and Funding

Costs involved would include stationery, photocopying, printing and binding as well as the purchase of software from the University of Witwatersrand (namely statistical and referencing packages). All costs incurred will be borne by the principal investigator.

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PROTOCOL: APPENDIX A (PART 1)

Study No.	Year at Presentation	Age at Presentation	Sex	Cardiac Diagnosis					Associated Comorbidities/Possible underlying risk factors				
				Congenital		Acquired		Structurally normal heart	Prematurity	Malignancy	HIV	Central Venous catheter	Other (including underlying sepsis and previous endocarditis)
				Acyanotic CHD	Cyanotic CHD	Rheumatic Heart Disease (acute VS Chronic)	Other						

(*CHD- Congenital heart disease; HIV- Human Immunodeficiency Virus)

PROTOCOL: APPENDIX A (PART 2)

Echocardiographic Findings			Blood Culture Result	Cardiac Surgery preceding endocarditis	Surgery undertaken for infective endocarditis	Complications						
Site of vegetation	Size of vegetation	Other				CNS	Worsening Valvular Lesion	CCF	Vascular Complications	Septic Complications	Death	Multiple Complications

(*CNS- Central Nervous System; CCF- Congestive cardiac failure)

APPENDIX C: ETHICS CLEARANCE

R14/49 Dr Meera Chandrakant Nathoo Ooka

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M160860

NAME: (Principal Investigator)	Dr Meera Chandrakant Nathoo Ooka
DEPARTMENT:	Paediatrics and Child Health Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	An Analysis of Paediatric Patients with Infective Endocarditis at Chris Hani Baragwanath Academic Hospital over a 22 year Period
DATE CONSIDERED:	26/08/2016
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Antoinette Cilliers
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	21/11/2016

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 301, Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in August and will therefore be due in the month of August each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX D: PLAGIARISM DECLARATION

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I _____**Meera Ooka**_____ (Student number: **0601674N**) am a student registered for the degree of _____**Masters of Medicine in Paediatrics**___ in the academic year __**2018**_.

I hereby declare the following:

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- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

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