CONFIDENTIAL

INFECTIVE ENDOCARDITIS IN CENTRAL SOUTH AFRICA IN THE HIV ERA- A SURGICAL PERSPECTIVE

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"Submitted in fulfilment of the requirements in respect of the master's degree MMed in the Department of Cardiothoracic Surgery in the Faculty of Health Science at the University of the Free State."

March 2021

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I. Declaration of authorship (own work) reading

"I, Taha H Gwila, declare that the coursework master's degree publishable manuscript on that I herewith submit in a publishable manuscript format for the master's degree qualification MMed at the University of the Free State is my independent work, and that I have not previously submitted it for a qualification at another institution of higher education."

2020/11/30

Principle Investigator Date

II. Acknowledgements

I would like to thank my wife and family who supported me during this journey. I am also grateful for the efforts made by my supervisor Professor Francis Smit and co-supervisors Dr Lezelle Botes and Mr Manie Hanekom to guide and assist me during this process and will be forever grateful.

Table of Contents

I. Declaration of authorship (own work) reading ii
II. Acknowledgements iii
III. ABSTRACT 1
IV. Important Abbreviations 3
V. List of Figures 4
VI. List of Tables 5
VII. List of Appendices 6
1. Literature Review 7
1.1 Background 7
1.2 Epidemiology 7
1.2.1 Infective endocarditis 7
1.2.2 Human Immunodeficiency Virus 8
1.2.3 Rheumatic Heart Disease 9
1.2.4 Other conditions associated with infective endocarditis 11
1.3 Microbiology 12
1.3.1 Culture-negative infective endocarditis 12
1.4 Pathophysiology 13
1.4.1 Colonization of damaged epithelium 14
1.4.2 Colonization of inflamed valve tissues 15
1.5 Clinical manifestations 15
1.6 Diagnosis 15
1.6.1 Duke criteria for the diagnosis of infective endocarditis 16
1.6.2 Imaging 18
1.7 Treatment 20
1.7.1 Prophylaxis 20
1.7.2 Medical therapy 21
1.7.3 Surgical management 21
1.8 Complications 23
1.8.1 Cardiac complications 23

1.8.2 Neurologic complications 24
1.8.3 Systemic emboli and splenic abscess 24
1.8.4 Prolonged fever 24
1.9 Survival 24
1.10 Study rationale 26
1.11 Aim 27
1.12 Objectives 28
List of References 29
Chapter 2- Publishable article 37
1. Abstract: 37
2. Abbreviations: 38
2.1 Introduction 39
2.2 Patients and Methodology 40
2.2.1 Design of study 40
2.2.2 Statistics 42
2.2.3 Ethical considerations 42
2.3 Results 42
2.3.1 HIV infection and demographic data 42
2.3.2 Clinical data 43
2.3.3 Surgical interventions 45
2.3.4 Microbiology 46
2.3.5 Post-operative complications and outcomes 47
2.3.6 Correlation between EuroSCORE II and Mortality. 49
2.3.7 Mortality and CD4 count 49
2.3.8 Survival 50
2.4 Discussion 51
2.5 Limitations 52
2.6 Conclusion 53
2.7 Funding statement 53
2.8 Acknowledgement 53

2.9 Author contributions statement 53
2.10 Conflict of interest statement 54
2.11 List of tables 55
2.12 List of figures 58
3. List of Appendices 63
Appendix - A: Letter of approval from HSREC 63
Appendix - B: Permission from DOH 63
Appendix - C: Permission from HOD 63
Appendix - E: Research protocol approved by HSREC. 63
Appendix - E: Data Collection sheet 111
Appendix - F: Instructions to authors 112
Appendix - G: Turnitin Plagiarism Report 121

III. ABSTRACT

Introduction
Infective endocarditis (IE) remains an evolving disease with a persistently high mortality and morbidity. In Africa, it is predominantly a disease of the young in contrast to the developed world. South Africa represents a very high prevalence of HIV at 21.67% of global HIV infections. Other factors in South Africa include the high prevalence of rheumatic valvular heart disease, low socio-economic status and poverty makes the patient population completely different from the developed world.

The primary aim was to determine the influence of HIV infection on infective endocarditis patients in central South Africa. The secondary aim was to compare the HIV positive patients and HIV negative patients in the context of this disease.

Objectives: To determine the demographics, presentation, indication for surgery, microorganisms, and outcomes of HIV positive versus HIV negative patients presenting with Infective endocarditis.

Methods: Retrospective, analytical cohort study that reviewed the records of adult patients who were tested for HIV and treated surgically for infective endocarditis between 2009 to 2019. Data was compared between the two groups using chi-square or Fisher exact tests for categorical variables. Median and interquartile ranges were used for continuous variables and frequencies and proportions for categorical variables. Significance was set as $p < 0.05$.

Results: From the 141 IE patients who underwent surgery for IE, 105 patients were tested for HIV, 31% (n=33) tested positive. The mean age for both groups was comparable 38.87 versus 39.51 years. Eighty-eight percent (n=29) of positive patients were on HAART. In both groups, there was a male preponderance, 55% vs 46% and 56% vs 44% respectively. The majority of HIV positive (91%) and negative patients (71%) were of African descent, more than 50% of both groups presented with NYHA III&IV, both groups had a medium-high risk of developing IE (HIV (+) 72%; HIV (-) 62%). Prevention of embolization was the main indication for surgery in HIV (+) group and heart failure in the negative group. In both groups a greater proportion of patients had left sided native valve endocarditis 95% and RHD was predominantly the underlying pathology 60%, requiring mechanical prostheses mainly in the mitral 46% and aortic 33% position. Right sided endocarditis represents <5% and only 2 out 105 patients confirmed IVDA's, Staphylococcus and Streptococcus dominated cultured organisms with staphylococcus species being more frequent, culture

negative endocarditis remains high in both groups, with 47% HIV (-) group vs 33%. Morbidity was limited in both groups 12% vs 11% with no major difference. The overall mortality was higher in the HIV (+) group (39% vs 34%); however, the in-hospital mortality was higher in the HIV (-) group (17% vs 12%).

Conclusion

Infective endocarditis remains a deadly disease with high short- and long-term mortality. HIV infection has minimal to no impact on perioperative and in- hospital morbidity and mortality, left heart endocarditis is the dominant disease within the HIV patients due to the rheumatic valvular heart disease as opposed to right heart endocarditis. The high prevalence of culture negative endocarditis warrants further investigation. Given the low number of patients in this cohort study, further prospective studies need to be conducted to establish a statistical significance between the HIV (+) and (-) groups.

Keywords: Infective Endocarditis; Cardiac surgery; Human immunodeficiency virus Etiology; Epidemiology, microorganisms, and outcomes.

IV. Important Abbreviations

ART	Anti-retroviral therapy
CHD	Congenital heart disease
ESC	European Society of Cardiology
FDG	Fluorodeoxyglucose
IE	Infective endocarditis
IQR	Inter quartile range
IVDA	Intravenous drug abuse
DM	Diabetes mellitus
HIV	Human Immunodeficiency virus
HAART	Highly active antiretroviral therapy
HF	Heart Failure
MRI	Magnetic resonance imaging
MSCT	Multi slice computer tomography
NHLS	National Health Laboratory Service
NYHA	New York Heart Association
HACEK	Haemophilus sp., Actinobacillus, actinomycetemcomitans, Cardiobacterium, Eikenella, Kingella
PCR	Polymerase chain reaction
PVE	Prosthetic valve endocarditis
RF	Renal failure
SPECT/CT	Single-photon emission CT
TAVR	Transcatheter aortic valve replacement
TOE/ TEE	Trans esophageal echocardiography
PET/CT	Positron emission tomography
PVE	Prosthetic valve endocarditis

V. List of Figures

Figure 1.1. Bacterial valve colonization……..……14

Figure 1.2. Bacterial valve colonization……..……18

Figure 1.3. An approach to the diagnostic use of echocardiography…….....19

Figure 2.1. Valve pathology in HIV positive and HIV negative patients……45

Figure 2.2. Correlation between EuroScore ii and Survival (mortality)……..49

Figure 2.3. Difference in the CD4 count in HIV patients for in-hospital and long-term mortality **p < 0.01……..……..50

Figure 2.4. Survival of HIV positive patients and HIV negative patients. Significance set as p< 0.05……..……51

VI. List of Tables

Table 1.1. Studies on the prevalence of rheumatic heart disease in Africa.....10

Table 1.2. Definition of infective endocarditis according to the modified Duke Criteria.....16

Table 1.3. Definition of the terms used in the modified Duke Criteria.....17

Table 2.1. Demographics and prevalence.....43

Table 2.2. Clinical data HIV (+) versus HIV (-).....44

Table 2.3a. Primary valve pathology in HIV (+) and HIV (-) patients.....45

Table 2.3b. Types of surgical interventions for HIV (+) and HIV (-) patients.....46

Table 2.4. Microorganisms cultured in HIV (+) and HIV (-) groups.....47

Table 2.5. Post-operative complications and outcomes of HIV(+) and HIV(-) groups.....48

VII. List of Appendices

Appendix A. Letter of approval from Research Ethics Committee

Appendix B. Permission from DOH/NHLS

Appendix C. Permission from HOD

Appendix D. Copy of the research protocol approved by the HSREC

Appendix E. Data Collection Form

Appendix F. Instructions to authors of the named peer reviewed journal

Appendix G. A summary report compiled in the Turnitin Plagiarism Search Engine

1. Literature Review

1.1 Background

Infective endocarditis (IE) refers to an active intracardiac infection that resides on one or more heart valve surfaces. Other cardiac structures can also be involved as well as endovascular infection can also occur. Other cardiac structures include the sub valvular apparatus, cardiac muscles, and pericardium (Mauri et al., 2001). Infections of the inner surface of the heart are to as infective endocarditis, which can be caused by any microorganism form bacterial or fungal species (Thiene and Basso, 2006).

1.2 Epidemiology

1.2.1 Infective endocarditis

Infective endocarditis (IE) is a rare but remains an evolving disease with persistently high mortality and morbidity (Prendergast, 2006). In the United States and Western Europe, the incidence of community-acquired native-valve endocarditis in most recent studies is 1.7 to 6.2 cases per 100,000 person-years (Mylonakis and Calderwood, 2001). Surprisingly, the incidence has not declined over the last 30 years, and now with more health care interventions, such as pacer/defibrillators, and an increasingly elderly population with degenerative valvular heart disease, the number susceptible to endocarditis is increasing. Given the weak evidence for endocarditis prophylaxis, there remains a large population at risk (Bashore et al., 2006).

Epidemiological studies suggest a bimodal age distribution, with the younger population dominated by patients with rheumatic heart disease or congenital heart disease and injection drug use (Mauri et al., 2001). As increased longevity has given rise to degenerative valvular disease, placement of prosthetic valves, and increased exposure to nosocomial bacteremia, the median age of patients has gradually increased; it was 30 to 40 years during the pre-antibiotic era and 47 to 69 years more recently (Mylonakis and Calderwood, 2001). Men are reported to be more often affected than women (in a ratio of 2:1) (Benyon et al., 2006).

1.2.2 Human Immunodeficiency Virus

Sub-Saharan Africa with the South African population currently has the largest prevalence of HIV/AIDS in the world. The region has almost a third of the world's HIV positive population with less than 2% of the global population. The HIV prevalence dramatically increased during the 1990's with epidemiological studies showing increases from <1% to 24.5% between the start and end of the decade (Barron et al., 2013).

The local government response was very slow and indecisive which aided in the increase. From the early 2000's government changed their stance regarding HIV, which has led to a multitude of campaigns to affect change. These campaigns have made major strides in curbing increases in HIV prevalence, but the percentages are not declining. In 2016 government adopted the UNAIDS 90-90-90 strategy which aims to have 90% of patients with HIV diagnosed and on combination antiretroviral treatment with a nighty percent viral suppression (UNAIDS, 2016a).

Combination antiretroviral therapy is of critical importance and without it, patients experience increased CD4+ T cell loss combined with immunological abnormalities, which can result in increased susceptibility to opportunistic infections. Combination therapy has been pivotal in reducing HIV viral load, allowing the increase of CD4+ T cells and reducing the risk of developing AIDS (Deeks et al., 2015). These patients however still present a higher-than-normal risk of developing bloodstream infections and IE (Taramasso et al., 2016).

The relationship and implications of patients having HIV and developing IE are not yet clear. Due to the HIV infection and the susceptibility to secondary infections, one would expect IE to be more prevalent in HIV positive patients, but it is not considered a complication of HIV/AIDS. It is almost limited exclusively to HIV patients who are IV drug users in the western societies (Currie et al., 1995; Yunis & Stone 1998). Outcomes observed in patients with active systematic disease was poor, especially

with extreme immune suppression (CD4 count < 200 cells/mL) (Pulvirenti et al., 1996). HIV infection on its own therefor does not seem to predispose patients to more severe outcomes of IE or a risk factor despite the immune suppression observed (Currie, 1995).

1.2.3 Rheumatic Heart Disease

A large spectrum of heart diseases may predispose the onset of infective endocarditis. Rheumatic valve disease, particularly mitral and aortic valve steno-incompetence, has been considered for years as the major risk factor. In the 1970s, rheumatic valve disease was the predisposing lesion for infective endocarditis, accounting for 20% to 25% of cases, whereas in the 1980s, it dropped to 7–10%. Although the frequency of rheumatic valve disease has diminished in Europe and North America, it is still endemic in Third World countries where it represents by far the leading predisposing factor for infective endocarditis, especially in children (Table 1.1) (Thiene and Basso, 2006).

Table 1.1. Studies on the prevalence of rheumatic heart disease in Africa (reproduced from Nkomo, 2007).

PREVALENCE OF RHEUMATIC HEART DISEASE IN AFRICA					
Country (city)	Year of study	Number screened	Age (years)	Prevalence (per 100 population)	Echo
Algeria (Setif)	1990	11228	6 - 19	2	? No
Algeria (Oran)	1990	15430	6 - 19	1.94	? No
Egypt (Cairo)	1986	60022	6 - 15	1.5	? No
Cameroon (Yaounde)	1988-9	-	6 - 19	2.1	No
Congo (Brazzaville)	1996	2153	5 - 16	1.4	Yes
DR Congo (Kinshasa - Kinsenso ans Sanga Mamba)	1996	4848	5 - 16	14	Yes
Ethiopia (Butajira)	1992	3235	13.4 (3.5)	4.6	? Yes
Ethiopia (Addis Ababa)	1999	9388	13 – 15 (7.1 los SES, 1.0 high SES)	6.4	Yes
Ivory coast (4 areas)	1977-8	20013	6 - 22	1.45	No
Kenya (Kakamega)	1985	3631	5 -15	1.7	No
Kenya (Nairobi)	1994	1115	5 -15	2.7	Yes
Mali (Bamako)	1986	14351	5 -15	2.9	? Yes
Nigeria (Lagos)	1978	12755	6 -12	3	No
Republic of Guinea (Conakry)	1992	27110	6 -25	3.9	Yes
South Africa (Soweto)	1972	12050	2 -18	6.9 (peak 19.2 in the age group 15-18 years)	No
South Africa (lnanda)	1984	4408	4 -18	1	No
Sudan (Safaha Town)	1986-1989	13332	5 -15	3	Yes
Zambia (Lusaka)	1986	5200	5 -15	14.6	Yes in subset
Zambia (Lusaka)	1987	11 944	5 -16	12.5	Yes in 25%

The incidence of RHD worldwide has declined over the last years, yet it remains endemic in overcrowded areas where basic health care facilities are unreachable (Okello et al., 2012). In the South African populations, recent study by (Koshy et al., 2018) reported 80 % of infective endocarditis patients had RHD as a predisposing heart pathology, indicating a significant part of the South African population at risk of developing IE. Rheumatic heart disease is a one of few, if not only the preventable acquired heart disease affecting poor and middle-income countries that can lead to high morbidity and mortality, attention to early recognition and management is crucial to prevent the risk of developing a more serious and deadly disease namely infective endocarditis (Peters et al., 2019).

1.2.4 Other conditions associated with infective endocarditis

Other conditions associated with an increased incidence of infective endocarditis include poor dental hygiene, long-term hemodialysis, and diabetes mellitus. (Mylonakis and Calderwood, 2001). The presence of diabetes mellitus (DM) has been associated with even worse outcomes in patients with IE. The prevalence of DM among IE-patients is around 17%, recently found that the duration and complications of diabetes mellitus are an independent risk for IE. There was a stepwise increase in the associated risk of IE with increasing duration of DM – an effect independent of age and there was an increase in the associated risk of IE with increased severity and number of diabetic late-stage complications (Østergaard et al., 2019).

Infection with human immunodeficiency virus (HIV) may independently increase the risk of infective endocarditis. In the developed world patients infected with HIV, infective endocarditis is usually associated with injection-drug use or long-term indwelling intravenous catheters (Mylonakis and Calderwood, 2001).

Transcatheter interventions are becoming more and more used in the recent era, with technology improvement, old frail patients who were not considered operable for aortic valve surgery are now TAVR candidates, with more cardiac interventions for other comorbid conditions, this will eventually lead to more risk of developing

bacteraemia and IE. This specific cohort represents a serious challenge for management of TAVR related endocarditis (Regueiro et al., 2016). The incidence of IE post TAVR was 1.1% per person- year, within the 1st six month of their procedure, and an in-hospital mortality and 1-year mortality ranging between 47%-75% respectively. These extremely high figures raise the importance of developing more better and effective policies of prevention and better valve characteristics, in opposed to treating this subgroup of patient that were deemed very high risk for surgery before the initial procedure (Cahill et al., 2017).

1.3 Microbiology

The number of organisms involved with infective endocarditis are evolving with more uncommon species namely the HACEK group were cultured (Mauri et al., 2001). To date gram + bacteria represent the most cultured organisms, more recently studies showed Staphylococcus aureus is more dominant than Streptococcus viridans (Mylonakis and Calderwood, 2001). A change in the patient profile from being younger age with structural heart disease to older frail patients with more health care-associated endocarditis has been described in the developed world (Selton-Suty et al., 2012).

1.3.1 Culture-negative infective endocarditis

Culture-negative infective endocarditis is not uncommon, and it can be as high as 31% of the total IE cases, giving a diagnostic and therapeutic challenge, the most obvious explanation to this phenomenon is the administration of antibiotics prior to obtain the blood cultures. Specific serological testing with specialized media is needed to isolate such organisms, that consumes time because of the slow growth reported (Raoult et al., 2005).

It has been shown that long-term pre-operative antimicrobial treatment had a negative impact on microbiological tests done on resected endocardial material. After 2 weeks of therapy, all valve cultures were negative, but PCR was positive in half of

the cases. PCR aided in diagnostic work-up, especially in blood culture-negative cases (Halavaara et al., 2019).

1.4 Pathophysiology

Numerous processes and steps are involved that allow a microorganism to migrate to the heart valves, replicate and form large vegetations. The majority of infective endocarditis (IE) occurs in the setting of predisposing cardiac disease (Mauri et al., 2001).

The pathophysiological picture of infective endocarditis is demonstrated by several mechanisms:

- Direct extension of infection which can lead to severe valvular dysfunction (valvular regurgitation being the most common manifestation),
- Embolization causing distal infarction or infection,
- Hematogenous seeding of distant organs may create abscesses, and
- Immune complex deposition producing organ dysfunction such as glomerulonephritis and arthritis (Mauri et al., 2001).

The adherence of the bacteria to the damaged endothelial surface takes place in two possible mechanisms (figure 1.1).

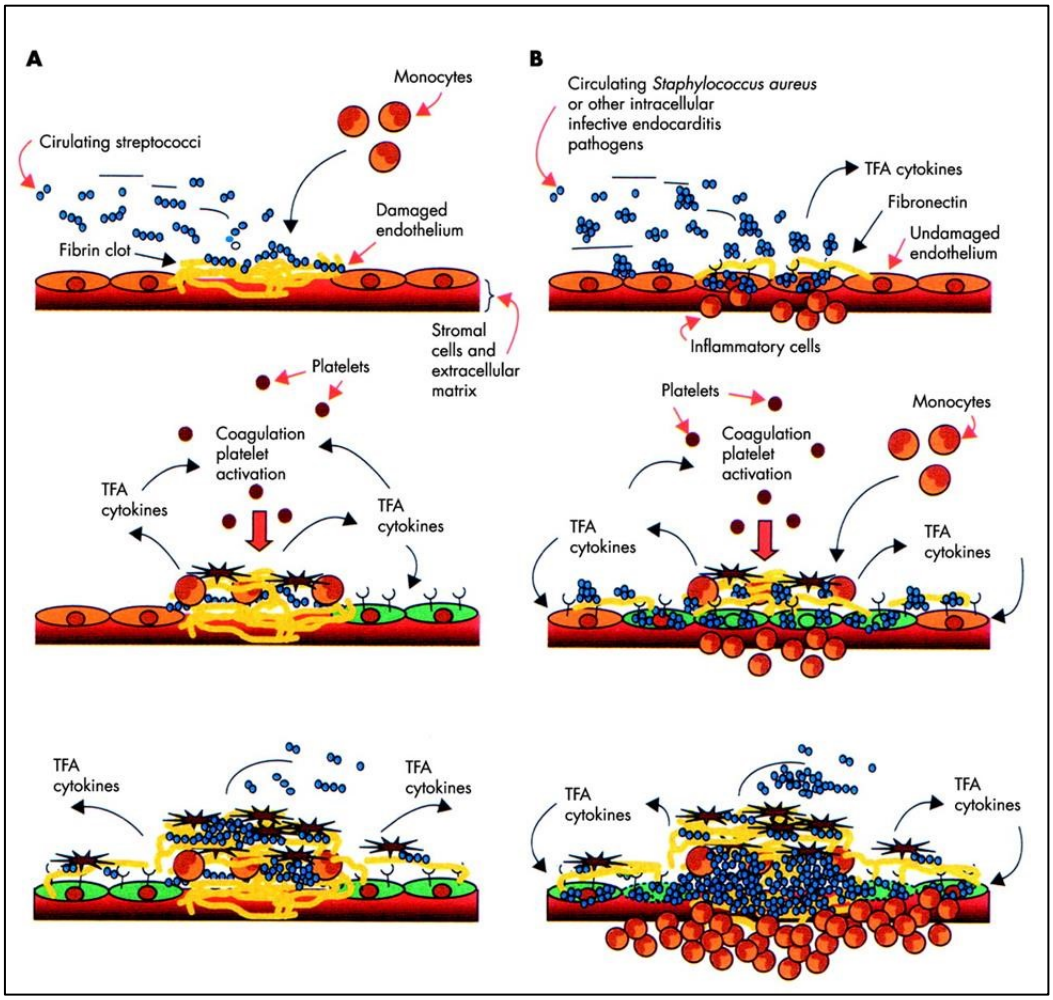

Figure 1.1. Bacterial valve colonization (reproduced from Prendergast, 2005).

1.4.1 Colonization of damaged epithelium

Stromal cells that are exposed, in conjunction with extracellular matrix proteins lead to the forming of fibrin-platelet clots that can bind to the streptococci. The clots can attract monocytes that produce tissue factor activity (TFA) and cytokine which lead to the activation of coagulation cascades. The cascades lead to the attraction and activation of blood platelets, which induce integrin, cytokine and TFA from endothelial cells, which promote vegetative growth (Prendergast, 2005).

1.4.2 Colonization of inflamed valve tissues

Localized inflammation causes the endothelial cells to express integrin's which bind plasma fibrinonectin on to which the microorganisms can bind, which result in then their internalization into the endothelial cells. This leads the cells to trigger inflammation and coagulation, which all promotes vegetative growth. The cells are eventually lysed by the secretion of hemolysins that are membrane active proteins (Prendergast, 2005).

1.5 Clinical manifestations

Infective endocarditis can frequently present as to intra or extracardiac manifestations according to the virulence of the infection and timing of presentation. Most commonly, fever is observed, except for patients with severe heart, liver or chronic renal failure and patient who received antibiotic treatment, it might not be present. Additional observed symptoms include malaise, weight loss and nightly sweats. High percentage of patients present clinically with a heart murmur, conjunctivitis or petechiae on the skin (Mylonakis and Calderwood, 2001).

Classic textbook signs may still be seen in the developing world, although peripheral stigmata of infective endocarditis (Osler's nodes, Janeway lesions) are increasingly uncommon elsewhere, as patients generally present at an early stage of the disease (Benyon et al., 2005).

1.6 Diagnosis

The combination of three important aspects (clinical observations, laboratory results and echocardiographic information are crucial for the diagnosis of infective endocarditis (Mylonakis and Calderwood, 2001). In 1994, the Duke criteria for the diagnosis of infective endocarditis were proposed to increase the number of definite diagnoses (Mauri et al., 2001).

1.6.1 Duke criteria for the diagnosis of infective endocarditis

The Duke criteria stratify patients with suspected infective endocarditis (IE) into three categories (Table 1.2):

- Definite cases – identifies either clinically or pathologically (IE proved at surgery/autopsy),
- Possible cases – not meeting the criteria for definite IE and
- Rejected cases – no pathological evidence of IE at autopsy or surgery (Baddour et al., 2005).

Table 1.2. Definition of infective endocarditis according to the modified Duke criteria (reproduced from Bayer et al., 1998).

Definite IE
Pathological criteria • Microorganisms: demonstrated by culture or histology in a vegetation, in a vegetation that has embolized, or in an intracardiac abscess, or • Pathological lesions: vegetation or intracardiac abscess present, confirmed by histology showing active endocarditis. **Clinical criteria**, using specific definitions listed below. • 3 major criteria, or • 1 major and 3 minor criteria, or • 5 minor criteria
Possible IE
• Findings consistent with IE that fall short of "Definite" but not "Rejected."
Rejected
• Firm alternate diagnosis for manifestations of endocarditis, or • Resolution of manifestations of endocarditis with antibiotic therapy for $\leq$4 days, or • No pathological evidence of IE at surgery or autopsy, after antibiotic therapy for $\leq$4 days

A diagnosis of IE is based on the presence of either major or minor clinical criteria. Clinically definite IE by the Duke Criteria requires the presence of two major criteria, one major criterion and three minor criteria, or five minor criteria (Table 1.3).

Table 1.3. Definition of the terms used in the modified Duke Criteria (Reproduced from Bayer et al., 1998).

Definition of the terms used in the modified Duke Criteria

Major criteria

1. Positive blood culture for IE

A. Typical microorganism consistent with IE from 2 separate blood cultures as noted below:

(i) viridans streptococci, [1] Streptococcus bovis , or HACEK group, or

(ii) community -acquired Staphylococcus aureus or enterococci, in the absence of a primary focus, or

B. Microorganisms consistent with IE from persistently positive blood cultures defined as

(i) ≥2 positive cultures of blood samples drawn >12 hours apart or

(ii) all of 3 or a majority of ≥4 separate cultures of blood (with first and last sample drawn ≥1 hour apart)

2. Evidence of endocardial involvement

A. Positive echocardiogram fo r IE defined as

(i) oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation, or

(ii) abscess, or

(iii) new partial dehiscence of prosth etic valve, or

B. New valvular regurgitation (worsening or changing of preexisting murmur not sufficient)

Minor criteria

1. Predisposition: predisposing heart condition or intravenous drug use

2. Fever: temperature 38.0 °C

3. Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions

4. Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth spots, and rheumatoid factor

5. Microbiological evidence: positive blood culture but does not meet a major criterion as noted above [2] or serological evidence of active infection with organism consistent with IE

6. Echocardiographic findings: consistent with IE but do not meet a major criterion as noted above

---

[1] Includes nutritionally variant strains (Abiotrophia species).

[2] Excludes single positive cultures for coagulase -negative staphylococci and organisms that do not cause endocarditis.

1.6.2 Imaging

1.6.2.1 Echocardiography

Echocardiography plays an important role in the diagnosis and management of infective endocarditis (Baddour et al., 2005). The information that can be provided using echocardiogram facilitate the surgical decision making, such information including the size and mobility of the vegetations, structure and function of affected valve, and overall ventricular function (figure 1.2) (Mauri et al., 2001).

Figure 1.2. Bacterial valve colonization [3D TEE en-face view of mitral valve demonstrating multiple vegetations (arrows)] (reproduced from Prendergast, 2005).

Echocardiography is not an appropriate screening test in the evaluation of patients with fever or a positive blood culture that is unlikely to reflect IE. Nevertheless, some form of echocardiography should be performed in all patients suspected of having IE (Prendergast, 2005).

Transesophageal echocardiography (TEE) is safe in experienced hands and has a sensitivity for the detection of vegetations in IE (figure 1.3). TEE images benefit from higher ultrasonic frequencies, which improve spatial resolution and the elimination of interference from interposed tissues. TEE has a substantially higher sensitivity

(76% to 100%) and specificity (94%) than TTE for perivalvular extension of infection because the TEE transducer in the esophagus is in physical proximity to the aortic root and basal septum, where most such complications occur (Bayer et al., 1998).

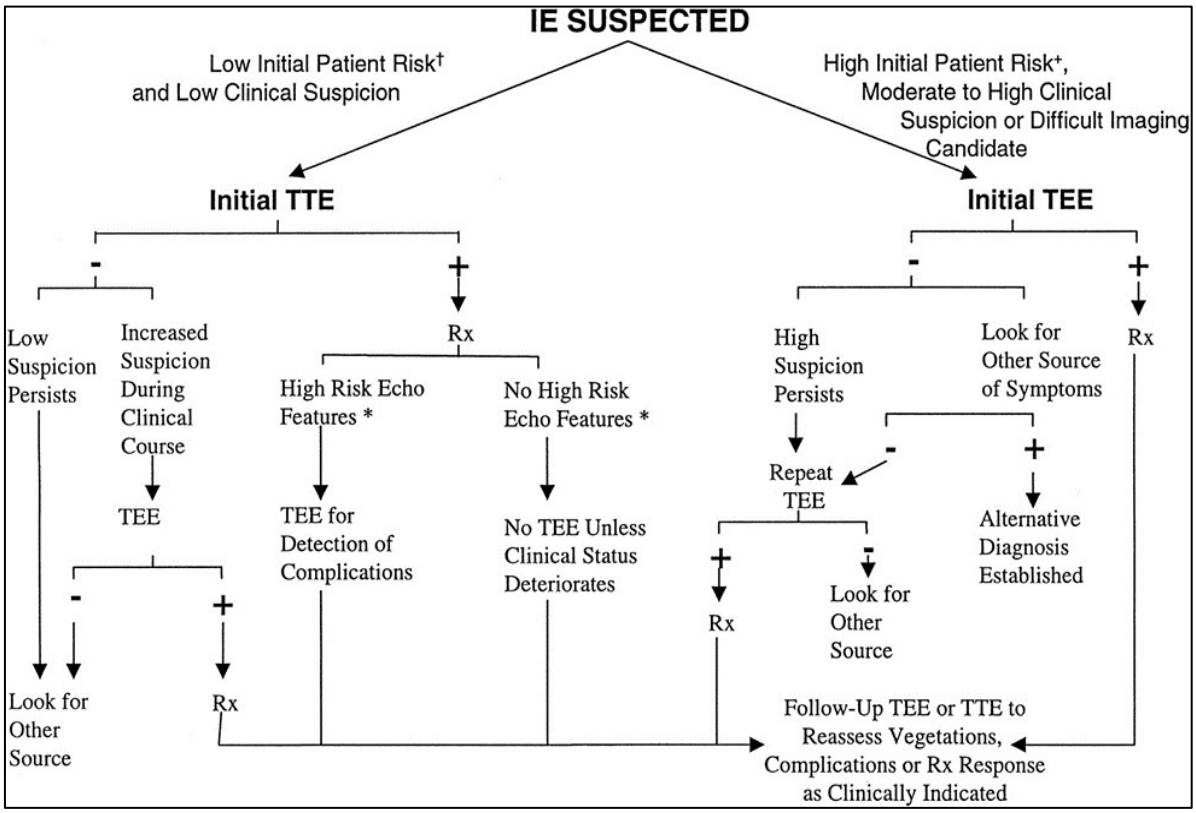

Figure 1.3. An approach to the diagnostic use of echocardiography (echo). *High-risk echocardiographic features include large and/or mobile vegetations, valvular insufficiency, a suggestion of perivalvular extension, or secondary ventricular dysfunction. † For example, a patient with fever and a previously known heart murmur and no other stigmata of IE. +High initial patient risks include prosthetic heart valves, many congenital heart diseases, previous endocarditis, new murmur, heart failure, or other stigmata of endocarditis. Rx indicates antibiotic treatment for endocarditis (Adapted from Bayer et al., 1998).

1.6.2.2 Multi-slice computed tomography (MSCT)

The use of CT coronary angiography is shown to be safe and good alternative technique for evaluation of coronary arteries if needed in the settings of acute aortic valve endocarditis where risk of embolization is high with conventional coronary angiography (Hekimian et al., 2010). MSCT is helpful in evaluating the extent of infection and abscess formation around the aortic valve and aortic root. It has been shown that the accuracy is as good as TOE (Feuchtner et al., 2009). CT scan with

contrast can be used as an acceptable alternative to MRI in evaluating intracranial bleeds and infarcts in critically ill patients with IE (Goddard et al., 2005).

1.6.2.3 Magnetic Resonance Imaging

In acute infective endocarditis, MRI demonstrated a frequent intracerebral lesion in up to 80% of patients irrespective of their neurological symptoms. (Snygg-Martin et al., 2008). Cerebral MRI also aids in the diagnosis of IE as it adds an extra criterion to the Duke's criteria for patients who were asymptomatic but positive cerebral finding (Li et al., 2000).

1.6.2.4 Nuclear Imaging

Radiolabelled White blood cells SPECT/CT and FDG PET/CT usage to aid the diagnosis of IE in the category of possible IE by Duke's criteria has shown good results, 18F-FDG PET/CT also reported useful tool to detect extra cardiac metastatic infectious emboli (Bonfiglioli et al., 2013). In prosthetic valve dysfunction FDG PET/CT is capable of distinguishing infective etiologies from others and adds a novel criterion in diagnosing prosthetic valve endocarditis (Saby et al., 2013).

1.7 Treatment

The optimal management of infective endocarditis (IE) relies on a close collaboration between a broad range of medical specialties Known as the 'Endocarditis Team' that includes cardiology, cardiac surgery, anesthesiology, infectious diseases, internal medicine, neurology, intensive care, microbiology, and radiology. This is a class IIa indication level of evidence B according to the 2015 ESC guidelines in the management of complicated IE (Habib et al., 2015).

1.7.1 Prophylaxis

Treatment starts with prevention that includes general measures for all population (dental and skin hygiene, avoidance of tattooing and piercing, encouraging of using peripheral IV accesses over central catheters) and antibiotic prophylaxis for high and

intermediate risk populations performing high risk procedures including dental, cardiac, and vascular interventions (Duval and Leport, 2008).

High-risk population according to the 2015 ESC guidelines summarized as follows:

1- Patients with intracardiac implants (valve prostheses or devices) had higher risk of developing IE and higher morbidity and mortality (Lalani et al., 2013).
2- Patients with previous history of endocarditis, the chance of developing a second episode is higher with higher adverse outcomes (Chu et al., 2005).
3- Patients with unattended cyanotic congenital heart disease (CHD) and operated CHD with prosthetic implants within the six months of surgery. (Baumgartner et al., 2010; Knirsch and Nadal, 2011).

1.7.2 Medical therapy

Medical treatment in the form of antimicrobial therapy to eradicate the causative organism using bactericidal regimens is the hallmark of managing this disease. With the surgical role in removing infected tissue and treating structural complications (Durack et al., 1974; Wilson et al., 1978).

Bactericidal antibiotics with adequate therapeutic serum levels for a longer duration of treatment (4-6) weeks is necessary to eradicate dormant organisms, the duration of treatment differs between shorter as in sensitive bacteria and longer course of management for more resistant species (Prendergarst, 2006).

1.7.3 Surgical management

Early surgical intervention is important in the management of IE, however deciding when to intervene is more complicated. For patients with NYHA 3 and 4 heart failure, large vegetations possessing embolic risk and uncontrolled sepsis despite accurate type and dosing of antibiotics urgent surgical intervention is recommended. The exception being patients who suffered cerebral infarction or more importantly intracerebral hemorrhage whose surgery should be delayed between two and four weeks. The patient risk and benefit analysis should be performed in an individual

manner to determine the urgency of surgical intervention. The decision to intervene should always be based on the benefits exceeding the operative risk involved (Kang, 2015).

1.7.3.1 Surgery for heart failure

One of the most severe and common complication of infective endocarditis is heart failure, and this represents the most frequent indication for early surgical intervention in both native and prosthetic valve endocarditis irrespective of age and stage of heart failure (cardiogenic shock) (Habib et al., 2015).

1.7.3.2 Surgery for infection control

Uncontrolled infection in the form of local extension of infection (abscesses, false aneurysm or enlarging vegetations), or PVE caused by virulent organisms (Staph infection and HACEK gram -ve species), persistent positive blood cultures despite adequate and accurate antimicrobial therapy, or fungi and multi-resistant organisms cultured, early surgery is indicated (Habib et al., 2015; Kang, 2015).

1.7.3.3 Surgery to prevent embolism.

Systemic embolization is very common in EI. At presentation twenty to fifty percent of patients developed embolic phenomena, it falls down to 6-20 % after initiation of antibiotic therapy. The risk continues to be high for the 1st two weeks of treatment (Vilacosta et al., 2002), hence surgery must be performed in an urgent basis (within days) to prevent embolic events (Thuny et al., 2005).

The decision to operate for emboli prevention is not as clear, it has to be individualized for each patient, the main indications for early operation are based on certain findings, more importantly the size and mobility of the vegetations, previous one or more embolic event, presence of other complications, and the duration of antibiotic therapy (Thuny et al., 2011).

The 2015 ESC guidelines recommend urgent surgical intervention for patients who has >1 cm vegetations on the mitral or aortic valves with previous one or more embolic events despite appropriate antibiotic therapy as well as for patients with severe valve dysfunction. Surgery can also be performed on patients with very large vegetation of >3cm, and for those who has an isolated vegetation of >1.5 cm surgery may be performed if the valves can be preserved (Thuny et al., 2005).

Surgery for Infective endocarditis has a very high mortality even in experienced centers exceeding any valvular heart surgery (Thuny et al, 2012). The reported in hospital and one-year mortality according to multicenter study results were 15-20% and up to 40% respectively (Kang et al., 2012).

1.8 Complications

Complications related to IE are quite frequent, the number and rate of developing these complications differs between the studies, where 57 % of patients having one complication and 26% with two and about 14% with three or more complications (Mocchegiani et al., 2009). These complications can be either cardiac or extracardiac, where intracardiac is related to the direct spread of infections and extra cardiac can be related to embolic event or immune complex (Habib et al., 2015). The development of such complications also depends on the causative organisms, the time between developing the disease and the initiation of treatment and treatment modality (Cahill et al., 2017).

1.8.1 Cardiac complications

The most important cardiac complication of infective endocarditis is the development of heart failure, the presence of moderate to severe HF at presentation is the most significant predictor of in-hospital and late mortality (Nadji et al., 2009). Heart failure usually develops from direct destruction of cardiac valves by the infection leading to acute or worsening preexisting regurgitation, and less commonly the development of fistula or obstruction of a valve due to a large vegetation (Anguera et al., 2005).

1.8.2 Neurologic complications

As described above embolic phenomena is very common, it affects the brain in 65% of cases with 20-40% of which develop neurological complications (Mylonakis and Calderwood, 2001). Stoke is proven to be an independent worse prognostic factor for IE patients (Thuny et al., 2007). The majority of reported cerebrovascular accidents were mainly ischemic; the presence of hemorrhagic stroke poses a great challenge in management of this subgroup in terms of early surgical interventions. Surgery should be delayed to >4 weeks (Yoshioka et al., 2012).

1.8.3 Systemic emboli and splenic abscess

Systemic embolization is a frequent complication of left sided endocarditis, where majority happens before admissions (Hubert et al., 2013). The brain and spleen being the most common sites. Splenic infarcts are usually asymptomatic, persistent fever and bacteremia raises the possibility of splenic abscesses, and further work up is needed (abdominal sonar, CT, or MRI) for diagnosis (Bonfiglioli et al., 2013). Surgery is rarely indicated for splenic infarction but should be considered in case of rupture or large abscesses refractory to antibiotics (Akhyari et al., 2012).

1.8.4 Prolonged fever

Normally fever subsides 2 to 3 days of initiation of antibiotics in non-virulent infections. Fever that lasts more than 2 weeks is considered prolonged and should raise the possibility of more serious complication as in local extension of infection to the paravalvular areas and myocardium forming abscesses. It can also occur due to septic emboli forming remote abscesses, one should also consider drug reactions especially if recurrent fever after resolving (Mylonakis and Calderwood, 2001).

1.9 Survival

Despite advances in medical knowledge, technology and antimicrobial therapy, infective endocarditis (IE) is still associated with devastating outcomes. Irrespective of the follow-up period, a significantly higher mortality rate was reported in IE patients, and the burden of IE-related complications was immense. The overall pooled

mortality estimates for IE patients who underwent short- and long-term follow-up were 20% and 37% respectively (Abegaz et al., 2017).

Even after successful treatment of an episode of infective endocarditis, long-term mortality and morbidity remain high. Factors predictive of long-term mortality are age > 55 years, congestive heart failure, and the initial presence of a few symptoms of endocarditis. Moreover, early valve replacement has the potential to improve long-term survival in a wide range of patients with infective endocarditis (Netzer et al., 2002).

According to the 2015 ESC Guidelines for the management of infective endocarditis, prognosis was influenced by 4 important factors categorized as follows:

1) Patient's characteristics:
    a. Old age
    b. DM
    c. PVE
    d. Comorbidities (frailty, immunosuppression).
2) Clinical complications of IE:
    a. HF
    b. RF
    c. Hemorrhagic stroke
    d. Septic shock.

3) Causative microorganism:
    a. Staph. aureus
    b. Fungi
    c. Non-HACEK Gram-negative bacilli

4) Echocardiographic findings
    a. Periannular complications
    b. Severe left-sided valve regurgitation
    c. Poor LVEF
    d. PAH
    e. Large vegetations

f. Severe prosthetic valve dysfunction
g. Premature mitral valve closure and other signs of elevated diastolic pressures.

To summarize, assessing prognosis can be easily established for all patients admitted with IE by using their clinical, microbiological and echo data to aid in decision making with regards to the initial management plan for better outcomes (Habib et al., 2015). Patients who present with heart failure and complicated peri-annular endocarditis and/ or culture positive for S. aureus represents a highest mortality and early surgical treatment is required (San et al., 2007). The worst outcome reported was amongst those patients who needed surgery but could not receive it due to the prohibited risk for surgical intervention (Mirabel et al., 2014).

1.10 Study rationale

Infective endocarditis (IE) remains an evolving disease with persistently high mortality and morbidity (Prendergast, 2006). The incidence of infective endocarditis has not declined over the last 30 years, and now with more health care interventions, such as pacer/defibrillators, and an increasingly elderly population with degenerative valvular heart disease, the number susceptible to endocarditis is increasing. Given the weak evidence for endocarditis prophylaxis, there remains a large population at risk (Bashore et al., 2006).

While the incidence of rheumatic valve heart disease has dropped significantly in the western and developed nations, yet still endemic in the developing countries, and accounts as the major risk factor for developing infective endocarditis (Thiene and Basso, 2006). Sub-Saharan Africa with the South African population currently has the largest prevalence of HIV/AIDS in the world. Combination therapy has been pivotal in reducing HIV viral load, allowing the increase of CD4+ T cells and reducing the risk of developing AIDS (Deeks et al., 2015). These patients however still present a higher-than normal risk of developing bloodstream infections and IE (Taramasso et al., 2016).

The relationship and implications of patients having HIV and developing IE are not yet clear. Due to the HIV infection and the susceptibility to secondary infections, one would expect IE to be more prevalent in HIV positive patients, but it is not considered a complication of HIV/AIDS. It is almost limited exclusively to HIV patients who are IV drug users in the western societies (Currie et al., 1995; Yunis and Stone 1998).

Outcomes observed in patients with active systematic disease was poor, especially with extreme immune suppression (CD4 count < 200 cells/mL) (Pulvirenti. *et al.*, 1996). HIV infection on its own therefor does not seem to predispose patients to more severe outcomes of IE or a risk factor except in patients with severe immunosuppression (Currie et al., 1995).

In recent studies in South Africa, clinical features, and natural history of infective endocarditis within the context of HIV and HAART have not been extensively studied and relied largely on, uncontrolled, studies reporting from different areas of the country. The need for well-structured, well-designed trials representing the current disease patterns is of high importance (Naidoo and Shien 2009; Koegelenberg et al., 2003; Koshy et al., 2018).

1.11 Aim

The aim of the study was to compare the outcomes between HIV positive and HIV negative surgical patients with infective endocarditis in central South Africa in the current era.

1.12 Objectives

- Identify adult patients with infective endocarditis according to the modified Duke's criteria in patients that received heart valve surgeries between 2009-2019 from the departmental database.
- Determine underlining pathologies and risks for endocarditis.
- Risk stratifications (Euro score II) and comorbidities.
- Type of surgical interventions, outcomes, and complications.
- Comparison of outcome and survival between the HIV positive and negative groups.

List of References

Abegaz TM, Bahagavathul AS, Gebreyohannes EA, Mekonnen AB, Abebe TB. Short- and long-term outcomes in infective endocarditis patients: a systematic review and meta-analysis. BMC Cardiovasc Disord 2017; 17; 291.

Akhyari P, Mehrabi A, Adhiwana A, Kamiya H, Nimptsch K, Minol JP, Tochtermann U, Godehardt E, Weitz J, Lichtenberg A, Karck M, Ruhparwar A. Is simultaneous splenectomy an additive risk factor in surgical treatment for active endocarditis? Langenbecks Arch Surg 2012; 397: 1261–1266.

Alarcon A, Ripoll T, Navas E, Gonzalez-Juanatey C, Cabell CH, Sarria C, GarciaBolao I, Farinas MC, Leta R, Rufi G, Miralles F, Pare C, Evangelista A, Fowler VG Jr, Mestres CA, de Lazzari E, Guma JR. Aorto-cavitary fistulous tract formation in infective endocarditis: clinical and echocardiographic features of 76 cases and risk factors for mortality. Eur Heart J 2005; 26: 288–297.

Anguera I, Miro JM, Vilacosta I, Almirante B, Anguita M, Munoz P, Roman JA, de Alarcon A, Ripoll T, Navas E, et al, Aorto-Cavitary Fistula in Endocarditis Working Group. Aorto-cavitary fistulous tract formation in infective endocarditis. Clinical and echocardiographic features of 76 cases and risk factors for mortality. Eur Heart J 2005; 26: 288 –297.

Baddour LM, Wilson WR,Bayer AS, Fowler VG, Bolger AF, Levison ME, Ferrieri P, Gerber MA, Tani LY, Gewitz MH, Tong DC, Steekelberg JM, Baltimore RS, Shulman ST, Burns JC, Falace DA, Newburger JW, Pallasch TS, Takahashi M, Taubert KA. Infective endocarditis: Diagnosis, antimicrobial therapy, and management of complications: A statement for healthcare professionals from the Committee on Rheumatic fever, endocarditis, and Kawasaki disease, council on cardiovascular disease in the young, and the councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association: Endorsed by the Infectious Disease Society of America. Circulation 2005; 111: e394 – e434.

Barron P, Pillay Y, Doherty T, Sherman G, Jackson D, Bhardwaj S, Robinson P, and Goga A. Eliminating mother-to-child HIV transmission in South Africa. Bull World Health Organ 2013; 91: 70–74.

Bashore TM, Cabell C, Fowler V. Update on Infective Endocarditis. Curr Probl Cardiol 2006; 31(4): 274 – 352.

Baumgartner H, Bonhoeffer P, De Groot NM, de Haan F, Deanfield JE, Galie N, Gatzoulis MA, Gohlke-Baerwolf C, Kaemmerer H, Kilner P, Meijboom F, Mulder BJ, Oechslin E, Oliver JM, Serraf A, Szatmari A, Thaulow E, Vouhe PR, Walma E. ESC Guidelines for the management of grown-up congenital heart disease (new version 2010). Eur Heart J 2010; 31: 2915–2957.

Bayer AS, Bolger AF, Taubert KA, Wilson W, Steckelberg J, Karchmer AW, Levison M, Chambers HF, Dajani AS, Gewits MH, Newburger JW, Gerber MA, Shulman ST, Pallash TJ, Gage TW, Ferrieri P. Diagnosis and management of infective endocarditis and its complications. Circulation 1998; 98: 2936 – 2948.

Beynon RP, Bahl VK and Prendergast BD. Infective endocarditis. BMJ 2006; 333: 334 – 339.

Bloch M. Frailty in people living with hiv. AIDS Res Ther 2018; 15(19): 1-5.

Bonfiglioli R, Nanni C, Morigi JJ, Graziosi M, Trapani F, Bartoletti M, Tumietto F, Ambrosini V, Ferretti A, Rubello D, Rapezzi C, Viale PL, Fanti S. 18F-FDG PET/CT diagnosis of unexpected extracardiac septic embolisms in patients with suspected cardiac endocarditis. Eur J Nucl Med Mol Imaging 2013; 40: 1190–1196.

Cahill TJ, Baddour LM, Habib G, Hoen B, Salaun E, Pettersson GB, Schäfers HJ, Prendergast BD. Challenges in Infective Endocarditis. J Am Coll Cardiol 2017; 69: 325–344.

Chu VH, Sexton DJ, Cabell CH, Reller LB, Pappas PA, Singh RK, Fowler VG Jr., Corey GR, Aksoy O, Woods CW. Repeat infective endocarditis: differentiating relapse from reinfection. Clin Infect Dis 2005; 41: 406–409.

Currie PF, Sutherland GR, Jacob AJ, Bell JE, Brettle RP, Boon NA. A review of endocarditis in acquired immunodeficiency syndrome and human immunodeficiency virus infection. Eur Heart J 1995; 16(suppl B): 15–8.

Deeks SG, Overbaugh J, Buchbinder PA, S. Hiv infection Nat Rev Dis Primers 2015;1: 15035.

Durack DT, Pelletier LL, Petersdorf RG. Chemotherapy of experimental streptococcal endocarditis. II. Synergism between penicillin and streptomycin against penicillinsensitive streptococci. J Clin Invest 1974; 53:829–833.

Duval X, Leport C. Prophylaxis of infective endocarditis: current tendencies, continuing controversies. Lancet Infect Dis 2008; 8: 225–232.

Feuchtner GM, Stolzmann P, DichtlW, Schertler T, Bonatti J, Scheffel H, Mueller S, Plass A, Mueller L, Bartel T,Wolf F, Alkadhi H. Multislice computed tomography in infective endocarditis: comparison with transesophageal echocardiography and intraoperative findings. J Am Coll Cardiol 2009; 53: 436–444.

Goddard AJ, Tan G, Becker J. Computed tomography angiography for the detection and characterization of intra-cranial aneurysms: current status. Clin Radiol 2005;60: 1221–1236.

Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, Dulgheru R, El Khoury G, Erba PA, Iung B, Miro JM, Mulder BJ, Plonska-Gosciniak E, Price S, Roos-Hesselink J, Snygg-Martin U, Thuny F, Tornos Mas P, Vilacosta I, Zamorano JL; ESC Scientific Document Group. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J. 2015 Nov 21; 36(44):3075-3128. doi: 10.1093/eurheartj/ehv319. Epub 2015 Aug 29. PMID: 26320109.

Halavaara, M., Martelius, T., Järvinen, A., Antikainen, J., Kuusela, P., Salminen, US. & Anttila, V-J. Impact of pre-operative antimicrobial treatment on microbiological findings from endocardial specimens in infective endocarditis. Eur J Clin Microbiol Infect Dis 2019; 38(3), 497-503.

Hekimian G, Kim M, Passefort S, Duval X, Wolff M, Leport C, Leplat C, Steg G, Iung B, Vahanian A, Messika-Zeitoun D. Preoperative use and safety of coronary angiography for acute aortic valve infective endocarditis. Heart 2010; 96: 696–700.

Hubert S, Thuny F, Resseguier N, Giorgi R, Tribouilloy C, Le Dolley Y, Casalta JP, Riberi A, Chevalier F, Rusinaru D, Malaquin D, Remadi JP, Ammar AB, Avierinos JF, Collart F, Raoult D, Habib G. Prediction of symptomatic embolism in infective endocarditis: construction and validation of a risk calculator in a multicenter cohort. J Am Coll Cardiol 2013; 62: 1384–1392.

Imbert G, Bothello E, Collart F, Habib G. Contribution of systematic serological testing in diagnosis of infective endocarditis. J Clin Microbiol 2005; 43: 5238–5242.

Kang DH, Kim YJ, Kim SH, Sun BJ, Kim DH, Yun SC, Song JM, Choo SJ, Chung CH, Song JK, Lee JW, Sohn DW. Early surgery versus conventional treatment for infective endocarditis. N Engl J Med 2012; 366: 2466-73.

Kang DH. Timing of surgery in infective endocarditis. Heart. 2015; 101(22):1786-91. doi: 10.1136/heartjnl-2015-307878. Epub 2015 Aug 18. PMID: 26285598.

Koegelenberg CFN, Doubell AF, Orth H, Reuter H. Infective endocarditis in the Western Cape Province of South Africa: a three-year prospective study. Q J Med 2003; 96: 217-225.

Koshy J.J., M. Engel, P. Human, H. Carrara, J. Brink, and P. Zilla. Long term outcome and EuroSCORE II validation in native valve surgery for active infective endocarditis in a South African cohort. SAHJ 2018; 15(2): 116-126.

Knirsch W, Nadal D. Infective endocarditis in congenital heart disease. Eur J Pediatr. 2011; 170(9):1111-27.

Lalani T, Chu VH, Park LP, Cecchi E, Corey GR, Durante-Mangoni E, Fowler VG Jr., Gordon D, Grossi P, Hannan M, Hoen B, Munoz P, Rizk H, Kanj SS, Selton-Suty C, Sexton DJ, Spelman D, Ravasio V, Tripodi MF, Wang A. In-hospital and 1-year mortality in patients undergoing early surgery for prosthetic valve endocarditis. JAMA Intern Med 2013; 173: 1495–1504.

Li JS, Sexton DJ, Mick N, Nettles R, Fowler VG Jr, Ryan T, Bashore T, Corey GR. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis 2000; 30: 633–638.

Manoff SB, Vlahov D, Herskowitz A, Solomon L, Muñoz A, Cohn S, Willoughby SB, Nelson KE. Human immunodeficiency virus infection and infective endocarditis among injecting drug users. Epidemiology 1996; 7: 566–70.

Mauri L, de Lemos JA, O'Gara PT. Infective Endocarditis. Curr Probl Cardiol 2001; 26(9): 558 – 610.

Mirabel M, Sonneville R, Hajage D, Novy E, Tubach F, Vignon P, Perez P, Lavoue S, Kouatchet A, Pajot O, Mekontso-Dessap A, Tonnelier JM, Bollaert PE, Frat JP, Navellou JC, Hyvernat H, Hssain AA, Timsit JF, Megarbane B, Wolff M, Trouillet JL. Long-term outcomes and cardiac surgery in critically ill patients with infective endocarditis. Eur Heart J 2014; 35: 1195–1204.

Mocchegiani R, Nataloni M. Complications of infective endocarditis. Cardiovasc Hematol Disord Drug Targets 2009; 9: 240–248.

Mylonakis E, Calderwood SB. Infective endocarditis in adults. NEJM 2001; 345(18): 1318 – 1330.

Nadji G, Rusinaru D, Remadi JP, Jeu A, Sorel C, Tribouilloy C. Heart failure in leftsided native valve infective endocarditis: characteristics, prognosis, and results of surgical treatment. Eur J Heart Fail 2009; 11: 668–675.

Naidoo DP, Shein K. HIV and valvular heart disease in South Africa. SA Heart 2009; 6: 64-74.

Nkomo VT. 2007. Epidemiology and prevention of valvular hart diseases and infective endocarditis in Africa. Heart 2007; 93: 1510-1519.

Netzer RO, Altwegg SC, Zollinger E, Täuber M, Carrel T, Seiler C. Infective endocarditis: determinants of long-term outcome. Heart. 2002; 88(1):61-6.

Østergaard L, Mogensen UM, Bundgaard JS, Dahl A, Wang A, Torp-Pedersen C, Gislason G, Køber L, Køber N, Dejgaard TF, Frandsen CS, Fosbøl EL. Duration and complications of diabetes mellitus and the associated risk of infective endocarditis. Int J Cardiol. 2019; 278: 280-284.

Okello E, Kakande B, Sebatta E, Kayima J, Kuteesa M, Mutatina B, Nyakoojo W, Lwabi P, Mondo CK, Odoi-Adome R, Juergen F. Socioeconomic and environmental risk factors among rheumatic heart disease patients in Uganda. PLoS One 2012; 7: e43917.

Peters, F., Karthikeyan, G., Abrams, J., Muhwava, L., Zuhlke, L.: Rheumatic heart disease: current status of diagnosis and therapy Cardiovascular Diagnosis and Therapy 2019; 2:10.

Prendergast BD. The changing face of infective endocarditis. Heart 2005; 92: 879 – 885.

Prendergast BD. The changing face of infective endocarditis Heart 2006; 92:879-885.

Pulvirenti JJ, Kerns E, Benson C, Lisowski J, Demarais P, Weinstein RA. Infective endocarditis in injection drug users: importance of human immunodeficiency virus serostatus and degree of mmunosuppression. Clin Infect Dis 1996; 22: 40–5.

Raoult D, Casalta JP, Richet H, Khan M, Bernit E, Rovery C, Branger S, Gouriet F, Imbert G, Bothello E, Collart F, Habib G. Contribution of systematic serological testing in diagnosis of infective endocarditis. J Clin Microbiol 2005; 43:5238–5242.

Regueiro A, Linke A, Latib A, et al. Association Between Transcatheter Aortic Valve Replacement and Subsequent Infective Endocarditis and In-Hospital Death. JAMA. 2016;316(10):1083–1092.

Ribera E, Miró JM, Cortés E, Cruceta A, Merce J, Marco F, Planes A, Paré JC, Moreno A, Ocaña I, Gatell JM, Pahissa A. Influence of HIV-1 infection and degree of immunosuppression on the clinical characteristics and outcome of infective endocarditis in intravenous drug users. Arch Intern Med 1998; 158: 2043–50.

Saby L, Laas O, Habib G, Cammilleri S, Mancini J, Tessonnier L, Casalta JP, Gouriet F, Riberi A, Avierinos JF, Collart F, Mundler O, Raoult D, Thuny F. Positron emission tomography/computed tomography for diagnosis of prosthetic valve endocarditis: increased valvular 18F-fluorodeoxyglucose uptake as a novel major criterion. J Am Coll Cardiol 2013; 61: 2374–2382.

San Roman JA, Lopez J, Vilacosta I, Luaces M, Sarria C, Revilla A, Ronderos R, Stoermann W, Gomez I, Fernandez-Aviles F. Prognostic stratification of patients with left-sided endocarditis determined at admission. Am J Med 2007;120: 369–367.

Selton-Suty C, CélardM, Le Moing V, Doco-Lecompte T, Chirouze C, Iung B, Strady C, Revest M, Vandenesch F, Bouvet A, Delahaye F, Alla F, Duval X, Hoen B. Preeminence of Staphylococcus aureus in infective endocarditis: a 1-year populationbased survey. Clin Infect Dis 2012; 54: 1230–9.

Shtaya AA, Perek S, Kibari A, Cohen S. Bartonella henselae Endocarditis: An Usual Presentation of an Unusual Disease. Eur J Case Rep Intern Med. 2019; 6(3): 001038.

Snygg-Martin U, Gustafsson L, Rosengren L, Alsio A, Ackerholm P, Andersson R, Olaison L. Cerebrovascular complications in patients with left-sided infective endocarditis are common: a prospective study using magnetic resonance imaging andNneurochemical brain damage markers. Clin Infect Dis 2008; 47: 23–30.

Spijkerman IJB, van Ameijden EJC, Mientjes GHC, Coutinho RA, van den Hoek A. Human immunodeficiency virus infection and other risk factors for skin abscesses and endocarditis among injection drug users. Clin Epidemiol 1996; 49: 1149–54.

Taramasso L, Tatarelli P, Di Biagio A. Bloodstream infections in hiv-infected patients. Virulence 2016; 7: 320–328.

Tattevin P, Limonta S, The different weight of indications for cardiac surgery in patients with infective endocarditis. Int J Cardiol 2019; 282: 31-32.

Thiene G, Basso C. Pathology and pathogenesis of infective endocarditis in native heart valves. Cardiovasc Pathol 2006;15: 256 – 263.

Thuny F, Beurtheret S, Mancini J, Gariboldi V, Casalta JP, Riberi A, Giorgi R,Gouriet F, Tafanelli L, Avierinos JF, Renard S, Collart F, Raoult D, Habib G. The timing of surgery influences mortality and morbidity in adults with severe complicated infective endocarditis: a propensity analysis. Eur Heart J 2011; 32: 2027– 2033.

Thuny F, Di Salvo G, Belliard O, Avierinos JF, Pergola V, Rosenberg V, Casalta JP, Gouvernet J, Derumeaux G, Iarussi D, Ambrosi P, Calabro R, Riberi A, Collart F, Metras D, Lepidi H, Raoult D, Harle JR, Weiller PJ, Cohen A, Habib G. Risk of embolism and death in infective endocarditis: prognostic value of echocardiography: a prospective multicenter study. Circulation 2005; 112: 69–75.

Thuny F, Avierinos JF, Tribouilloy C, Giorgi R, Casalta JP, Milandre L, Brahim A, Nadji G, Riberi A, Collart F, Renard S, Raoult D, Habib G. Impact of cerebrovascular complications on mortality and neurologic outcome during infective endocarditis: a prospective multicentre study. Eur Heart J 2007; 28: 1155–1161.

Thuny F, Dominique Grisoli, Frederic Collart, Gilbert Habib, Didier Raoult, Management of infective endocarditis: challenges and perspectives, The Lancet, Volume 379, Issue 9819, 2012.

Vilacosta I, Graupner C, San Roman JA, Sarria C, Ronderos R, Fernandez C, Mancini L, Sanz O, Sanmartin JV, Stoermann W. Risk of embolization after institution of antibiotic therapy for infective endocarditis. J Am Coll Cardiol 2002; 39: 1489–1495.

Wilson WR, Geraci JE, Wilkowske CJ, Washington JA. Short-term intramuscular therapy with procaine penicillin plus streptomycin for infective endocarditis due to viridans streptococci. Circulation 1978; 57: 1158–1 161.

Yoshioka D, Sakaguchi T, Yamauchi T, Okazaki S, Miyagawa S, Nishi H, Yoshikawa Y, Fukushima S, Saito S, Sawa Y. Impact of early surgical treatment on postoperative neurologic outcome for active infective endocarditis complicated by cerebral infarction. Ann Thorac Surg 2012; 94: 489–495.

Yunis NA, Stone VE. Cardiac manifestations of HIV/AIDS: a review of disease spectrum and clinical management. J Acquir Immune Defic Syndr Hum Retrovirol 1998; 18: 145–54.

UNAIDS, http://www.unaids.org/en/resources/909090 (2016a). 90–90–90 - An ambitious treatment target to help end the AIDS epidemic 01 JANUARY 2017.

Chapter 2- Publishable article

Infective endocarditis in Central South Africa in the Human Immunodeficiency Virus era – a surgical perspective

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1. Abstract:

Introduction
The impact of the HIV status of infective endocarditis patients undergoing valve surgery in South Africa has been poorly described during the HIV pandemic. The aim of this study was to compare the preoperative risk factors and surgical outcomes between HIV positive and negative patients undergoing valvular surgery for infective endocarditis in central South Africa.

Objectives: To determine the demographics, clinical presentation, risk factors, indication for surgery, microorganisms, and surgical outcomes of HIV positive versus HIV negative patients presenting with Infective endocarditis.

Methods: retrospective, analytical cohort study that reviewed the records of adult patients who were tested for HIV and treated surgically for infective endocarditis between 2009 to 2019.

Results: From the141 IE patients, 105 patients were tested for HIV, 31% (n=33) tested positive the mean age for both groups was comparable 38.87 versus 39.51 years. Eighty-eight percent (n=29) of positive patients were on anti-retroviral therapy. In both groups, there was a male preponderance, 55% and 56% respectively. The majority of HIV positive (91%) and negative patients (71%) were of African descent**,** more than 50% of both groups presented with NYHA III&IV, both groups had a medium-high risk of developing IE (HIV (+) 72%; HIV (-) 62%). Prevention of embolization was the main indication for surgery in HIV(+) group and heart failure in the negative group, In both groups a greater proportion of patients had left sided native valve endocarditis 95% and RHD was predominantly the underlying pathology 60%, requiring mechanical prostheses mainly in the mitral 46% and aortic 33% position. Right sided endocarditis represents <5% and only 2 out 105 patients confirmed IVDA's, Staphylococcus and Streptococcus dominated cultured organisms with staphylococcus species being more frequent, culture negative endocarditis remains high in both groups, with 47% HIV (-) group vs 33%. Morbidity was limited in both groups 12% vs 11% with no major difference. The late mortality was higher in the HIV (+) group (27% vs 19%); however, the in-hospital mortality was higher in the HIV (-) group (17% vs 12%).

Conclusions:
Patients with HIV infection on antiretroviral therapy showed minimal to no impact on perioperative morbidity and mortality in patients undergoing surgery for left sided infective endocarditis. The main risk factor in this cohort was rheumatic valvular heart disease, which is a preventable condition. However, untreated HIV infection with low CD4 counts had significant high perioperative and late mortality. This shows the importance of the HAART program. The high prevalence of culture negative endocarditis warrants further investigation. Given the low number of patients in this cohort study, further prospective studies needs to be conducted to confirm our findings.

Keywords: Infective Endocarditis; Cardiac surgery; Human immunodeficiency virus Etiology; Epidemiology, microorganisms, and outcomes.

2. Abbreviations:

ART	Anti-Retroviral Therapy
IE	Infective endocarditis
IQR	Inter quartile range
IVDA	Intravenous drug abuse
DM	Diabetes mellitus
HIV	Human Immunodeficiency virus
HAART	Highly active antiretroviral therapy
NHLS	National Health Laboratory Service
NYHA	New York Heart Association
HACEK	Haemophilus sp., Actinobacillus, actinomycetemcomitans, Cardiobacterium, Eikenella, Kingella
PCR	Polymerase chain reaction
TFA	Tissue factor activity
3D	Three-dimensional
TEE	Transoesophageal echocardiography
TIA	Transilient Ischemic Attach
SD	Standard Deviation

2.1 Introduction

Infective endocarditis (IE) is an uncommon but progressively changing disease that poses high mortality and morbidity[1]. Major changes and challenges have been witnessed in the epidemiology, bacteriology, and clinical presentation of infective endocarditis as well as major advances in the diagnosis and management of this clinical disease [2,3].

In North America and western European countries, the incidence of community-acquired native-valve endocarditis ranges from 3 to 10 cases per 100,000 [2,4]. In Africa and southern Africa, the incidence of infective endocarditis has not declined over the last 30 years, and now with more health care interventions, such as pacer/defibrillators, and an increasingly elderly population with degenerative valvular heart disease, the number susceptible to endocarditis is actually increasing [5]. Given the weak evidence for endocarditis prophylaxis, there remains a large population at risk [6,7].

In Western populations, in particular chronic rheumatic heart disease is now an uncommon antecedent. Degenerative valve disease in elderly people, intravenous drug misuse, preceding valve replacement, or vascular instrumentation have become increasingly frequent, coinciding with an increase in staphylococcal infections and those due to fastidious organisms [8]. Although the prevalence of rheumatic valvular heart disease has diminished in the developed countries, it is still endemic in developing third word communities where it represents the main leading predisposing factor for IE [9].

Infective endocarditis in Africa remains a disease of the young [10]. Rheumatic heart disease still is the main predisposing factor where modern investigations and management are the privilege of those living in better socioeconomic conditions [8,11]. However, only a few large epidemiological studies have been performed in Africa and to date, knowledge of the clinical features and natural history of IE has relied largely on small, uncontrolled, outdated studies.

HIV/AIDS is a major burden of disease and death around the world. This is especially prominent and important in sub-Saharan Africa [12]. The global HIV-related death burden has decreased dramatically since 1996 when antiretroviral therapy (ART) was introduced [13]. The HIV epidemic had its greatest increase in prevalence during 1985 and 2000 in which it increased from +- 2.4 million to 28 million people [14].

The distribution of infection is dramatically different in different parts of the world according to the Global Burden of Disease survey 2015. The high income developed countries such as USA and Germany accounted for 2.15% (833 030) and 0.16% (60 550) respectively of the globally infected population. In stark contrast sub-Sahara Africa accounted for 75.87% (29.4 million) of which South Africa contributed around one third 21.67% (8.4 million) of the HIV infected population [15].

Infective endocarditis becomes more challenging in patients with HIV due to several factors. It is more difficult to assess perioperative morbidity and mortality due to limited series published with large patient groups. Patient management is more difficult due to the increased presence of active endocarditis and reduced cd4 counts, which could lead to less predictable surgical intervention and patient care [16]. The introduction of highly active antiretroviral therapy (HAART) in the current era led to the fact that HIV had no impact on patients with IE with regards to length of hospital stay or in-hospital mortality in comparison with HIV negative patients with similar risks and comorbidities [17].

The socio-economic conditions in Africa with poverty and famine expose children and adults to conditions that are rarely seen in the developed world [18]. Examples of such disease are rheumatic heart disease [19], endomyocardial fibrosis [20] and HIV-related cardiomyopathy [21]. The clinical features and conditions of disease in South Africa makes the patient population completely different from that encountered in the developed nations [5]. It would therefore be beneficial to obtain a better understanding of the South African population to develop better patient management strategies.

The primary aim of this retrospective study was to evaluate infective endocarditis in the HIV era in central South Africa, and the secondary aims were to determine the influence of HIV on infective endocarditis patients in regard to demographics, presentations, underlying pathologies, surgical outcomes, complications, and mortality.

2.2 Patients and Methodology

2.2.1 Design of study

A retrospective analytical cohort study that reviewed the records of adult patients who were tested for HIV and surgically treated for IE between 2009 and 2019. The Department of Cardiothoracic Surgery at Universitas academic hospital is a tertiary 600-bed hospital in Bloemfontein. It is the only referral center offering a tertiary service for cardiac surgery in central South Africa serving a population of approximately 3 million people. Most of the population lives in poor socio-economic conditions and are of mixed or African descent. The normal surgical principles were followed for IE, which included proper debridement, replace/repair, and eradication of all infected material.

The records of the patients were analyzed, and demographic, pre-operative, intraoperative and post-operative outcomes, and complications were recorded for each patient. Mortality data were recorded in-hospital and mid-term. Mid-term mortality data were obtained from both hospitals' electronic records (Meditech), as well as the Department of Home Affairs.

Results were reported following the guidelines for reporting morbidity and mortality for cardiac valvular operations [22].

Clinical data were collected from the department's electronic database as well as patient records from the hospital archive and the National Health Laboratories Service (NHLS) online database.

The diagnosis of infective endocarditis was made according to the 1994 Duke criteria [29].

HIV infection

HIV infection was established if a patient had two positive ELISA test or a positive ELISA test plus a positive Western blot test, or a pre-operative rapid test in the ward. HIV infection was classified according to the 1993 Centre for Disease Control (CDC) recommendations.

Indications for surgery was recorded as uncontrolled sepsis, progressive heart failure and vegetations presenting as an oscillating intracardiac mass on the valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation on echocardiography.

Timing of Surgery

- Emergency surgery: lifesaving intervention during resuscitation within minutes of the decision to operate and performed in the next available operating theatre – "break-in" to existing lists if required.
- Urgent surgery: Acute onset or deterioration of conditions that threaten life within hours of the decision to operate and normally once resuscitation completed, performed in the daytime "emergency" list or out-of-hours emergency theatre (including at night).
- Elective surgery: is a surgical procedure planned or booked in advance of routine admission to a hospital performed in the elective theatre list booked & planned before or during the same admission.

Mortality

- In-hospital (operative) mortality is death within 30 days of operation regardless of the patient's geographic location.
- Late mortality is death beyond 90 days after surgery.

Survival

- Survival is calculated from the day of surgery in months till the date last seen, and for those who were lost to follow up, it's the date which the department of Home Affairs was contacted (31 January 2020) (figure 2.4).

2.2.2 Statistics

Statistical analyses were performed using GraphPad Prism version 9.0.0 (GraphPad Software, La Jolla, CA, USA, www.graphpad.com). Demographic and clinical data were compared between HIV positive and HIV negative groups using Mann-Whitney U test for continuous variables and chi-square or Fisher exact tests for categorical variables. Median and interquartile ranges were used for continuous variables, frequencies, and proportions for categorical variables. Significance was set as $p < 0.05$.

A point-biserial correlation was used to measure the strength and direction of the association that exists between one continuous variable (EuroScore) and one dichotomous variable (mortality).

Values for point-biserial range from -1.00 to 1.00. Values of 0.15 or higher mean that the item is performing well. Good items typically have a point-biserial exceeding 0.25.

2.2.3 Ethical considerations

This study was approved by the Health Sciences Research Ethics Committee of the University of the Free State (**UFS-HSD2019/0630/2506).**

2.3 Results

The HIV status were available for 105 patients out of 141 consecutive patients that presented with IE between 2009 and 2019 that were surgically treated.

2.3.1 HIV infection and demographic data

From the 105 IE patients tested for HIV, 31% (n=33) tested positive and 69% (n=72) tested negative. The mean age for both groups was comparable 38.87 versus 39.51 years. Eighty-eight percent (n=29) of positive patients were on ART. In both groups, there was a male preponderance, 55% and 56% respectively. The majority of HIV positive (71%) and negative patients (91%) were of African descent (Table 2.1). The groups did not differ significantly regarding age and gender ($p>0.05$).

Table 2.1. Demographics and prevalence.

Variable	HIV (+) n=33 33/105 (31%)	HIV (-) n=72 72/105 (69%)	p-value
Age (mean ± SD)	38.87 ± 10.2	39.51 ± 14.07	0.96
Gender ***Male*** ***Female***	18 (54.5%) 15 (45.5%)	40 (56%) 32 (44%)	>0.99
Race ***African*** ***Caucasian*** ***Mixed race***	30 (91%) 2 (6%) 1 (3%)	51 (71%) 14 (19%) 5 (7%)	-

2.3.2 Clinical data

Based on the modified Dukes criteria 66% (n=69/105) of the patients presented with a definite diagnosis of IE and 34% (n=36/105) with a possible diagnosis of IE. In HIV positive group, the majority of patients had a CD4 count >200cells/uL, both groups presented with NYHA III/IV (51%) heart failure.

Both groups had an intermediate-high risk of developing IE HIV (+) 72%, HIV (-) 86%. In the HIV (+) group, most patients received surgery to prevent embolization/extensive vegetation (72%) as the predominant indication for surgery and in the HIV (-) group predominantly due to heart failure (64%). A total of 73% of the HIV (+) group had one single indication for surgery and 27% who had more than one or two indications combined, same with HIV (-) 64% vs 36%. Most patients received emergency/ urgent surgery in both groups (64% vs 56%) and more patients in the HIV (-) group received a reoperation (22%). The median EuroSCORE II was higher in the HIV (-) group (6.78) compared to the HIV (+) group (3.97). No statistical differences were calculated for any of the clinical variables between the two groups (Table 2.2).

Table 2.2 Clinical data HIV (+) versus HIV (-).

Variable	HIV (+) n=33 33/10			HIV (-) n=72 72/105			
	n (%)	Range	Median (IQR)	n (%)	range	Median (IQR)	p-value
IE diagnosis (Duke)							
Definite	23 (70%)			46 (64%)			0.66
Possible	10 (30%)			26 (36%)			
CD4 cunts (cells/uL)							
CD4 C (<200) cells/uL	2 (6%)	114-125	119.5 (114125)				
CD4 C (>200) cells/uL	28 (85%)	226-1648	497 (361.5 734.3)				
CD4 C unknown	3 (9%)	-	-				
NYHA							
NYHA 1+2	16 (48%)	-	-	35 (49%)	-		>0.99
NYHA 3+4	17 (52%)	-	-	37 (51%)	-		
Risk to develop IE							
High and medium risk	24(73%)			62 (86%)			0.24
Low risk	9 (27%)			10 (14%)			
Indication for surgery							
Heart failure	16 (48%)			46 (64%)			0.1362
Uncontrolled sepsis	5 (15%)			15 (21%)			0.4913
Embolism/Extensive vegetation	24 (72%)			45 (62%)			0.3054
Single indication	24 (73%)			46 (64%)			0.3725
Multiple indications	9 (27%)			26 (36%)			0.3725
Vegetation (ECHO)							
Yes	27 (82%)			55 (76%)			0.5323
No	6 (18%)			17 (24%)			
Operative priority							
Salvage/emergency/ Urgent	21 (64%)			40 (56%)			0.4359
Elective	12(36%)			32 (44%)			
Reoperation							
No	28 (85%)			56 (78%)			0.4004
Yes	5 (15%)			16 (22%)			
EuroSCORE							
	-	0.69 - 74.14	3.97 (2.05 – 14.4)	-	0.56-49.89	6.78 (3.75 – 16)	0.21

2.3.3 Surgical interventions

More than 60% of patients had Rheumatic Heart Disease (RHD) requiring mechanical aortic and mitral valves prostheses because of their young age. In both HIV positive and negative groups, a greater proportion of patients had native valve pathologies (Table 2.3a, Figure 2.1.)

Table 2.3a: Primary valve pathology in HIV (+) and HIV (-) patients.

Valve Pathology			
Variable	HIV(+) n=33 33/105	HIV(-) n=72 72/105	
	n (%)	n (%)	p-value
RHD	21 (64%)	42 (58%)	0.6066
NRHD	12 (36%)	30 (42%)	
NATIVE VALVE	32 (97%)	62 (86%)	0.1667 (F)
PROSTHESIS	1 (3%)	10 (14%)	
Left side endocarditis	30 (91%)	70 (97%)	
Right side endocarditis	3 (9%)	2 (3%)	

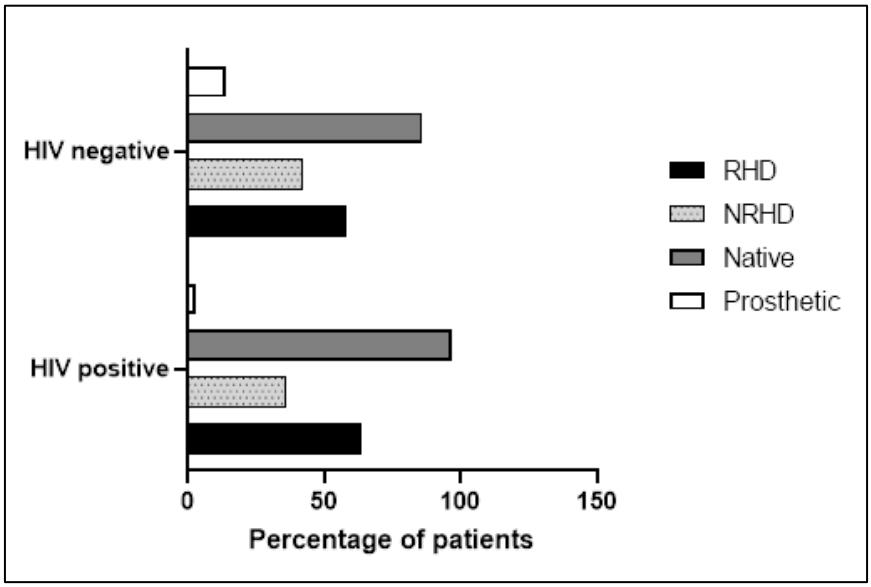

Figure 2.1. Valve pathology in HIV positive and HIV negative patients.

RHD = Rheumatic heart disease, NRDH = Non-rheumatic heart disease.

The vast majority of patient had left sided endocarditis in contrast to right side, the latter only represent n=3 (9%) and n=2 (2.7%) in HIV positive and negative, respectively, and only two patients reported drug abuse (Table 2.3b).

Table 2.3b. Types of surgical interventions for HIV (+) and HIV (-) patients.

Variable	n; (%)	Replace mechanical	Replace Biological	Replace Homograft	Valvuloplasty	Ross	Debridement
HIV (+) n=33 (n; %)							
Aortic	20 (61%)	11 (33%)	0	1 (3%)	1(3%)	0	0
Mitral	10 (30%)	16 (48%)	2 (6%)	0	2 (6%)	0	3(9%)
Tricuspid	23 (70%)	0	2 (6%)	0	7 (21%)	0	1 (3%)
Pulmonary	32 (97%)	0	0	1 (3%)	0	0	0
HIV (-) n=72 (n; %)							
Aortic	40 (56%)	24 (33%)	3 (4%)	2 (3%)	1(1%)	1	0
Mitral	26 (36%)	33 (46%)	2 (3%)	0	10 (14%)	(1%)	1 (1%)
Tricuspid	56 (78%)	0	1 (1%)	0	14 (19%)	0	1 (1%)
Pulmonary	66 (92%	0	1 (1%)	4 (6%)	0	0	1 (1%)

2.3.4 Microbiology

In both groups, staphylococcus and streptococcus dominated cultured organisms with staphylococcus species being more frequent. In the HIV (+) group 66% of the patients were culture positive compared to the 52% in the HIV (-) group meaning more patients in the HIV (-) group had a culture negative endocarditis.

Enterococcus faecium is more prevalent in HIV (+) group (14% vs 2%) (Table 2.4).

Table 2.4. Microorganisms cultured in HIV (+) and HIV (-) groups.

Variable	HIV (+) n=33 (n; %)	HIV (-) n=72 (n; %)	p-value
Culture negative	**11 (33%)**	**34 (47%)**	**0.1819**
Culture positive	**22 (66%)**	**38 (52%)**	
Organisms			
Staphylococcus	7 (32%)	13(34%)	*
Streptococcus	2 (9%)	11 (29%)	*
E coli	0 (0%)	2 (5%)	*
Pseudomonas aeruginosa	2 (9%)	2 (5%)	*
Klebsiella pneumoniae	0 (0%)	2 (5%)	*
Acinetobacter baumannii	2 (9%)	0 (0%)	*
Micrococcus species (MCCSP)	1 (4%)	0 (0%)	*
Aerococcus viridans	0 (0%)	1 (2%)	*
Klebsiella terrigena	1 (4%)	0 (0%)	*
Enterococcus faecium	3 (14%)	1 (2%)	*
Bacillus cereus	2 (9%)	1 (2%)	*
Klebsiella oxytoca	1 (4%)	0 (0%)	*
Candida parapsilosis	1 (4%)	0 (0%)	*
Gemella haemolysis	1 (4%)	0 (0%)	*
Bartonella quintana	0 (0%)	2 (5%)	*

[*numbers too small to calculate p-values].

2.3.5 Post-operative complications and outcomes

The number of complications in both groups was limited (HIV (+) 12% vs HIV (-) 11%). The HIV (+) patients presented with more septic emboli to the limbs (6% vs 1%), septicemia (21% vs 10%) and post-op stroke (15% vs 3%) than the HIV (-) group.

The in-hospital mortality was higher in the HIV (-) group (17% vs 12%), however midterm mortality was higher in the HIV (+) group (27% vs 19%).

Table 2.5. Post-operative complications and outcomes of HIV (+) and HIV (-) groups.

Variable	HIV (+) n=33 (n; %)	HIV (-) n=72 (n; %)	p-value
Operative complications			
Re-op for bleeding or tamponade	3 (9%)	5 (7%)	
Re-op for valvular graft dysfunction	1 (3%)	0 (0%)	
Re-op for other non-cardiac reasons	0 (0%)	2 (3%)	
Infection			
Sternum deep	1 (3%)	5 (7%)	
Leg, Arm	2 (6%)	1 (1%)	0.1589
Septicaemia	7 (21%)	7 (10%)	
Neurological			
Post-op stroke	5 (15%)	2 (3%)	
TIA	0 (0%)	1 (1%)	0.0629
Coma > 24 hours	1 (3%)	1 (1%)	
Paralysis	1 (3%)	2 (3%)	
Pulmonary			
Prolonged ventilation	1 (3%)	6 (8%)	0.7505 (F)
Pneumonia	2 (6%)	3 (4%)	
Renal failure			
Dialysis yes	4 (12%)	8 (11%)	0.7022
Dialysis no	3 (9%)	5 (7%)	
Vascular			
Acute limb ischemia	0 (0%)	2 (3%)	>0.9999 (F)
Other			
Heart block	1 (3%)	4 (6%)	
Cardiac arrest	1 (3%)	1 (1%)	
Anticoagulant event	0 (0%)	1 (1%)	
Tamponade	0 (0%)	0 (0%)	0.5749
Gastro-intestinal event	0 (0%)	1 (1%)	
Multi-system failure	3 (9%)	5 (4%)	
Other	3 (9%)	2 (3%)	
Mortality			
Overall mortality	13 (39%)	26 (36%)	0.7465
In-hospital mortality	4 (12%)	12 (17%)	0.7709 (F)
Late mortality	9 (27%)	14 (19%)	0.4367

2.3.6 Correlation between EuroSCORE II and Mortality.

The point-biserial correlation between the EuroScore II and Mortality was calculated as 0.0300. The value indicates that there is little to no correlation between EuroSCORE II and operative mortality (figure 2.2).

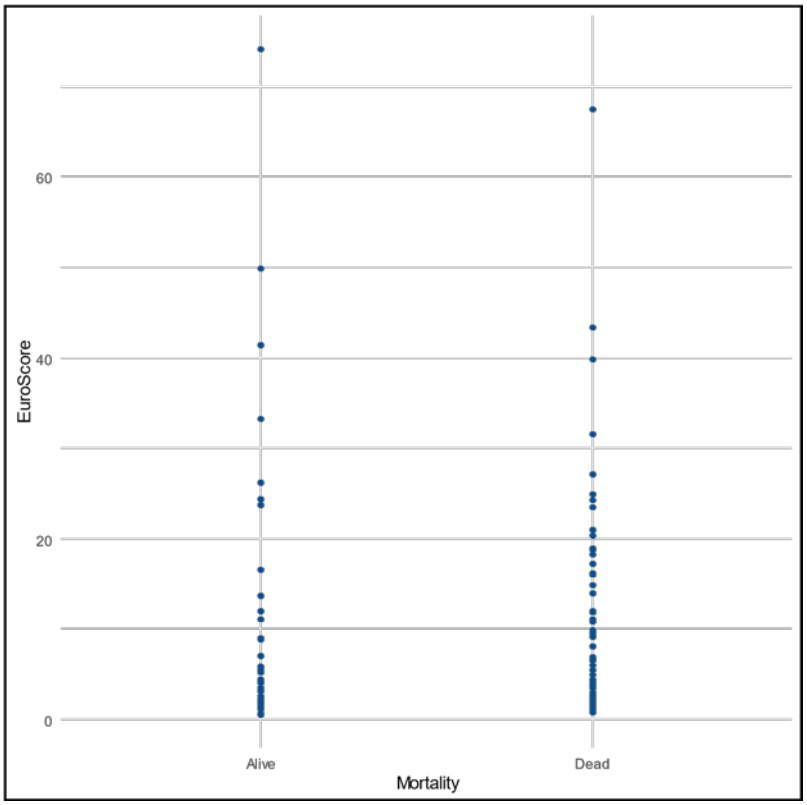

Figure 2.2. Correlation between EuroSCORE II and operative mortality.

2.3.7 Mortality and CD4 count

There was a significant difference (p =0.0018, 95 % CI -533.0 to – 155.0) between the CD4 count of operative survivals compared to those who died peri-operatively (figure 2.3). The CD4 count for in-hospital mortality [median (range) 175.5 (114 -467)] was significantly lower than for long-term mortality [median (range) 476 (355 -1000)]. Patients who were immune compromised with a CD4 counts less than 200 cell/uL had a 100% in-hospital mortality, but because of the low numbers (no=2) statistical significance cannot be derived.

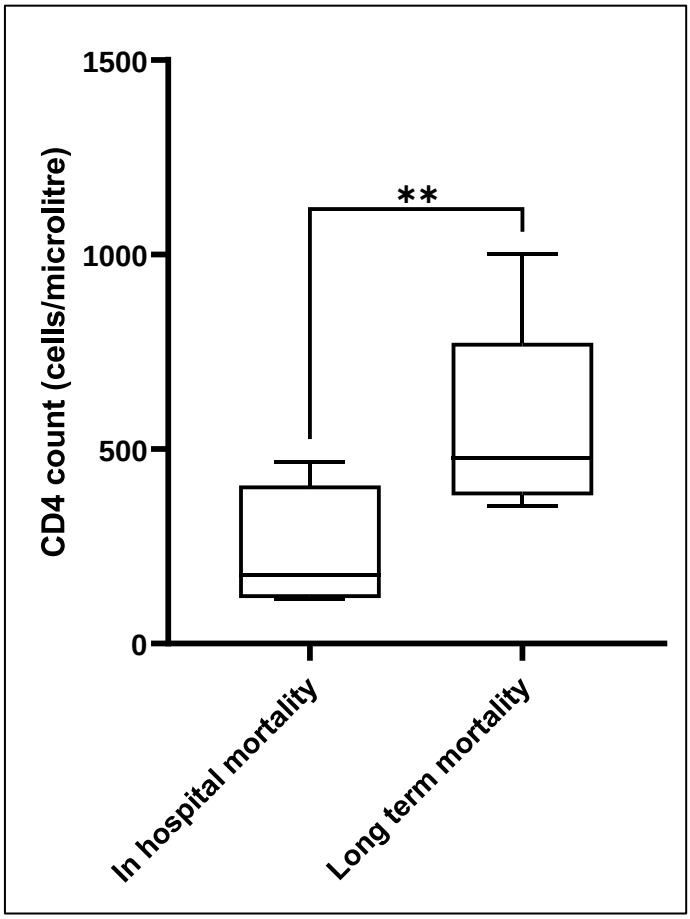

Figure 2.3. Difference in the CD4 count in HIV patients for in-hospital and long-term mortality **p < 0.01.

2.3.8 Survival

The survival of the HIV negative patients was higher (median 69.5 months, minimum 10 months, and maximum 130 months) than the HIV positive patients (median 50.5 months, minimum 9 months, and maximum 102 months), however, this difference was not significant (p = 0.092, 95 %CI = -34.00 to 2.00).

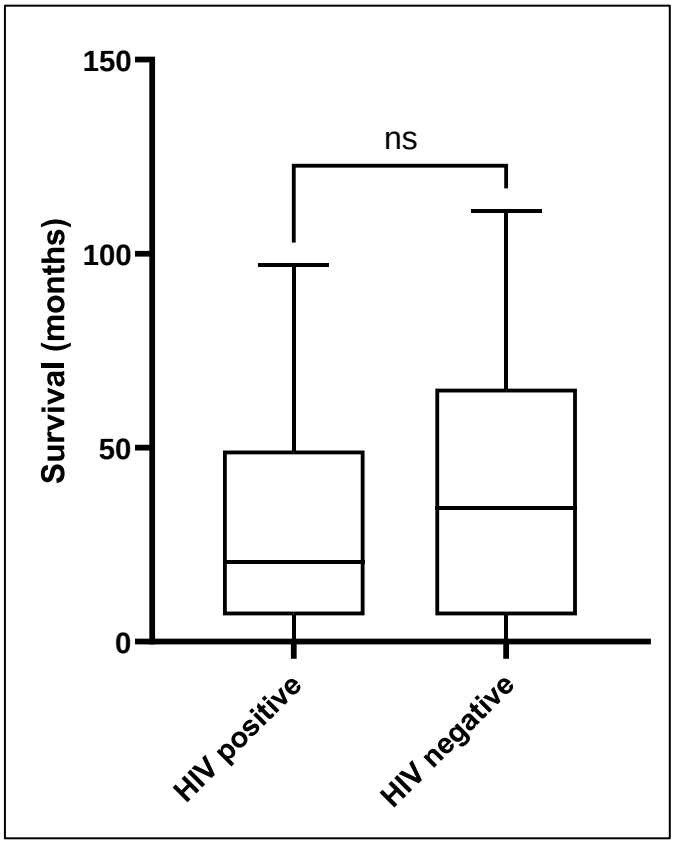

Figure 2.4. Survival of HIV positive patients and HIV negative patients. Significance set as $p < 0.05$.

2.4 Discussion

This study is one of the largest series in South Africa, with the largest cohort of known HIV status, the incidence of HIV in this cohort is 31%, which is higher compared to 14% prevalence in the Free State population according to the South African statistics during the same period [23].

In the 1st world setting, infective endocarditis in HIV infected patients is known to be almost exclusively in IVDAs and right-side endocarditis being commoner than the left side. In our population where rheumatic heart disease is still prevalent and represents more than 60% of the predisposing risk factors, together with the high prevalence of HIV infection makes left sided endocarditis in this group more common than right side. Rheumatic heart disease is a preventable disease at a primary health care level, if we can address it promptly, we can prevent up to 60% of cases.

The right sided disease was reported in less than 5% of the total cohort compared to 14% in a similar cohort, [24] IVDA's is relatively uncommon and only 2 cases (2%) were reported in this study.

The availability HAART therapy led to increase life expectancy of HIV infected patients [17]. In our series 88% of HIV positive patients were on HAART, with a median CD4 count of 497 cell/Ul, and only two patients reported with in-hospital death had a CD4 count <200 cell/Ul, this is going with the current literature that reports poor outcomes in immunosuppressed HIV patient with CD4 count <200 (AIDS) [25].

We showed that the lower the CD4 count the higher the long-term mortality. This showed that patients treated for HIV infection ie, suppressed viral load and normal CD 4 count in surgically treated infective endocarditis patients had similar outcomes with non-HIV infected patients. HIV infection has no effect on the Duke's criteria and that Duke's criteria does not consider HIV infected patients as a separategroup [26]. There was no significant deference between the two groups with regards to calculated EuroScore II, and there was no association between the EuroSCORE II and mortality in this cohort of patients, supporting the previously published observation by Koshy et al (2018) in Cape Town [27].

Due to the young age and the rheumatic nature of the underlining valvular pathology observed, mechanical prosthesis was the main surgical intervention in both aortic and mitral positions. Culture negative endocarditis is relatively higher compared to international registries, and similar to the locally published data being as high as 47% in the HIV negative group and 33% in the positive group. Internationally in the early 80's there was a prevalence ranging between 2.5 and 31% [28]. Where is only 10% reported by The International Collaboration on Endocarditis–Prospective Cohort Study in 2009 [7]. South Africa in contrast were reported 40% culture negative among the left heart endocarditis [24].

Staphylococcus is the commonest organism cultured between the two groups followed by streptococcus species, this is in line with most national and international registries [7].

The perioperative mortality was 17% for HIV (-) and 12% for HIV (+) group, this is also in line with the recently published study from cape town reporting 17% in-hospital mortality [24].

2.5 Limitations

1) This study was limited by its design being retrospective single-center study with difficulties obtaining information from patient's files and records.
2) The small sample size made the statistical analysis and sub analysis difficult, further updating the study with additional patient numbers to achieve a cohort that can yield a statistical difference in the results.

3) A significant number of HIV testing was performed using rapid test in the ward and data recording was sub optimal giving rise to high numbers of untested patients in the cohort studied.

4) The long term follow up and survival data was obtained from the national clinical database as well as the department of home affairs, it was limited in that we were not given the authority to access more detailed data as cause of death.

2.6 Conclusion

The effect of HIV in HIV positive patient's on antiretroviral therapy was minimal with no impact on perioperative morbidity and mortality in patients undergoing surgery for left sided infective endocarditis. The main risk factor in this cohort was rheumatic valvular heart disease, which is a preventable condition. Untreated HIV infection with low CD4 counts has significant high perioperative and late mortality. This shows the importance of HAART program. The high prevalence of culture negative endocarditis warrants further investigation. Given the low number of patients in this cohort study, further prospective studies need to be conducted to confirm our findings.

Infective endocarditis remains a deadly disease with high short- and long-term mortality. HIV infection has minimal to no impact on perioperative and in- hospital morbidity and mortality, left heart endocarditis is the dominant disease within the HIV patients due to the rheumatic valvular heart disease as opposed to right heart endocarditis. The high prevalence of culture negative endocarditis warrants further investigation. Given the low number of patients in this cohort study, further prospective studies need to be conducted to establish a statistical significance between the HIV (+) and (-) groups.

2.7 Funding statement

This work was supported by the University of the Free State and the Department of Cardiothoracic Surgery.

2.8 Acknowledgement

We would like to thank the team of perfusion technologists in the Department of Cardiothoracic Surgery who assisted in the data collection process.

2.9 Author contributions statement

Taha Gwila - Investigation, Writing – original draft.

Lezelle Botes – Supervision, Formal analysis

Marilee Jansen van Vuuren – Data Curation

Hermanus A Hanekom – Supervision, Project administration

Carlos-A. Mestres - Writing – review & editing.

Francis E Smit - Conceptualization, Supervision, Writing – review & editing.

2.10 Conflict of interest statement

None declared.

2.11 List of tables

Table 2.1. Demographics and prevalence.

Variable	HIV (+) n=33 33/105 (31%)	HIV (-) n=72 72/105 (69%)	p-value
Age (mean ± SD)	38.87 ± 10.2	39.51 ± 14.07	0.96
Gender ***Male*** ***Female***	18 (54.5%) 15 (45.5%)	40 (56%) 32 (44%)	>0.99
Race ***African*** ***Caucasian*** ***Mixed race***	30 (91%) 2 (6%) 1 (3%)	51 (71%) 14 (19%) 5 (7%)	-

Table 2.2 Clinical data HIV (+) versus HIV (-).

Variable	HIV (+) n=33 33/10			HIV (-) n=72 72/105			
	n (%)	Range	Median (IQR)	n (%)	range	Median (IQR)	p-value
IE diagnosis (Duke)							
Definite	23 (70%)			46 (64%)			0.66
Possible	10 (30%)			26 (36%)			
CD4 cunts (cells/uL)							
CD4 C (<200) cells/uL	2 (6%)	114-125	119.5 (114125)				
CD4 C (>200) cells/uL	28 (85%)	226-1648	497 (361.5 734.3)				
CD4 C unknown	3 (9%)	-	-				
NYHA							
NYHA 1+2	16 (48%)	-	-	35 (49%)	-		>0.99
NYHA 3+4	17 (52%)	-	-	37 (51%)	-		
Risk to develop IE							
High and medium risk	24(73%)			62 (86%)			0.24
Low risk	9 (27%)			10 (14%)			
Indication for surgery							
Heart failure	16 (48%)			46 (64%)			0.1362
Uncontrolled sepsis	5 (15%)			15 (21%)			0.4913

Embolism/Extensive vegetation	24 (72%)			45 (62%)			0.3054
Single indication	24 (73%)			46 (64%)			0.3725
Multiple indications	9 (27%)			26 (36%)			0.3725
Vegetation (ECHO)							
Yes	27 (82%)			55 (76%)			0.5323
No	6 (18%)			17 (24%)			
Operative priority							
Salvage/emergency/ Urgent	21 (64%)			40 (56%)			0.4359
Elective	12(36%)			32 (44%)			
Reoperation							
No	28 (85%)			56 (78%)			0.4004
Yes	5 (15%)			16 (22%)			
EuroSCORE							
	-	0.69 - 74.14	3.97 (2.05 – 14.4)	-	0.56- 49.89	6.78 (3.75 – 16)	0.21

Table 2.3a: Primary valve pathology in HIV (+) and HIV (-) patients.

Valve Pathology			
Variable	HIV(+) n=33 33/105	HIV(-) n=72 72/105	
	n (%)	n (%)	p-value
RHD	21 (64%)	42 (58%)	0.6066
NRHD	12 (36%)	30 (42%)	
NATIVE VALVE	32 (97%)	62 (86%)	0.1667 (F)
PROSTHESIS	1 (3%)	10 (14%)	
Left side endocarditis	30 (91%)	70 (97%)	
Right side endocarditis	3 (9%)	2 (3%)	

Table 2.3b. Types of surgical interventions for HIV (+) and HIV (-) patients.

Variable	n; (%)	Replace mechanical	Replace Biological	Replace Homograft	Valvuloplasty	Ross	Debridement
HIV (+) n=33 (n; %)							
Aortic	20 (61%)	11 (33%)	0	1 (3%)	1(3%)	0	0
Mitral	10 (30%)	16 (48%)	2 (6%)	0	2 (6%)	0	3(9%)
Tricuspid	23 (70%)	0	2 (6%)	0	7 (21%)	0	1 (3%)
Pulmonary	32 (97%)	0	0	1 (3%)	0	0	0
HIV (-) n=72 (n; %)							
Aortic	40 (56%)	24 (33%)	3 (4%)	2 (3%)	1(1%)	1	0
Mitral	26 (36%)	33 (46%)	2 (3%)	0	10 (14%)	(1%)	1 (1%)
Tricuspid	56 (78%)	0	1 (1%)	0	14 (19%)	0	1 (1%)
Pulmonary	66 (92%	0	1 (1%)	4 (6%)	0	0	1 (1%)

2.12 List of figures

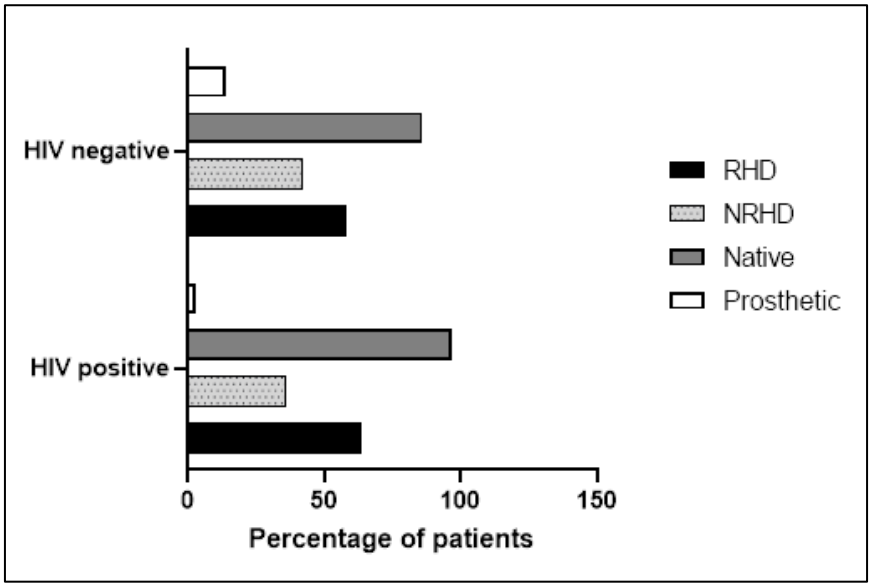

Figure 2.1. Valve pathology in HIV positive and HIV negative patients.

RHD = Rheumatic heart disease, NRDH = Non-rheumatic heart disease.

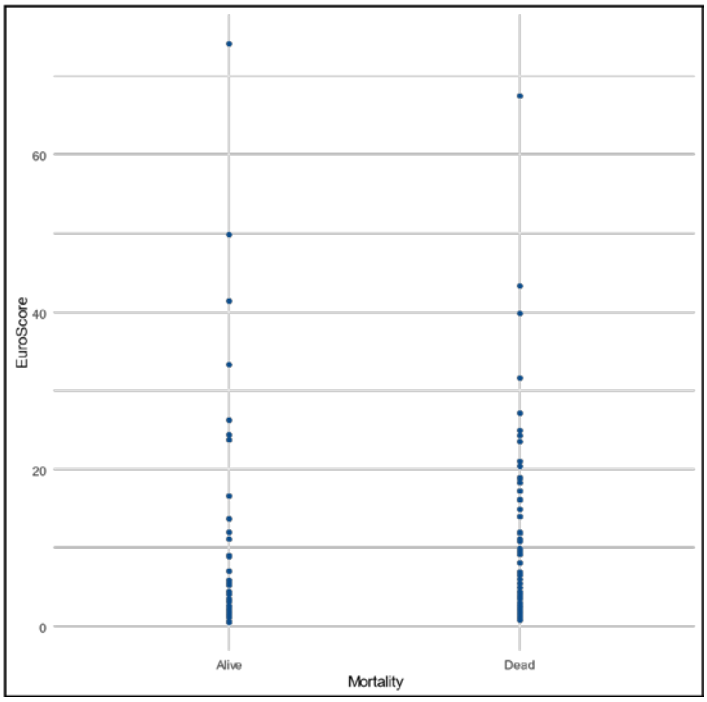

Figure 2.2. Correlation between EuroSCORE II and operative mortality.

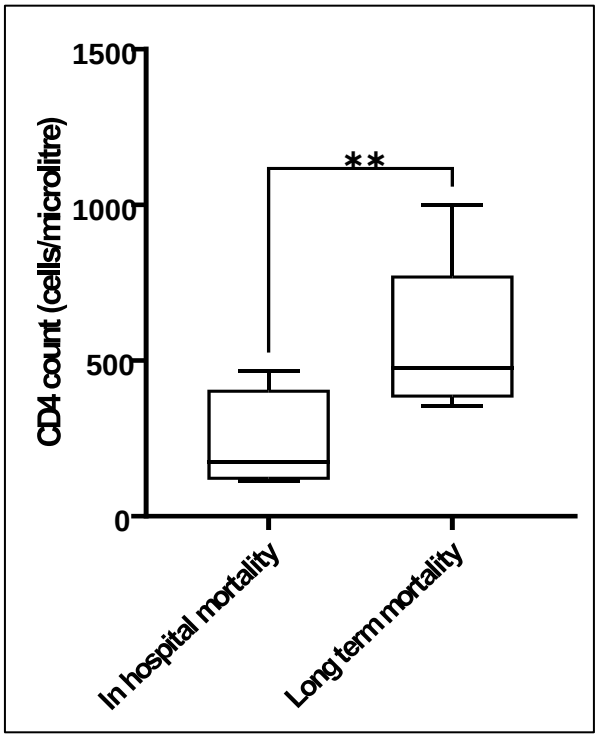

Figure 2.3. Difference in the CD4 count in HIV patients for in-hospital and long-term mortality **p < 0.01.

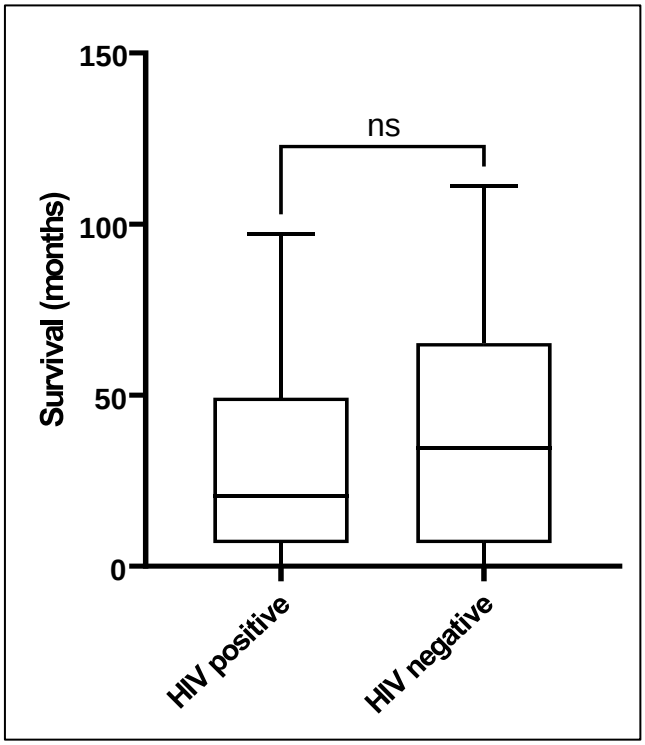

Figure 2.4. Survival of HIV positive patients and HIV negative patients. Significance set as p< 0.05.

List of References:

1. Prendergast BD. The changing face of infective endocarditis. Heart 2006; 92: 879 – 85.
2. Cahill TJ, Baddour LM, Habib G, Hoen B, Salaun E, Pettersson GB, et al. Challenges in infective endocarditis. J Am Coll Cardiol 2017; 69: 325-44.
3. Koegelenberg CFN, Doubell AF, Orth H, Reuter H. Infective endocarditis in the Western Cape Province of South Africa: a three-year prospective study. QJM 2003; 96(3): 217-25.
4. Dayer MJ, Jones S, Prendergast B, Baddour LM, Lockhart PB, Thornhill MH. Incidence of infective endocarditis in England, 2000-13: A secular trend, interrupted time-series analysis. Lancet 2015; 385: 1219-28.
5. Pecoraro AJ, Doubell AF. Infective endocarditis in South Africa. Cardiovasc Diagn Ther 2020;10(2): 252-61.
6. Bashore TM, Cabell C, Fowler V. 2006. Update on infective endocarditis. Curr Probl Cardiol 2006*;* 31(4): 274–352.
7. Murdoch DR, Corey GR, Hoen B, Miró JM, Fowler Jr VG, Bayer AS, *et al*. Clinical presentation, etiology and outcome of infective endocarditis in the 21st century: the international collaboration on endocarditis-prospective cohort study. Arch Intern Med 2009; 169(5): 463–73.
8. Beynon RP, Bahl VK, Prendergast BD. Infective endocarditis. BMJ 2006; 333: 334–9.
9. Thiene G, Basso C. Pathology and pathogenesis of infective endocarditis in native heart valves. Cardiovasc Pathol 2006;15(5): 256-63.
10. Willoughby ML, Basera W, Perkins SR, Comitis GAM, Fourie B, Lawrenson JB, et al. Infective endocarditis in infants and children in the Western Cape, South Africa: a retrospective analysis. Cardiol Young 2019; 29(10): 1282-6.
11. Nkomo VT. Epidemiology and prevention of valvular hart diseases and infective endocarditis in Africa. Heart 2007; 93(12): 1510 - 9.
12. Murray CJ, Ortblad KF, Guinovart C, Lim SS, Wolock TM, Roberts DA, *et al*. Global, regional, and national incidence and mortality for HIV, tuberculosis, and malaria during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2014;13: 384(9947): 1005-70.
13. Granich R, Gupta S, Hersh B, Williams B, Montaner J, Young B, et al. Trends in AIDS deaths, new infections and ART coverage in the top 30 countries with the highest AIDS mortality burden; 1990-2013. PLoS One 2015; 10(7): e0131353.

14. Wilkinson E, Junqueira DM, Lessells R, Engelbrecht S, van Zyl G, de Oliveira T, *et al*. The effect of interventions on the transmission and spread of HIV in South Africa: a phylodynamic analysis. Sci Rep 2019; 9: 2640.
15. Wang H, Wolock TM, Carter A. Estimates of global, regional, and national incidence, prevalence, and mortality of HIV, 1980–2015: the Global Burden of Disease Study 2015. Lancet HIV 2016; 3(8): e361-e87.
16. Miro JM, del Rio A, Mestres CA. Infective endocarditis and cardiac surgery in intravenous drug abusers and HIV-1 infected patients. Cardiol Clin 2003; 21: 167–84.
17. Vasudev R, Shah P, Bikkina M, Shamoon F. Infective endocarditis in HIV, International Journal of Cardiology, Volume 214, 2016, 216-217, ISSN 0167-5273.
18. Rheumatic fever and rheumatic heart disease. World Health Organ Tech Rep Ser. 2004; 923:1-122.
19. Ntusi NB, Mayosi BM. Epidemiology of heart failure in sub-Saharan Africa. Expert Rev Cardiovasc Ther 2009; 7(2): 169-80.
20. Mocumbi AO, Ferreira MB, Sidi D, Yacoub MH. A population study of endomyocardial fibrosis in a rural area of Mozambique. N Engl J Med 2008;3; 359(1): 43-9.
21. Pugliese A, Isnardi D, Saini A, Scarabelli T, Raddino R, Torre D. Impact of highly active antiretroviral therapy in HIV-positive patients with cardiac involvement. J Infect 2000; 40(3): 282-4.
22. Edmunds LH, Clark RE, Cohn LH, Grunkemeier GL, Miller DC, Weisel RD. Guidelines for Reporting Morbidity and Mortality after Cardiac Valvular Operations. Asian Cardiovascular and Thoracic Annals. 1996; 4(2):126-129.
23. https://www.statssa.gov.za/publications/P0302/P03022019.pdf, (Mid- year population estimates, 2019 (29, July 2019 10;00am)
24. De Villiers, MC, Viljoen, C A, Manning, K, van der Westhuizen, C, Seedat, A, Rath, M, Graham, M, & Ntsekhe, M. The changing landscape of infective endocarditis in South Africa. SAMJ *2019*: *109*(8), 592-596.
25. Losa JE, Miro JM, Del Rio A, Moreno-Camacho A, Garcia F, Claramonte X, Marco F, Mestres CA, Azqueta M, Gatel JM. Infective endocarditis not related to intravenous drug abuse in HIV-1-infected patients: report of eight cases and review of the literature. Clin Microbiol Infect 2003; 9(1): 45-54.
26. Cecchi E, Massimo I, Massimo T, Davide F; De Rosa, Giuseppe F. Rita Infective endocarditis in drug addicts: role of HIV infection and the diagnostic accuracy of Duke criteria, J Cardiovasc Med 2007; 8(3):169-175.

27. Koshy JJ, Engel, Human MP, Carrara H, Brink J, Zilla P. Long term outcome and EuroSCORE II validation in native valve surgery for active infective endocarditis in a South African cohort. SAHJ 2018; 15(2): 116-126.
28. Van Scoy RE. Culture-negative endocarditis. Mayo Clin Proc 1982; 57(3):149-54.
29. Li JS, Sexton DJ, Mick N, Nettles R, Fowler VG Jr, Ryan T, Bashore T, Corey GR. Proposed modifications to the duke criteria for the diagnosis of infective endocarditis, Clin Infect Dis 2000; 30:633–638.

3. List of Appendices

Appendix - A: Letter of approval from HSREC

Appendix - B: Permission from DOH

Appendix - C: Permission from HOD

Appendix - E: Research protocol approved by HSREC.

Appendix - D: Collection data forms

Appendix - I: Instructions to authors

Appendix - J: Turnitin Plagiarism Report

Appendix - A: Letter of approval from HSREC

UNIVERSITY OF THE FREE STATE
UNIVERSITEIT VAN DIE VRYSTAAT
YUNIVESITHI YA FREISTATA

UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

Health Sciences Research Ethics Committee

11-Jun-2019

Dear **Dr Taha Gwila**

Ethics Clearance: **Infective endocarditis in Central South Africa in the HIV era**
Principal Investigator: **Dr Taha Gwila**
Department: **Cardiothoracic Surgery Department (Bloemfontein Campus)**

APPLICATION APPROVED

Please ensure that you read the whole document

With reference to your application for ethical clearance with the Faculty of Health Sciences, I am pleased to inform you on behalf of the Health Sciences Research Ethics Committee that you have been granted ethical clearance for your project.

Your ethical clearance number, to be used in all correspondence is:**UFS-HSD2019/0630/2506**

The ethical clearance number is valid for research conducted for one year from issuance. Should you require more time to complete this research, please apply for an extension.

We request that any changes that may take place during the course of your research project be submitted to the HSREC for approval to ensure we are kept up to date with your progress and any ethical implications that may arise. This includes any serious adverse events and/or termination of the study.

A progress report should be submitted within one year of approval, and annually for long term studies. A final report should be submitted at the completion of the study.

The HSREC functions in compliance with, but not limited to, the following documents and guidelines: The SA National Health Act. No. 61 of 2003; Ethics in Health Research: Principles, Structures and Processes (2015); SA GCP(2006); Declaration of Helsinki; The Belmont Report; The US Office of Human Research Protections 45 CFR 461 (for non-exempt research with human participants conducted or supported by the US Department of Health and Human Services- (HHS), 21 CFR 50, 21 CFR 56; CIOMS; ICH-GCP-E6 Sections 1-4; The International Conference on Harmonization and Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Tripartite), Guidelines of the SA Medicines Control Council as well as Laws and Regulations with regard to the Control of Medicines, Constitution of the HSREC of the Faculty of Health Sciences.

For any questions or concerns, please feel free to contact HSREC Administration: 051-4017794/5 or email EthicsFHS@ufs.ac.za.

Thank you for submitting this proposal for ethical clearance and we wish you every success with your research.

Yours Sincerely

Dr. SM Le Grange
Chair : Health Sciences Research Ethics Committee

Health Sciences Research Ethics Committee
Office of the Dean: Health Sciences
T: +27 (0)51 401 7795/7794 | E: ethicsfhs@ufs.ac.za
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www.ufs.ac.za

Appendix - B: Permission from DOH

health

Department of Health
FREE STATE PROVINCE

29 May 2019

Dr T Gwila
Dept. of Cardiothoracic
UFS

Dear Dr T Gwila

Subject: Infective endocarditis in Central South Africa in the HIV era.

- Please ensure that you read the whole document, Permission is hereby granted for the above – mentioned research on the following conditions:
- Serious Adverse events to be reported to the Free State department of health and/ or termination of the study
- Ascertain that your data collection exercise neither interferes with the day to day running of **Universitas Hospital** nor the performance of duties by the respondents or health care workers.
- Confidentiality of information will be ensured and please do not obtain information regarding the identity of the participants.
- **Research results and a complete report should be made available to the Free State Department of Health on completion of the study (a hard copy plus a soft copy).**
- Progress report must be presented not later than one year after approval of the project to the Ethics Committee of the University of the Free State and to Free State Department of Health.
- Any amendments, extension or other modifications to the protocol or investigators must be submitted to the Ethics Committee of the University of the Free State and to Free State Department of Health.
- **Conditions stated in your Ethical Approval letter should be adhered to and a final copy of the Ethics Clearance Certificate should be submitted to** sebeelats@fshealth.gov.za / lithekom@fshealth.gov.za **before you commence with the study**
- No financial liability will be placed on the Free State Department of Health
- **Please discuss your study with Universitas Hospital CEO's on commencement for logistical arrangements see 2nd page for contact details.**
- Department of Health to be fully indemnified from any harm that participants and staff experiences in the study
- Researchers will be required to enter in to a formal agreement with the Free State department of health regulating and formalizing the research relationship (document will follow)
- You are encouraged to present your study findings/results at the Free State Provincial health research day
- Future research will only be granted permission if correct procedures are followed see http://nhrd.hst.org.za

Trust you find the above in order.

Kind Regards

Dr D Motau
HEAD: HEALTH
Date: 28/05/19

Head : Health
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Appendix - C: Permission from HOD

PERMISSION FROM HEAD OF DEPARTMENT OF CARDIOTHORACIC SURGERY

Dear HSREC/Whom it may concern

PROJECT TITLE:

Infective endocarditis in Central South Africa in the HIV era

I, Prof Francis Smit am the Head of Department in the Cardiothoracic Surgery and grant Dr Taha Gwila, the principal investigator for the above-mentioned project permission to conduct his study. He may use the patient data in the departmental database to conduct and complete his MMED study as he will be aiming to evaluate the current prevalence of infective endocarditis in an HIV era in Central South Africa.

The research study can commence as soon as the Health Sciences Research Ethics Committee grant him approval.

Yours faithfully

02/04/2019

HEAD OF DEPARTMENT **DATE**

Appendix - D: Research protocol approved by HSREC

1/4/2019

Appendix - D: Research protocol approved by HSREC A

Infective endocarditis in Central South Africa in the HIV era

by

Dr. Taha H Gwila

MBBCh, Tripoli University, 2010

A THESIS

Submitted in partial fulfillment of the requirements for the degree

MASTER OF MEDICINE IN CARDIOTHORACIC SURGERY

Department of Cardiothoracic surgery
College of Medicine

University of the Free State
Bloemfontein
Free State

Supervised by:

Prof. FE Smit (PhD)

April 2019

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Table of Contents

1. Introduction 74
Literature review 75
2. Infective Endocarditis 75
2.1 Background 75
2.2 Epidemiology 76
2.3 Microbiology 76
2.3.1 Culture-negative infective endocarditis
2.4 Pathogenesis 83
2.5 Pathophysiology 87
2.6 Clinical manifestations 88
2.7 Diagnosis 88
2.7.1 Duke criteria for diagnosis of infective endocarditis .
2.7.2 Echocardiography 88
2.8 Treatment 93
2.9 Complications .....
2.9.1 Cardiac Complications .....
2.9.2 Neurologic Complications .....
2.9.3 Systemic Emboli and Splenic Abscess .....
2.9.4 Prolonged Fever .....
2.9.5 Renal complications .....
2.10 Survival .....
2.11 Study rationale 100
2.11.1 Aim 101
2.11.2 Objectives 101
Methodology 102
3.6 Ethical aspects and good clinical practice 106
3.6.1 Ethical clearance 106

3.6.2 Safety variables 106
3.6.3 Premature discontinuation of the study 106
3.6.4 Good Clinical Practice (GCP) 106
3.6.5 Financial implications to the patient 107
3.6.6 Confidentiality 107
3.6.7 Contact details of the researchers 107
2. Time Frame 109
3. Budget 110
4. References 111
5. Appendices .....

1. Introduction

Infective endocarditis (IE) remains an evolving disease with a persistently high mortality and morbidity (Prendergast, 2006). Non-invasive imaging, molecular science, diagnostic protocols, and curative surgery have all become commonplace in the developed countries, yet the incidence remains unchanged and annual mortality approaches 40% (Benyon *et al*., 2006).

Major changes have been witnessed in the epidemiology, bacteriology and clinical presentation of infective endocarditis as well as major advances in the diagnosis and management of this clinical disease (Koegelenberg *et al*., 2002).

In Western populations in particular, chronic rheumatic heart disease is now an uncommon antecedent, whereas degenerative valve disease in elderly people, intravenous drug misuse, preceding valve replacement, or vascular instrumentation have become increasingly frequent, coinciding with an increase in staphylococcal infections and those due to fastidious organisms (Benyon *et al*., 2006).

Infective endocarditis in Africa remains a disease of the young. Rheumatic heart disease still is the main predisposing factor where modern investigations and management are the privilege of the well-off few who live in large urban areas (Benyon *et al*., 2006; Nkomo, 2007). However, only a few large epidemiological studies have been performed in Africa and to date, knowledge of the clinical features and natural history of IE has relied largely on small, uncontrolled, outdated studies. Therefore, the aim of the study will be to evaluate the current prevalence of infective endocarditis in an HIV era in Central South Africa.

2. Infective Endocarditis

2.1 Background

Infective endocarditis (IE) refers to an active intracardiac infection that resides on one or more heart valve surfaces. Other cardiac structures can also be involved, and endovascular infection can also occur. Other cardiac structures include the sub valvular apparatus, cardiac muscles, and pericardium (Mauri, de Lemos and O'Gara, 2001). Infections of the inner surface of the heart is now referred to as infective endocarditis which can be caused by any microorganism form bacterial or fungal species (Thiene and Basso, 2006).

2.2 Epidemiology

1 Infective endocarditis:

Infective endocarditis (IE) is a rare but remains an evolving disease with persistently high mortality and morbidity (Prendergast, 2006). In the United States and Western Europe, the incidence of community-acquired nativevalve endocarditis in most recent studies is 1.7 to 6.2 cases per 100,000 person-years (Mylonakis and Calderwood, 2001). Surprisingly, the incidence has not declined over the last 30 years, and now with more health care interventions, such as pacer/defibrillators, and an increasingly elderly population with degenerative valvular heart disease, the number susceptible to endocarditis is increasing. Given the weak evidence for endocarditis prophylaxis, there remains a large population at risk (Bashore, Cabell and Fowler, 2006).

Epidemiological studies suggest a bimodal age distribution, with the younger population dominated by patients with rheumatic heart disease or congenital heart disease and injection drug use (Mauri *et al.,* 2001). As increased longevity has given rise to degenerative valvular disease, placement of prosthetic valves, and increased exposure to nosocomial bacteremia, the median age of patients has gradually increased; it was 30 to 40 years during the pre-antibiotic era and 47 to 69 years more recently (Mylonakis and Calderwood, 2001).

Men are reported to be more often affected than women (in a ratio of 2:1) (Benyon, Bahl and Prendergast, 2005).

2 HIV:

Sub-Saharan Africa with the South African population currently has the largest prevalence of HIV/AIDS in the world. The region has almost a third of the world's HIV positive population with less than 2% of the global population. The HIV prevalence dramatically increased during the 1990's with epidemiological studies showing increases from <1% to 24.5% between the start and end of the decade (Barron *et al.,* 2013).

The local government response was very slow and indecisive which aided in the increase. From the early 2000's government changed their stance

regarding HIV which has led to a multitude of campaigns to affect change. These campaigns have made major strides in curbing increases in HIV prevalence, but the percentages are not declining. In 2016 government adopted the UNAIDS 90-90-90 strategy which aims to have 90% of patients with HIV diagnosed and on combination antiretroviral treatment with a nighty percent viral suppression (UNAIDS, 2016a).

Combination antiretroviral therapy is of critical importance and without it, patients experience increased CD4+ T cell loss combined with immunological abnormalities, which can result in increased susceptibility to opportunistic infections (Deeks, 2015). Combination therapy has been pivotal in reducing HIV viral load, allowing the increase of CD4+ T cells and reducing the risk of developing AIDS (Deeks, 2015). These patients however still present a higher-than-normal risk of developing bloodstream infections and IE (Taramasso, 2016).

The relationship and implications of patients having HIV and developing IE are not yet clear. Due to the HIV infection and the susceptibility to secondary infections, one would expect IE to be more prevalent in HIV positive patients, but it is not considered a complication of HIV/AIDS. It is almost limited exclusively to HIV patients who are IV drug users in the western societies (Currie, 1995; Yunis, 1998). Outcomes observed in patients with active systematic disease was poor, especially with extreme immune suppression (CD4 count < 200 cells/mL) (Pulvirenti *et al.,* 1996). HIV infection on its own therefor does not seem to predispose patients to more severe outcomes of IE or a risk factor despite the immune suppression observed (Currie, 1995).

3 RHD:

A large spectrum of heart diseases may predispose the onset of infective endocarditis. Rheumatic valve disease, particularly mitral and aortic valve steno-incompetence, has been considered for years as the major risk factor. In the 1970s, rheumatic valve disease was the predisposing lesion for infective endocarditis, accounting for 20% to 25% of cases, whereas in the1980s, it dropped to 7–10% (Thiene and Basso, 2006). Although the frequency of rheumatic valve disease has diminished in Europe and North America, it is still endemic in Third World countries where it represents by far the leading predisposing factor for infective endocarditis, especially in children (Table 1) (Thiene and Basso, 2006).

Table 1: Studies on the prevalence of rheumatic heart disease in Africa (reproduced from Nkomo, 2007).

PREVALENCE OF RHEUMATIC HEART DISEASE IN AFRICA					
Country (city)	Year of study	Number screened	Age (years)	Prevalence (per 100 population)	Echo
Algeria (Setif)	1990	11228	6 - 19	2	? No
Algeria (Oran)	1990	15430	6 - 19	1.94	? No
Egypt (Cairo)	1986	60022	6 - 15	1.5	? No
Cameroon (Yaounde)	1988-9	-	6 - 19	2.1	No
Congo (Brazzaville)	1996	2153	5 - 16	1.4	Yes
DR Congo (Kinshasa - Kinsenso ans Sanga Mamba)	1996	4848	5 - 16	14	Yes
Ethiopia (Butajira)	1992	3235	13.4 (3.5)	4.6	? Yes
Ethiopia (Addis Ababa)	1999	9388	13 – 15 (7.1 los SES, 1.0 high SES)	6.4	Yes
Ivory coast (4 areas)	1977-8	20013	6 - 22	1.45	No
Kenya (Kakamega)	1985	3631	5 -15	1.7	No
Kenya (Nairobi)	1994	1115	5 -15	2.7	Yes
Mali (Bamako)	1986	14351	5 -15	2.9	? Yes
Nigeria (Lagos)	1978	12755	6 -12	3	No
Republic of Guinea (Conakry)	1992	27110	6 -25	3.9	Yes
South Africa (Soweto)	1972	12050	2 -18	6.9 (peak 19.2 in the age group 15-18 years)	No
South Africa (Inanda)	1984	4408	4 -18	1	No
Sudan (Safaha Town)	1986-1989	13332	5 -15	3	Yes
Zambia (Lusaka)	1986	5200	5 -15	14.6	Yes in subset
Zambia (Lusaka)	1987	11 944	5 -16	12.5	Yes in 25%

The incidence of RHD worldwide has declined over the last years, yet it remains endemic in overcrowded areas where basic health care facilities are unreachable (Okello, 2012).

In the south African population recent study by (Koshy *et al.,* 2018) reported 80 % of infective endocarditis patients had RHD as a predisposing heart pathology, indicating a significant part of the South African population at risk of developing IE.

Rheumatic heart disease is a one of few, if not only the preventable acquired heart disease affecting poor and middle-income countries that can lead to high morbidity and mortality, attention to early recognition and management is crucial to prevent the risk of developing a more serious and deadly disease namely infective endocarditis (Peters, 2019)

Other conditions associated with an increased incidence of infective endocarditis include poor dental hygiene, long-term hemodialysis, and diabetes mellitus. (Mylonakis and Calderwood, 2001). The presence of diabetes mellitus (DM) has been associated with even worse outcomes in patients with IE. The prevalence of DM among IE-patients is around 17%, recently found that the duration and complications of diabetes mellitus are an independent risk for IE. There was a stepwise increase in the associated risk of IE with increasing duration of DM – an effect independent of age and there was an increase in the associated risk of IE with increased severity and number of diabetic late-stage complications (Østergaard *et al*., 2018).

Infection with human immunodeficiency virus (HIV) may independently increase the risk of infective endocarditis. Among patients infected with HIV, infective endocarditis is usually associated with injection-drug use or long-term indwelling intravenous catheters (Mylonakis and Calderwood, 2001).

Transcatheter interventions are becoming more and more used in the recent era, with technology improvement, old frail patients who were not considered operable for aortic valve surgery are now a TAVR candidates, with more cardiac interventions for other comorbid conditions, this will eventually lead to more risk of developing bacteraemia and IE. This specific cohort represent a serious challenge for management of TAVR related endocarditis Regueiro et al (2016) reported the incidence of IE post TAVR was 1.1% per person- year, within the 1st six month of their procedure, and an

in-hospital mortality and 1 year mortality ranging between 47%-75% respectively. These extremely high figures raise the importance of developing more better and effective policies of prevention and better valve characteristics, in opposed to treating this subgroup of patient that were deemed very high risk for surgery before the initial procedure (Cahill, 2017).

2.3 Microbiology

The number of organisms involved with infective endocarditis are evolving with more uncommon species namely the HACEK group were cultured. (Mauri *et al.,* 2001), to date gram +ve bacteria represents the most cultured organisms, more recently studies showed Staphylococcus aureus is more dominant then streptococcus viridans (Mylonakis and Calderwood, 2001). The change in patients' profile from being younger age with structural heart disease to older frail patients with more health care-associated endocarditis (Selton-Suty *et al*., 2012).

1.3.1 Culture-negative infective endocarditis

culture-negative infective endocarditis is not an uncommon entity it can be as high as 31% of the total IE cases, giving a diagnostic and therapeutic challenge, the most obvious explanation to this phenomenon is administration of antibiotics prior to obtain the blood cultures. Specific serological testing with specialized media is needed to isolate such organisms, that consumes time because of the slow growth reported (Raoult. 2005).

It has been shown that long-term pre-operative antimicrobial treatment had a negative impact on microbiological tests done on resected endocardial material. After 2 weeks of therapy, all valve cultures were negative, but PCR was positive in half of the cases. PCR aided in diagnostic work-up, especially in blood culture-negative cases (Halavaara *et al*., 2019).

2.3 Pathogenesis

Numerous processes and steps are involved that allow a microorganism to migrate to the heart valves, replicate and form large vegetations. The majority of infective endocarditis (IE) occurs in the setting of predisposing cardiac disease (Mauri *et al.*, 2001).

Adherence of the bacteria to the damaged endothelial service takes place in two possible mechanisms (fig. 1):

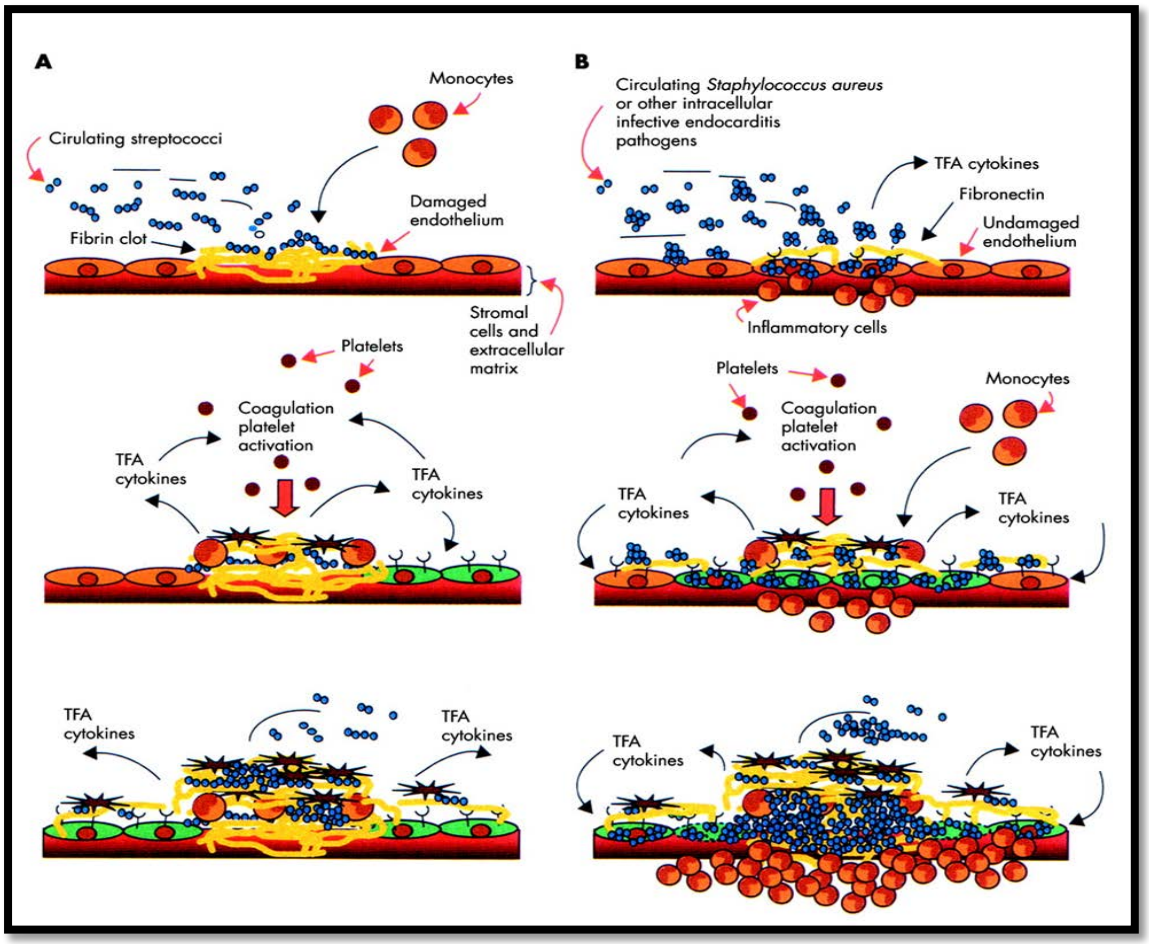

Figure 1: Bacterial valve colonization (reproduced from Prendergast, 2005).

1.4.1 Colonization of damaged epithelium

Stromal cells that are exposed, in conjunction with extracellular matrix proteins lead to the forming of fibrin-platelet clots that can bind to the streptococci. The clots can attract monocytes that produce tissue factor activity (TFA) and cytokine which lead to the activation of coagulation cascades. The cascades lead to the attraction and activation of blood platelets, which induce integrin, cytokine and TFA from endothelial cells, which promote vegetative growth. (Prendergast, 2005).

1.4.2 Colonization of inflamed valve tissues

Localized inflammation causes the endothelial cells to express integrin's which bind plasma fibrinonectin on to which the microorganisms can bind, which result in then their internalization into the endothelial cells. This leads the cells to trigger inflammation and coagulation, which all promotes vegetative growth. The cells are eventually lysed by the secretion of hemolysins that are membrane active proteins (Prendergast, 2005). Another diagram adapted from (Werdan *et al.*, 2014) describes the pathogen-host interaction and risk states (figure 2).

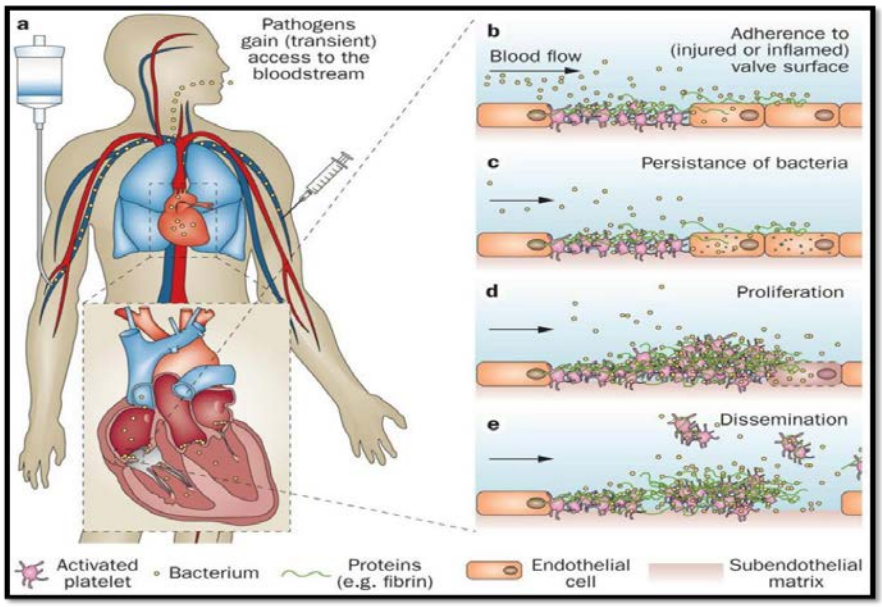

Figure 2. Pathogenesis of endocarditis

a. Pathogens gain access to the bloodstream, for example via an intravenous catheter, injection drug use or from a dental source. **b** Pathogens adhere to an area of abnormal cardiac valve surface. **c** Some pathogens, such as S. aureus, obtain intracellular access to the valve endothelium. **d** the infected vegetation is created by burying of the proliferating organism within a protective matrix of serum molecules. **e** Vegetation particles can detach and disseminate to form emboli. These may lead to complications such as ischemic stroke, mycotic aneurysms and infarcts or abscesses at remote sites. Figure adapted from Werdan et al (2014).

2.4 Pathophysiology

- The pathophysiological picture of infective endocarditis is demonstrated by several mechanisms:
- Direct extension of infection which can lead to severe valvular dysfunction (valvular regurgitation being the most common manifestation),
- Embolization causing distal infarction or infection,
- Hematogenous seeding of distant organs may create abscesses, and
- Immune complex deposition producing organ dysfunction such as glomerulonephritis and arthritis (Mauri *et al.*, 2001).

As a systemic disease, IE results in characteristic pathological changes in multiple target organs (Figure 3) (Morris *et al.*, 2003).

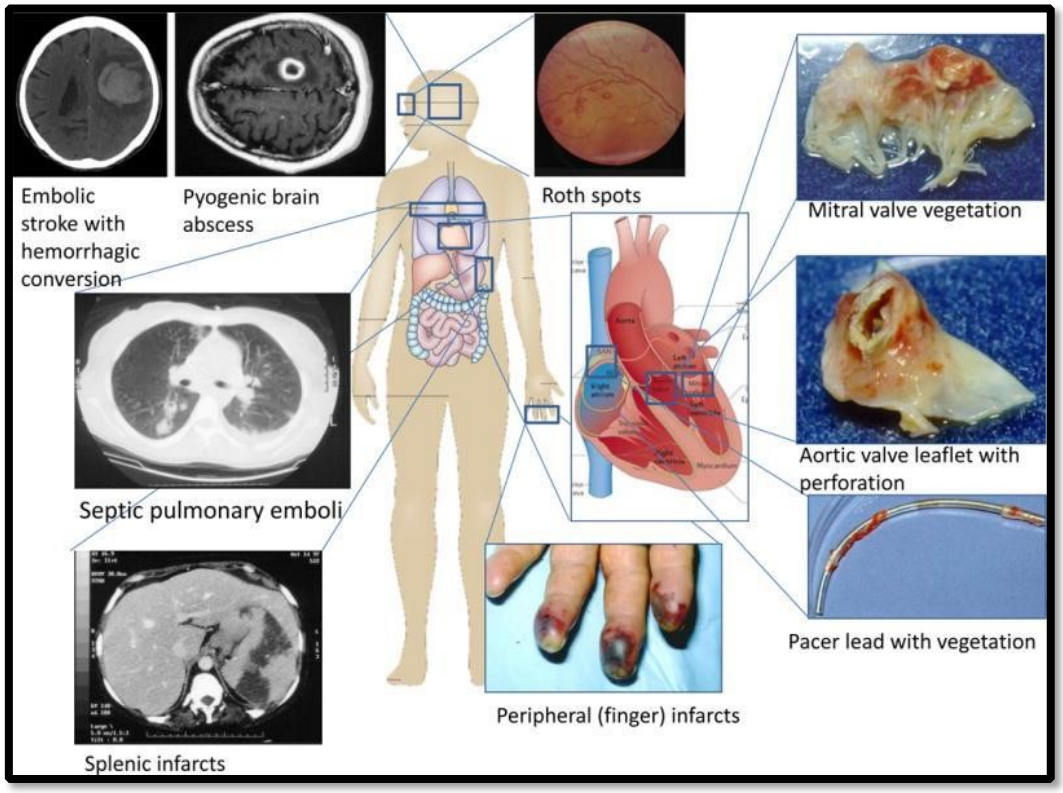

Figure 3. End-organ manifestations of endocarditis

A) CT scans of pyogenic brain abscess and embolic stroke with hemorrhagic conversion. **B)** CT scan demonstrating multiple septic pulmonary emboli. **C)** CT scan demonstrating peripheral wedge-shaped splenic infarcts. **D)** Roth spots on funduscopic exam. E) Infarcts affecting multiple fingers. F) Explanted mitral valve with vegetation. **G)** Explanted aortic valve leaflet with vegetation and perforation. **H)** Pacemaker lead with vegetation. Roth spots photo courtesy of Holland et al (2017).

2.5 Clinical manifestations

Infective endocarditis can frequently present as to intra or extracardiac manifestations according to the virulence of the infection and timing of presentation. Most commonly, fever is observed, except for patients with severe heart, liver or chronic renal failure and patient who received antibiotic treatment, it might not be present (Mylonakis and Calderwood, 2001).

Additional observed symptoms can include malaise, weight loss and nightly sweats. High percentage of patients present clinically with a heart murmur, conjunctivitis or petechiae on the skin (Mylonakis and Calderwood, 2001).

Classic textbook signs may still be seen in the developing world, although peripheral stigmata of infective endocarditis (Osler's nodes, Janeway lesions) are increasingly uncommon elsewhere, as patients generally present at an early stage of the disease (Benyon *et al*., 2005).

2.6 Diagnosis

The combination of three important aspects (clinical observations, laboratory results and echocardiographic information are crucial for the diagnosis of infective endocarditis (Mylonakis and Calderwood, 2001). In 1994, the Duke criteria for the diagnosis of infective endocarditis were proposed to increase the number of definite diagnoses (Mauri *et al.,* 2001).

1.6.1 Duke criteria for the diagnosis of infective endocarditis

The Duke criteria stratify patients with suspected infective endocarditis (IE) into 3 categories (Table 2):

- Definite cases – identifies either clinically or pathologically (IE proved at surgery/autopsy),
- Possible cases – not meeting the criteria for definite IE and
- Rejected cases – no pathological evidence of IE at autopsy or surgery (Badour *et al.,* 2005).

Table 2: Definition of infective endocarditis according to the modified Duke Criteria (reproduced from Bayer *et al.*, 1998).

Definite IE

- Pathological criteria
- Microorganisms: demonstrated by culture or histology in a vegetation, in a vegetation that has embolized, or in an intracardiac abscess, or
- Pathological lesions: vegetation or intracardiac abscess present, confirmed by histology showing active endocarditis.
- Clinical criteria, using specific definitions listed in Table 3
- major criteria, or
- 1 major and 3 minor criteria, or
- 5 minor criteria

Possible IE

- Findings consistent with IE that fall short of "Definite" but not "Rejected."

Rejected

- Firm alternate diagnosis for manifestations of endocarditis, or
- Resolution of manifestations of endocarditis with antibiotic therapy for $\leq$4 days, or
- No pathological evidence of IE at surgery or autopsy, after antibiotic therapy for $\leq$4 days

A diagnosis of IE is based on the presence of either major or minor clinical criteria. Clinically definite IE by the Duke Criteria requires the presence of two major criteria, 1 major criterion and 3 minor criteria, or 5 minor criteria (Table 3).

Table 3: Definition of the terms used in the modified Duke Criteria

(Reproduced from Bayer *et al.*, 1998).

Definition of the terms used in the modified Duke Criteria

Major criteria

1. Positive blood culture for IE

A. Typical microorganism consistent with IE from 2 separate blood cultures as noted below:

(i) viridans streptococci,[1] Streptococcus bovis, or HACEK group, or

(ii) community-acquired Staphylococcus aureus or enterococci, in the absence of a primary focus, or

B. Microorganisms consistent with IE from persistently positive blood cultures defined as

(i) ≥ 2 positive cultures of blood samples drawn >12 hours apart or

(ii) all of 3 or a majority of ≥ 4 separate cultures of blood (with first and last sample drawn ≥ 1 hour apart)

2. Evidence of endocardial involvement A.

Positive echocardiogram for IE defined as

(i) oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation, or

(ii) abscess, or

(iii) new partial dehiscence of prosthetic valve, or

B. New valvular regurgitation (worsening or changing of preexisting murmur not sufficient) Minor criteria

1. Predisposition: predisposing heart condition or intravenous drug use

2. Fever: temperature 38.0°C

3. Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions

4. Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth spots, and rheumatoid factor

5. Microbiological evidence: positive blood culture but does not meet a major criterion as noted above[2] or serological evidence of active infection with organism consistent with IE

6. Echocardiographic findings: consistent with IE but do not meet a major criterion as noted above

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[1] Includes nutritionally variant strains (Abiotrophia species).

[2] Excludes single positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis.

(Reproduced from Bayer *et al.*, 1998).

1.6.2 Imaging

1- Echocardiography:

Echocardiography plays an important role in the diagnosis and management of infective endocarditis (Baddour *et al*., 2005). The information that can be provided using echocardiogram facilitate the surgical decision making, such information including the size and mobility of the vegetations, structure and function of affected valve, and overall ventricular function (fig. 2) (Mauri *et al*., 2001).

Figure 2: Bacterial valve colonization (reproduced from Prendergast, 2005) [3D TEE en-face view of mitral valve demonstrating multiple vegetations (arrows)].

Echocardiography is not an appropriate screening test in the evaluation of patients with fever or a positive blood culture that is unlikely to reflect IE. Nevertheless, some form of echocardiography should be performed in all patients suspected of having IE (Prendergast, 2005).

Transesophageal echocardiography (TEE) is safe in experienced hands and has a sensitivity for the detection of vegetations in IE that is very high. TEE images benefit from higher ultrasonic frequencies, which improve spatial resolution and the elimination of interference from interposed tissues. TEE has a

substantially higher sensitivity (76% to 100%) and specificity (94%) than TTE for perivalvular extension of infection because the TEE transducer in the esophagus is in physical proximity to the aortic root and basal septum, where most such complications occur (Bayer *et al.,* 1998).

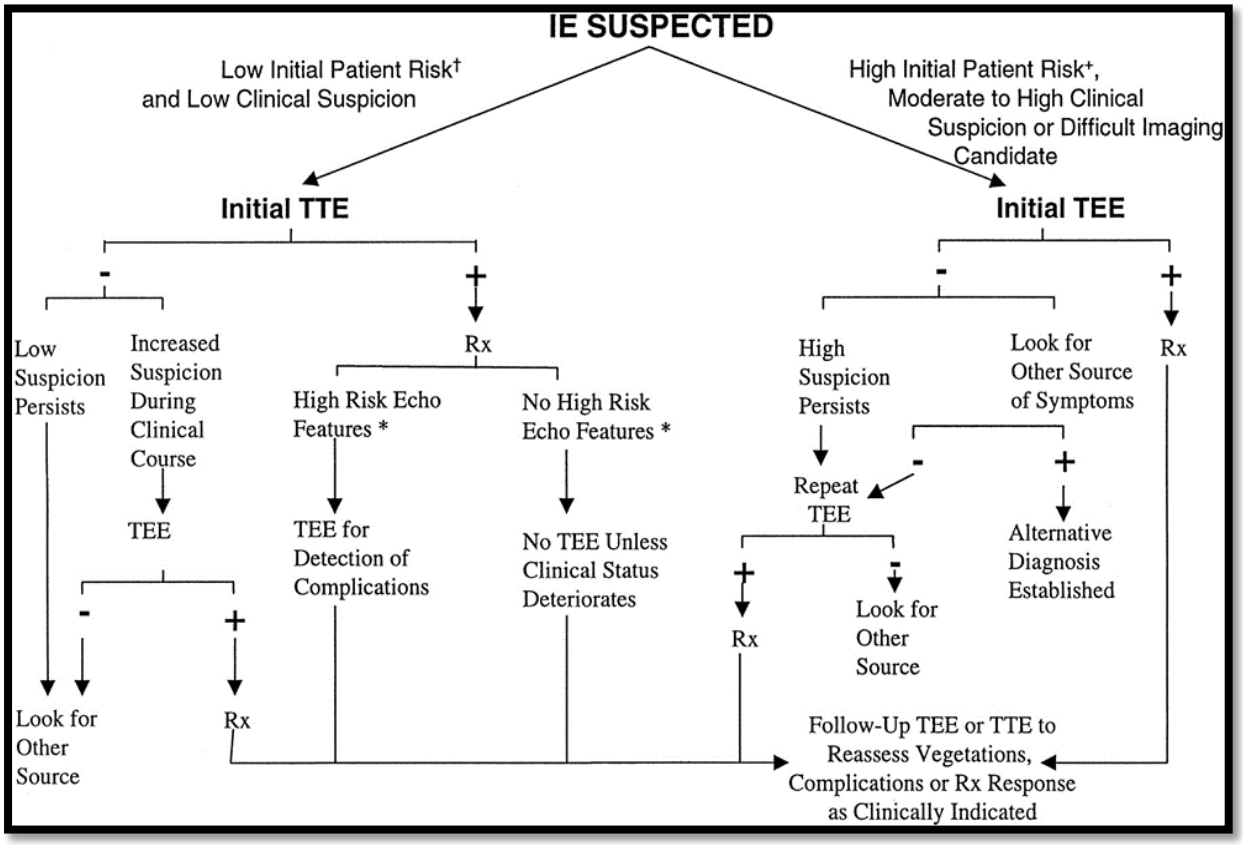


Figure 3: An approach to the diagnostic use of echocardiography (echo).

*High-risk echocardiographic features include large and/or mobile vegetations, valvular insufficiency, a suggestion of perivalvular extension, or secondary ventricular dysfunction. † For example, a patient with fever and a previously known heart murmur and no other stigmata of IE. +High initial patient risks include prosthetic heart valves, many congenital heart diseases, previous endocarditis, new murmur, heart failure, or other stigmata of endocarditis. Rx indicates antibiotic treatment for endocarditis (Adapted from Bayer *et al*., 1998).

2- Multislice computed tomography (MSCT):

The use of CT coronary angiography is shown to be safe and good alternative technique for evaluation of coronary arteries if needed in the settings of acute aortic valve endocarditis where

risk of embolization is high with conventional coronary angiography (Hekimian *et al.*, 2010).

MSCT is helpful in evaluating the extent of infection and abscess formation around the aortic valve and aortic root, it's been shown that the accuracy is as good as TOE, according to the comparative study performed by Feuchtner et al (2009).

CT scan with contrast can be used as an acceptable alternative to MRI in evaluating intracranial bleeds and infarcts in critically ill patients with IE (Goddard *et al.*, 2005).

3- MRI:

In acute infective endocarditis, MRI demonstrated a frequent intracerebral lesion in up to 80% of patients irrespective of their neurological symptoms. (SnyggMartin *et al.*, 2008). Cerebral MRI also aids in the diagnosis of IE as it adds an extra criterion to the Duke's criteria for patients who were asymptomatic but positive cerebral finding (Li *et al.*, 2000).

4- Nuclear imaging:

Radiolabeled White blood cells SPECT/CT and FDG PET/CT usage to aid the diagnosis of IE in the category of possible IE by Duke's criteria has shown good results, 18F-FDG PET/CT also reported useful tool to detect extra cardiac metastatic infectious emboli (Bonfiglioli *et al.*, 2013). In prosthetic valve dysfunction FDG PET/CT is capable of distinguishing infective etiologies from others and adds a novel criterion in diagnosing prosthetic valve endocarditis (Saby *et al.*, 2013).

2.7 Treatment

The optimal management of infective endocarditis (IE) relies on a close collaboration between a broad range of medical specialties Known as the **'Endocarditis Team'** that includes cardiology, cardiac surgery, anesthesiology, infectious diseases, internal medicine, neurology, intensive care, microbiology, and radiology. This is a class IIa indication level of evidence B according to the 2015 ESC guidelines in the management of complicated IE (2015 ESC Guidelines for the management of infective endocarditis).

2.7.1 Prophylaxis:

Treatment starts with prevention, which includes general measures for all population (dental and skin hygiene, avoidance of tattooing and piercing, encouraging of using peripheral IV accesses over central catheters). (Duval, Leport, 2008) and antibiotic prophylaxis for high and intermediate risk populations performing high-risk procedures including dental, cardiac, and vascular interventions.

High-risk population according to the 2015 ESC guidelines summarized as follows:

4- Pts with intracardiac implants (valve prostheses or devices) had higher risk of developing IE and higher morbidity and mortality (Lalani *et al.,* 2013).
5- Patients with previous history of endocarditis, the chance of developing a second episode is higher with higher adverse outcomes (Chu *et al.,* 2005).
6- Patients with unattended cyanotic congenital heart disease (CHD) and operated CHD with prosthetic implants within the six months of surgery (Baumgartner *et al.*, 2010; Knirsch and Nadal, 2011).

2.7.2 Medical therapy:

Medical treatment in the form of antimicrobial therapy to eradicate the causative organism using bactericidal regimens is the hallmark of managing this disease. With the surgical role in removing infected tissue and treating structural complications (Durack *et al.*,1974; Wilson *et al.*, 1978).

Bactericidal antibiotics with adequate therapeutic serum levels for a longer duration of treatment (4-6) weeks is necessary to eradicate dormant organisms, the duration of treatment differs between shorter as in sensitive bacteria and longer course of management for more resistant species (Prendergarst, 2006).

2.7.3 Surgical management:

Early surgical intervention is important in the management of IE, however deciding when to intervene is more complicated. For patients with NYHA 3 and 4 heart failure, large vegetations possessing embolic risk, and uncontrolled sepsis despite accurate type and dosing of antibiotics urgent surgical intervention is recommended. The exception being patients who suffered cerebral infarction, or more importantly intracerebral hemorrhage whose surgery should be delayed between two and four weeks. The patient risk and benefit analysis should be performed in an individual manner to determine the urgency of surgical intervention. The decision to intervene should always be based on the benefits exceeding the operative risk involved (Kang, 2015).

2.7.4 Surgery for heart failure:

The most sever and common complication of infective endocarditis is heart failure, and this represents the most frequent indication for early surgical intervention in both native and prosthetic valve endocarditis irrespective of age and stage of heart failure (cardiogenic shock), only if sever comorbidity prohibits surgery (Habib *et al.*, 2015).

2.7.5 Surgery for infection control:

Uncontrolled infection in the form of local extension of infection (abscesses, false aneurysm or enlarging vegetations), or PVE caused by virulent organisms (Staph infection and HACEK gram -ve species), persistent positive blood cultures despite adequate and accurate antimicrobial therapy, or fungi and multi-resistant organisms cultured, early surgery is indicated.

2.7.6 Surgery to prevent embolism:

Systemic embolization is very common in EI, at presentation twenty to fifty percent of patients developed embolic phenomena, it falls down to 6-20 % after initiation of antibiotic therapy, and the risk continues to be high for the 1st two weeks of treatment (Vilacosta *et al.*, 2002). Surgery must be performed in an urgent basis (within days) to prevent embolic events (Thuny *et al.*, 2005).

The decision to operate for emboli prevention is not as clear, it has to be individualized for each patient, the main indication for early operation is based on certain findings, more importantly the size and mobility of the vegetations, previous one or more embolic event, presence of other complications, and the duration of antibiotic therapy (Thuny *et al.*, 2011).

The 2015 ESC guidelines recommend urgent surgical intervention for patients who has >1 cm vegetations on the mitral or aortic valves with previous one or more embolic events despite appropriate antibiotic therapy (Thuny *et al.*, 2005). With sever valve dysfunction, surgery can also be performed on patients with large vegetation of >3cm, and for those who has an isolated vegetation of >1.5 cm surgery may be performed if the valves can be preserved.

Surgery for Infective endocarditis has a very high mortality even in experienced centers exceeding any valvular heart surgery (Thuny *et al*, 2012). The reported in-hospital and one-year mortality according to multicenter study results were 15-20% and up to 40% respectively (Kang *et al.*, 2012).

2.8 Complications

Complications related to IE are quite frequent, the number and rate of developing these complications differs between the studies, where 57 % of patients having one complication and 26% with two and about 14% with three or more complications (Mocchegiani *et al*, 2009).

These complications can be either cardiac or extracardiac, where intracardiac is related to the direct spread of infections and extra cardiac can be related to embolic event or immune complex (Habib *et al*, 2015). The development of such complications also depends on the causative organisms, the time between developing the disease and the initiation of treatment and treatment modality (Cahill *et al*, 2017)

2.8.1 Cardiac complications

The most important cardiac complication of infective endocarditis is the development of heart failure, the presence of moderate to severe HF at presentation is the most significant predictor of in-hospital and late mortality (Nadji *et al.*, 2009). Heart failure usually develops from direct destruction of cardiac valves by the infection leading to acute or worsening preexisting regurgitation, and less commonly the development of fistula or obstruction of a valve due to a large vegetation (Anguera *et al.*, 2005).

1.8.2 Neurologic complications

As described above embolic phenomena is very common, it affects the brain in 65% of cases with 20-40% of which develop neurological complications (Mylonakis and Calderwood, 2001). Stoke is proven to be an independent worse prognostic factor for IE patients (Thuny *et al.*, 2007). The majority of reported cerebrovascular accidents were mainly ischemic; the presence of hemorrhagic stroke poses a great challenge in management of this subgroup in terms of early surgical interventions. Surgery should be delayed to >4 weeks (Yoshioka *et al.*, 2012).

1.8.3 Systemic emboli and splenic abscess

Systemic embolization is a frequent complication of left sided endocarditis, where majority happens before admissions (Hubert *et al.*, 2013). The brain and spleen being the most common sites. Splenic infarcts are usually asymptomatic, persistent fever and bacteremia raises the possibility of splenic abscesses, and further work up is needed (abdominal sonar, CT, or MRI) for diagnosis (Bonfiglioli *et al.*, 2013). Rarely surgery is indicated for splenic infarction but should be considered in case of rupture or large abscesses refractory to antibiotics (Akhyari *et al.*, 2012).

1.8.4 Prolonged fever

Normally fever subsides 2 to 3 days of initiation of antibiotics in non-virulent infections. If fever that lasts more than 2 weeks is considered prolonged and should raise the possibility of more serious complication as in local extension of infection to the paravalvular areas and myocardium forming abscesses. It can also occur due to septic emboli forming remote abscesses, one should also consider drug reactions especially if recurrent fever after resolving (Mylonakis and Calderwood, 2001).

2.9 Survival

Despite advances in medical knowledge, technology and antimicrobial therapy, infective endocarditis (IE) is still associated with devastating outcomes. Irrespective of the follow-up period, a significantly higher mortality rate was reported in IE patients, and the burden of IE-related complications was immense. The overall pooled mortality estimates for IE patients who underwent short- and long-term follow-up were 20% and 37% respectively (Abegaz *et al.*, 2017).

Even after successful treatment of an episode of infective endocarditis, long-term mortality and morbidity remain high. Factors predictive of long-term mortality are age > 55 years, congestive heart failure, and the initial presence

of a few symptoms of endocarditis. Moreover, early valve replacement has the potential to improve long-term survival in a wide range of patients with infective endocarditis Netzer *et al.,* 2002).

According to the 2015 ESC Guidelines for the management of infective endocarditis, prognosis was influenced by 4 important findings categorized as follows:

Patient's characteristics:

a. Old age
b. DM
c. PVE
d. Comorbidities (frailty, immunosuppression).

Clinical complications of IE:

e. HF
f. RF
g. Hemorrhagic stroke
h. Septic shock.

Causative microorganism:

i. Staph. aureus
j. Fungi
k. Non-HACEK Gram-negative bacilli

Echocardiographic findings

l. Periannular complications
m. Severe left-sided valve regurgitation
n. Poor LVEF
o. PAH
p. Large vegetations
q. Severe prosthetic valve dysfunction

r. Premature mitral valve closure and other signs of elevated diastolic pressures.

Predictors of poor outcome in patients with IE (Habib *et al.*, 2015).

To summarize, assessing prognosis can be easily established for all patients admitted with IE by using their clinical, microbiological and echo data to aid in decision making with regards to the initial management plan for better outcomes (Habib *et al.*, 2015). Patients who present with heart failure and complicated Periannular endocarditis and/ or culture positive for staph. Aureus represents a highest mortality and early surgical treatment is required (San *et al.*, 2007). The worst outcome reported was amongst those patients who needed surgery but could not receive it due to the prohibited risk for surgical intervention (Mirabel *et al.*, 2014).

2.10 Study rationale

Infective endocarditis (IE) remains an evolving disease with persistently high mortality and morbidity (Prendergast, 2006). The incidence of infective endocarditis has not declined over the last 30 years, and now with more health care interventions, such as pacer/defibrillators, and an increasingly elderly population with degenerative valvular heart disease, the number susceptible to endocarditis is increasing. Given the weak evidence for endocarditis prophylaxis, there remains a large population at risk (Bashore *et al.*, 2006).

While the incidence of rheumatic valve heart disease has dropped significantly in the western and developed nations, yet still endemic in the developing countries, and accounts as the major risk factor for developing infective endocarditis (Thiene and Basso, 2006). Sub-Saharan Africa with the South African population currently has the largest prevalence of HIV/AIDS in the world. Combination therapy has been pivotal in reducing HIV viral load, allowing the increase of CD4+ T cells and reducing the risk of developing AIDS (Deeks et al., 2015). These patients however still present a higher-than normal risk of developing bloodstream infections and IE (Taramasso *et al.*, 2016).

The relationship and implications of patients having HIV and developing IE are not yet clear. Due to the HIV infection and the susceptibility to secondary infections, one would expect IE to be more prevalent in HIV positive patients, but it is not considered a complication of HIV/AIDS. It is almost limited exclusively to HIV patients who are IV drug users in the western societies (Currie *et al*., 1995; Yunis and Stone 1998).

Outcomes observed in patients with active systematic disease was poor, especially with extreme immune suppression (CD4 count < 200 cells/mL) (Pulvirenti *et al*., 1996). HIV infection on its own therefor does not seem to predispose patients to more severe outcomes of IE or a risk factor except in patients with severe immunosuppression (Currie *et al*., 1995).

In recent studies in South Africa, clinical features, and natural history of infective endocarditis within the context of HIV and HAART have not been extensively studied and relied largely on, uncontrolled, studies reporting from different areas of the country. The need for well-structured, well-designed trials representing the current disease patterns is of high importance (Naidoo and Shien 2009; Koegelenberg *et al*., 2003; Koshy *et al*., 2018).

2.11.1 Aim

The aim of the study was to compare the outcomes between HIV positive and HIV negative surgical patients with infective endocarditis in central South Africa in the current era.

2.11.2 Objectives

- Identify adult patients with infective endocarditis according to the modified Duke's criteria in patients that received heart valve surgeries between 2009-2019 from the departmental database.
- Determine underlining pathologies and risks for endocarditis.
- Risk stratifications (Euro score II) and comorbidities.
- Type of surgical interventions, outcomes, and complications.
- Comparison of outcome and survival between the HIV positive and negative groups.

Methodology

3.1 Study location

The research study will be conducted in the Department of Cardiothoracic Surgery, Faculty of Health Sciences, University of the Free State, Bloemfontein, South Africa.

3.2 Study population

3.2.1 The number of subjects

The data file for patients that presented with a (definite or possible IE) according to the modified Duke's criteria that received surgical treatment from 2009 to 2019 will be included in the study (+-150). Only patients older than 18 years will be included and the demographics age, sex, ethnic group diagnoses, pre-disposing factors, HIV status, pathogens, intraoperative and postoperative records and clinical outcomes, as well as long-term survival will be recorded for each patient.

3.2.2 Inclusion and exclusion criteria

3.2.2.1 Inclusion criteria

- All patients that presented with a possible or definite infective endocarditis based on the modified Duke's criteria II for surgical treatment during the period from 2009 to 2019.
- Only patients older than 18 years of age.

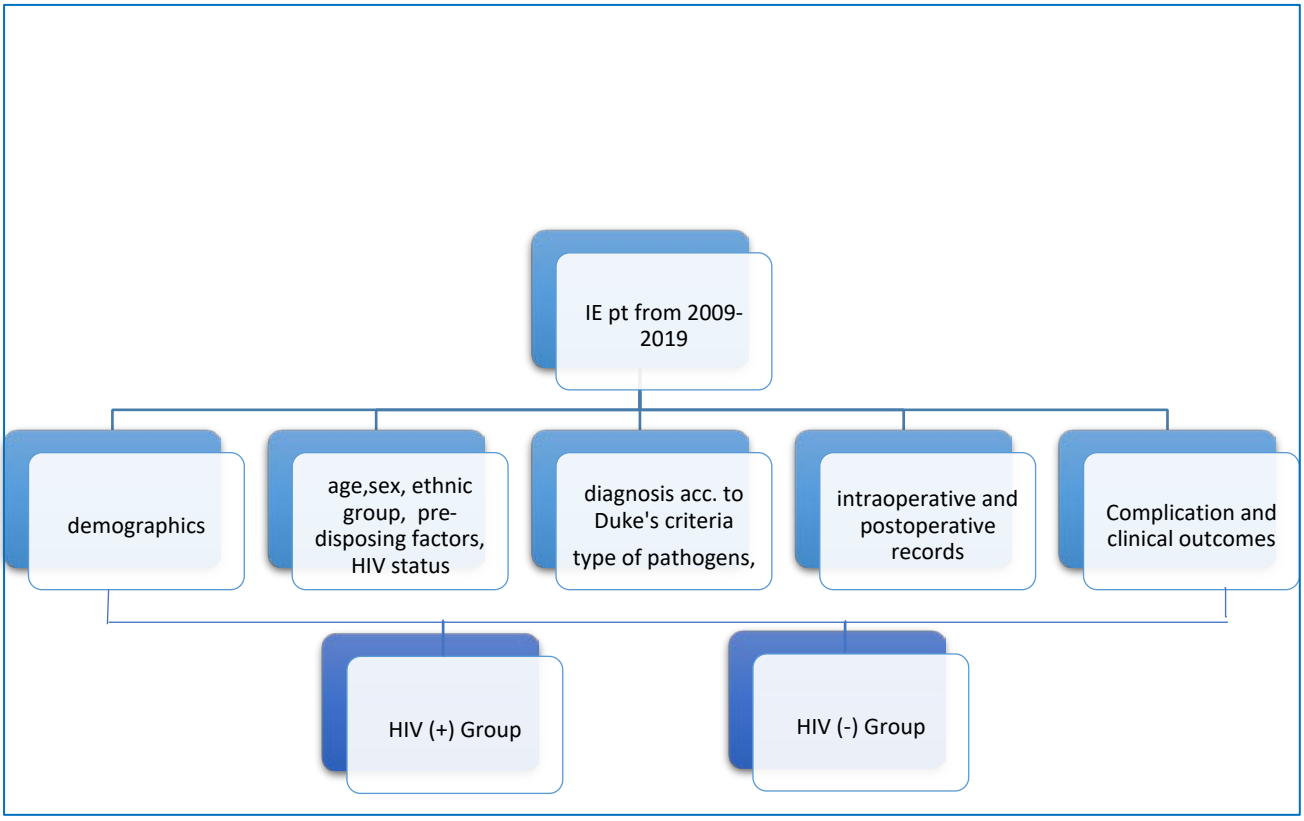
3.2.2.2 Exclusion criteria

- Patients rejected by the Modified Duke criteria for diagnosis of infective endocarditis.
- Patients younger than 18 years of age.

3.3 Study design

This study will be a retrospective analytical study that will include all patients presented with infective endocarditis who underwent surgical treatment between 2009 and 2019.

3.4 Study layout



3.4 Research team

Project leader

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University of the Free State (UFS)

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Prof FE Smit

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D-Tech Biomedical Technology
Senior Lecturer: Clinical Technology
Central University of Technology

Co-supervisor
Mr M Hanekom
MMedSc (Virology)
Scientist: Cardiothoracic Surgery
University of the Free State (UFS)

3.5 Data recorded.

Demographics, clinical presentations, operative and postoperative data as well as postoperative complications will be recorded. All the data will be sourced from the patient's medical file and the department's online data base from 2009-2019.

3.5.1 Preoperative data

The following demographic and clinical data will be recorded for each participant:

- **Age** (years)
- **Gender** (male/female)
- **Ethnicity** (black/white/Indian/colored)

- **Predisposing factors**. (Rheumatic heart disease, congenital heart disease, IV drug use and surgical procedures within 60 days of presentation.
- **Diagnosis** (Modified Duke's criteria) reference
- **Date of surgery** (elective, urgent or emergencies)
- **Blood cultures** (positive, negative)
- **HIV status** (tested /not tested, positive/ negative)

3.5.2 Intraoperative data

- **Type of surgery** (valve repair/ replacement or combined, congenital surgery and others)
- **Type of valves used** (mechanical, tissue, homograft)

3.5.3 Postoperative data

- **Complications** (intra and extra cardiac complications)
- **Outcomes** (in hospital mortality)
- **Survival** (long term mortality)

3.6 Statistical analysis

The data will be captured electronically by the researcher onto the data sheet (Appendix F). The captured data will be analyzed by a statistician utilizing appropriate statistical methods. Where applicable, continuous variables will be summarized descriptively, and frequencies will be subjected to a Chi^2 or Fisher's exact test. The latter will be used should any of the cell counts be less than 5. Where possible, the results between 2009 and 2019 will be presented graphically.

3.6 Ethical aspects and good clinical practice

3.6.1 Ethical clearance

The study will commence as soon as the ethical clearance is granted.

3.6.2 Safety variables

The study will pose no direct risk to any patients as this will be a retrospective study only reviewing data from patient files.

3.6.3 Premature discontinuation of the study

The study will be discontinued prematurely if the researcher or any of the study leaders feels that a patient's confidentiality might be breached or if any unethical procedures occur.

3.6.4 Good Clinical Practice (GCP)

The researchers will adhere to the guidelines of the South African Good Clinical Practice principles.

3.6.5 Financial implications to the patient

There will be no financial implications to the patient.

3.6.6 Confidentiality

Personal details of every patient participating in this study will be kept strictly confidential. At no time during the research may any of the patients' identification be made known to any other people other than the

researchers. The data sheet will not contain the names or surnames of the patients, only the unique hospital number. The information in the datasheet will only be accessible to the researcher.

3.6.7 Contact details of the researchers.

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  lbotes@cut.ac.za

3.6.8 Ethical Considerations

The datasheet will be kept safe on a password protected computer by the researcher. Patient identifiers such as names and surnames will also be removed from the datasheet and their unique hospital identification numbers will only identify patients.

2. Time Frame

Date	Task	Responsible person	Date of accomplishment
February	Literature search Compile protocol	PI, Department of Cardiothoracic Surgery	February 2019
March	Finalize protocol	PI, Department of Cardiothoracic Surgery	March 2019
March	Systematic review of the literature	PI, Department of Cardiothoracic Surgery	April 2019
April	Submit to Ethics Committee For ethical clearance	PI, Department of Cardiothoracic Surgery	April 2019
July	Retrospective audit of patient's data	Research team, Department of Cardiothoracic Surgery	July 2019
July	Data analysis	Statistician, Department of Cardiothoracic Surgery	July 2019
August	Prepare article for publication	Researchers, Department of Cardiothoracic Surgery	August 2019
September	Submit article	PI, department of Cardiothoracic Surgery	September 2019

3. Budget

Literature searches and printing costs as well as publication cost will be covered by the department of Cardiothoracic Surgery, UFS.

Clinical data gathering will not amount to any expenses for the patient, researcher or the hospital.

Item	Cost
Publication fees	ZAR 6000 (depending on journal, fee estimated from publication in Cardiovascular Journal of Africa)
Statistician	ZAR 5000
Language editing	ZAR 5000
total	**ZAR16000**

4. References

Abegaz TM, Bahagavathul AS, Gebreyohannes EA, Mekonnen AB, Abebe TB. Short- and long-term outcomes in infective endocarditis patients: a systematic review and meta-analysis. BMC Cardiovasc Disord 2017;17; 291.

Akhyari P, Mehrabi A, Adhiwana A, Kamiya H, Nimptsch K, Minol JP, Tochtermann U, Godehardt E, Weitz J, Lichtenberg A, Karck M, Ruhparwar A. Is simultaneous splenectomy an additive risk factor in surgical treatment for active endocarditis? Langenbecks Arch Surg 2012;397: 1261–1266.

Alarcon A, Ripoll T, Navas E, Gonzalez-Juanatey C, Cabell CH, Sarria C, Garcia-Bolao I, Farinas MC, Leta R, Rufi G, Miralles F, Pare C, Evangelista A, Fowler VG Jr, Mestres CA, de Lazzari E, Guma JR. Aorto-cavitary fistulous tract formation in infective endocarditis: clinical and echocardiographic features of 76 cases and risk factors for mortality. Eur Heart J 2005;26: 288–297.

Anguera I, Miro JM, Vilacosta I, Almirante B, Anguita M, Munoz P, Roman JA, de Alarcon A, Ripoll T, Navas E, et al, Aorto-Cavitary Fistula in Endocarditis Working Group. Aorto-cavitary fistulous tract formation in infective endocarditis. Clinical and echocardiographic features of 76 cases and risk factors for mortality. Eur Heart J 2005;26:288 –297.

Baddour LM, Wilson WR,Bayer AS, Fowler VG, Bolger AF, Levison ME, Ferrieri P, Gerber MA, Tani LY, Gewitz MH, Tong DC, Steekelberg JM, Baltimore RS, Shulman ST, Burns JC, Falace DA, Newburger JW, Pallasch TS, Takahashi M, Taubert KA. Infective endocarditis: Diagnosis, antimicrobial therapy, and management of complications: A statement for healthcare professionals from the Committee on Rheumatic fever, endocarditis, and Kawasaki disease, council on cardiovascular disease in the young, and the councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association: Endorsed by the Infectious Disease Society of America. Circulation 2005;111: e394 – e434.

Barron P, Pillay Y, Doherty T, Sherman G, Jackson D, Bhardwaj S, Robinson P, and Goga A. Eliminating mother-to-child HIV transmission in South Africa. Bull World Health Organ 2013;91: 70–74.

Bashore TM, Cabell C, Fowler V. Update on Infective Endocarditis. Curr Probl Cardiol 2006;31(4): 274 – 352.

Baumgartner H, Bonhoeffer P, De Groot NM, de Haan F, Deanfield JE, Galie N, Gatzoulis MA, Gohlke-Baerwolf C, Kaemmerer H, Kilner P, Meijboom F, Mulder BJ, Oechslin E, Oliver JM, Serraf A, Szatmari A, Thaulow E, Vouhe PR, Walma E. ESC Guidelines for the management of grown-up congenital heart disease (new version 2010). Eur Heart J 2010;31: 2915–2957.

Bayer AS, Bolger AF, Taubert KA, Wilson W, Steckelberg J, Karchmer AW, Levison M, Chambers HF, Dajani AS, Gewits MH, Newburger JW, Gerber MA, Shulman ST, Pallash TJ, Gage TW, Ferrieri P. 1998. Diagnosis and management of infective endocarditis and its complications. Circulation 98: 2936 – 2948.

Beynon RP, Bahl VK and Prendergast BD. 2006. Infective endocarditis. BMJ 333: 334 – 339.

Bloch M. Frailty in people living with hiv. AIDS Res Ther 2018;15(19): 1-5.

Bonfiglioli R, Nanni C, Morigi JJ, Graziosi M, Trapani F, Bartoletti M, Tumietto F, Ambrosini V, Ferretti A, Rubello D, Rapezzi C, Viale PL, Fanti S. 18F-FDG PET/CT diagnosis of unexpected extracardiac septic embolisms in patients with suspected cardiac endocarditis. Eur J Nucl Med Mol Imaging 2013;40: 1190–1196.

Cahill TJ, Baddour LM, Habib G, Hoen B, Salaun E, Pettersson GB, Schäfers HJ, Prendergast BD. Challenges in Infective Endocarditis. J Am Coll Cardiol 2017;69: 325–344.

Chu VH, Sexton DJ, Cabell CH, Reller LB, Pappas PA, Singh RK, Fowler VG Jr., Corey GR, Aksoy O, Woods CW. Repeat infective endocarditis: differentiating. relapse from reinfection. Clin Infect Dis 2005;41: 406–409.

Currie PF, Sutherland GR, Jacob AJ, Bell JE, Brettle RP, Boon NA. A review of endocarditis in acquired immunodeficiency syndrome and human immunodeficiency virus infection. Eur Heart J 1995;16(suppl B): 15–8. Deeks SG, Overbaugh J, Buchbinder PA, S. Hiv infection Nat Rev Dis Primers 2015;1: 15035.

Durack DT, Pelletier LL, Petersdorf RG. Chemotherapy of experimental streptococcal endocarditis. II. Synergism between penicillin and streptomycin against penicillin-sensitive streptococci. J Clin Invest 1974; 53:829–833. Duval X, Leport C. Prophylaxis of infective endocarditis: current tendencies, continuing controversies. Lancet Infect Dis 2008;8: 225–232.

Feuchtner GM, Stolzmann P, DichtlW, Schertler T, Bonatti J, Scheffel H, Mueller S, Plass A, Mueller L, Bartel T,Wolf F, Alkadhi H. Multislice computed tomography in infective endocarditis: comparison with transesophageal echocardiography and intraoperative findings. J Am Coll Cardiol 2009;53: 436–444.

Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, Dulgheru R, El Khoury G, Erba PA, Iung B, Miro JM, Mulder BJ, PlonskaGosciniak E, Price S, Roos-Hesselink J, Snygg-Martin U, Thuny F, Tornos Mas P,

Vilacosta I, Zamorano JL; ESC Scientific Document Group. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J. 2015 Nov 21;36(44):3075-3128. doi: 10.1093/eurheartj/ehv319. Epub 2015 Aug 29. PMID: 26320109.

Goddard AJ, Tan G, Becker J. Computed tomography angiography for the detection and characterization of intra-cranial aneurysms: current status. Clin Radiol 2005;60: 1221–1236.

Halavaara, M., Martelius, T., Järvinen, A., Antikainen, J., Kuusela, P., Salminen, U-S., & Anttila, V-J. Impact of pre-operative antimicrobial treatment on microbiological findings from endocardial specimens in infective endocarditis. Eur J Clin Microbiol Infect Dis 2019;38(3), 497-503.

Hekimian G, Kim M, Passefort S, Duval X, Wolff M, Leport C, Leplat C, Steg G, Iung B, Vahanian A, Messika-Zeitoun D. Preoperative use and safety of coronary angiography for acute aortic valve infective endocarditis. Heart 2010;96: 696–700.

Hubert S, Thuny F, Resseguier N, Giorgi R, Tribouilloy C, Le Dolley Y, Casalta JP, Riberi A, Chevalier F, Rusinaru D, Malaquin D, Remadi JP, Ammar AB, Avierinos JF, Collart F, Raoult D, Habib G. Prediction of symptomatic embolism in infective endocarditis: construction and validation of a risk calculator in a multicenter cohort. J Am Coll Cardiol 2013;62: 1384–1392.

Imbert G, Bothello E, Collart F, Habib G. Contribution of systematic serological testing in diagnosis of infective endocarditis. J Clin Microbiol 2005;43: 5238–5242.

Kang DH, Kim YJ, Kim SH, Sun BJ, Kim DH, Yun SC, Song JM, Choo SJ, Chung CH, Song JK, Lee JW, Sohn DW. Early surgery versus conventional treatment for infective endocarditis. N Engl J Med 2012; 366: 2466-73.

Kang DH. Timing of surgery in infective endocarditis. Heart. 2015 Nov;101(22):1786-91. doi: 10.1136/heartjnl-2015-307878. Epub 2015 Aug 18. PMID: 26285598.

Koegelenberg CFN, Doubell AF, Orth H, Reuter H. Infective endocarditis in the Western Cape Province of South Africa: a three-year prospective study. Q J Med 2003;96: 217-225.

J.J. Koshy, M. Engel, P. Human, H. Carrara, J. Brink, and P. Zilla. Long term outcome and EuroSCORE II validation in native valve surgery for active infective endocarditis in a South African cohort. SAHJ Vol. 15 No. 2 (2018).

Knirsch W, Nadal D. Infective endocarditis in congenital heart disease. Eur J Pediatr. 2011 Sep;170(9):1111-27. doi: 10.1007/s00431-011-1520-8. Epub 2011 Jul 20. PMID: 21773669.

Lalani T, Chu VH, Park LP, Cecchi E, Corey GR, Durante-Mangoni E, Fowler VG Jr., Gordon D, Grossi P, Hannan M, Hoen B, Munoz P, Rizk H, Kanj SS, SeltonSuty C, Sexton DJ, Spelman D, Ravasio V, Tripodi MF, Wang A. In-hospital and 1-year mortality in patients undergoing early surgery for prosthetic valve endocarditis. JAMA Intern Med 2013;173: 1495–1504.

Li JS, Sexton DJ, Mick N, Nettles R, Fowler VG Jr, Ryan T, Bashore T, Corey GR. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis 2000;30: 633–638.

Manoff SB, Vlahov D, Herskowitz A, Solomon L, Muñoz A, Cohn S, Willoughby SB, Nelson KE. Human immunodeficiency virus infection and infective endocarditis among injecting drug users. Epidemiology 1996;7: 566–70.

Mauri L, de Lemos JA, O'Gara PT. Infective Endocarditis. Curr Probl Cardiol 2001;26(9): 558 – 610.

Mirabel M, Sonneville R, Hajage D, Novy E, Tubach F, Vignon P, Perez P, Lavoue S, Kouatchet A, Pajot O, Mekontso-Dessap A, Tonnelier JM, Bollaert PE, Frat JP,
Navellou JC, Hyvernat H, Hssain AA, Timsit JF, Megarbane B, Wolff M, Trouillet JL. Long-term outcomes and cardiac surgery in critically ill patients with infective endocarditis. Eur Heart J 2014;35: 1195–1204.

Mocchegiani R, Nataloni M. Complications of infective endocarditis. Cardiovasc Hematol Disord Drug Targets 2009; 9: 240–248.

Mylonakis E, Calderwood SB. Infective endocarditis in adults. NEJM 2001;345(18): 1318 – 1330.

Nadji G, Rusinaru D, Remadi JP, Jeu A, Sorel C, Tribouilloy C. Heart failure in leftsided native valve infective endocarditis: characteristics, prognosis, and results of surgical treatment. Eur J Heart Fail 2009;11: 668–675.

Nkomo VT. 2007. Epidemiology and prevention of valvular hart diseases and infective endocarditis in Africa. Heart 2007;93: 1510-1519.
Netzer RO, Altwegg SC, Zollinger E, Täuber M, Carrel T, Seiler C. Infective endocarditis: determinants of long-term outcome. Heart. 2002 Jul;88(1):61-6. doi: 10.1136/heart.88.1.61. PMID: 12067947; PMCID: PMC1767177.

Østergaard L, Mogensen UM, Bundgaard JS, Dahl A, Wang A, Torp-Pedersen C, Gislason G, Køber L, Køber N, Dejgaard TF, Frandsen CS, Fosbøl EL. Duration and complications of diabetes mellitus and the associated risk of infective endocarditis. Int J Cardiol. 2019 Mar 1;278:280-284. doi: 10.1016/j.ijcard.2018.09.106. Epub 2018 Oct 1. PMID: 30291010.

Okello E, Kakande B, Sebatta E, Kayima J, Kuteesa M, Mutatina B, Nyakoojo W, Lwabi P, Mondo CK, Odoi-Adome R, Juergen F. Socioeconomic and environmental risk factors among rheumatic heart disease patients in Uganda. PLoS One 2012;7: e43917.

Peters, F., Karthikeyan, G., Abrams, J., Muhwava, L., Zuhlke, L. Rheumatic¨heart disease: current status of diagnosis and therapy Cardiovascular Diagnosis and Therapy 2019; 2:10.

Prendergast BD. 2005. The changing face of infective endocarditis. Heart 92: 879 – 885.

Prendergast BD. The changing face of infective endocarditis Heart 2006; 92:879-885.

Pulvirenti JJ, Kerns E, Benson C, Lisowski J, Demarais P, Weinstein RA. Infective endocarditis in injection drug users: importance of human immunodeficiency virus serostatus and degree of mmunosuppression. Clin Infect Dis 1996; 22: 40–5.

Raoult D, Casalta JP, Richet H, Khan M, Bernit E, Rovery C, Branger S, Gouriet F,
Imbert G, Bothello E, Collart F, Habib G. Contribution of systematic serological testing in diagnosis of infective endocarditis. J Clin Microbiol 2005; 43:5238–5242.

Regueiro A, Linke A, Latib A, et al. Association Between Transcatheter Aortic Valve Replacement and Subsequent Infective Endocarditis and In-Hospital Death. JAMA. 2016;316(10):1083–1092. doi:10.1001/jama.2016.12347

Ribera E, Miró JM, Cortés E, Cruceta A, Merce J, Marco F, Planes A, Paré JC, Moreno A, Ocaña I, Gatell JM, Pahissa A. Influence of HIV-1 infection and degree of immunosuppression on the clinical characteristics and outcome of infective endocarditis in intravenous drug users. Arch Intern Med 1998;158: 2043–50.

Saby L, Laas O, Habib G, Cammilleri S, Mancini J, Tessonnier L, Casalta JP, Gouriet F, Riberi A, Avierinos JF, Collart F, Mundler O, Raoult D, Thuny F. Positron emission tomography/computed tomography for diagnosis of prosthetic valve

endocarditis: increased valvular 18F-fluorodeoxyglucose uptake as a novel major criterion. J Am Coll Cardiol 2013;61: 2374–2382.

San Roman JA, Lopez J, Vilacosta I, Luaces M, Sarria C, Revilla A, Ronderos R, Stoermann W, Gomez I, Fernandez-Aviles F. Prognostic stratification of patients with left-sided endocarditis determined at admission. Am J Med 2007;120: 369–367.

Selton-Suty C, CélardM, Le Moing V, Doco-Lecompte T, Chirouze C, lung B, Strady C, Revest M, Vandenesch F, Bouvet A, Delahaye F, Alla F, Duval X, Hoen B. Preeminence of Staphylococcus aureus in infective endocarditis: a 1year population-based survey. Clin Infect Dis 2012; 54: 1230–9.

Shtaya AA, Perek S, Kibari A, Cohen S. Bartonella henselae Endocarditis: An Usual Presentation of an Unusual Disease. Eur J Case Rep Intern Med. 2019;6(3): 001038.

Snygg-Martin U, Gustafsson L, Rosengren L, Alsio A, Ackerholm P, Andersson R, Olaison L. Cerebrovascular complications in patients with left-sided infective endocarditis are common: a prospective study using magnetic resonance imaging andNneurochemical brain damage markers. Clin Infect Dis 2008;47: 23–30.

Spijkerman IJB, van Ameijden EJC, Mientjes GHC, Coutinho RA, van den Hoek A. Human immunodeficiency virus infection and other risk factors for skin abscesses and endocarditis among injection drug users. Clin Epidemiol 1996; 49: 1149–54.

Taramasso L, Tatarelli P, Di Biagio A. Bloodstream infections in hiv-infected patients. Virulence 2016;7: 320–328.

Tattevin P, Limonta S, The different weight of indications for cardiac surgery in patients with infective endocarditis. Int J Cardiol 2019;282: 31-32.

Thiene G and Basso C. Pathology and pathogenesis of infective endocarditis in native heart valves. Cardiovasc Pathol 2006;15: 256 – 263.

Thuny F, Beurtheret S, Mancini J, Gariboldi V, Casalta JP, Riberi A, Giorgi R, Gouriet F, Tafanelli L, Avierinos JF, Renard S, Collart F, Raoult D, Habib G. The timing of surgery influences mortality and morbidity in adults with severe complicated infective endocarditis: a propensity analysis. Eur Heart J 2011;32: 2027–2033.

Thuny F, Di Salvo G, Belliard O, Avierinos JF, Pergola V, Rosenberg V, Casalta JP, Gouvernet J, Derumeaux G, Iarussi D, Ambrosi P, Calabro R, Riberi A, Collart F, Metras D, Lepidi H, Raoult D, Harle JR, Weiller PJ, Cohen A, Habib G. Risk of embolism and death in infective endocarditis: prognostic value of

echocardiography: a prospective multicenter study. Circulation 2005;112: 69–75.

Thuny F, Avierinos JF, Tribouilloy C, Giorgi R, Casalta JP, Milandre L, Brahim A, Nadji G, Riberi A, Collart F, Renard S, Raoult D, Habib G. Impact of cerebrovascular complications on mortality and neurologic outcome during infective endocarditis: a prospective multicentre study. Eur Heart J 2007;28: 1155–1161.

Vilacosta I, Graupner C, San Roman JA, Sarria C, Ronderos R, Fernandez C, Mancini L, Sanz O, Sanmartin JV, Stoermann W. Risk of embolization after institution of antibiotic therapy for infective endocarditis. J Am Coll Cardiol 2002;39: 1489–1495.

Wilson WR, Geraci JE, Wilkowske CJ, Washington JA. Short-term intramuscular therapy with procaine penicillin plus streptomycin for infective endocarditis due to viridans streptococci. Circulation 1978;57: 1158–1 161.

Yoshioka D, Sakaguchi T, Yamauchi T, Okazaki S, Miyagawa S, Nishi H, Yoshikawa Y, Fukushima S, Saito S, Sawa Y. Impact of early surgical treatment on postoperative neurologic outcome for active infective endocarditis complicated by cerebral infarction. Ann Thorac Surg 2012;94: 489–495.

Yunis NA, Stone VE. Cardiac manifestations of HIV/AIDS: a review of disease spectrum and clinical management. J Acquir Immune Defic Syndr Hum Retrovirol 1998; 18: 145–54.

UNAIDS, http://www.unaids.org/en/resources/909090 (2016a).

Appendix - E: Data Collection sheet

date of surgery	UM Number	Surname	First name	Date of birth	Age	Date of admission	Gender	Race	NYHA	HIV status	CD4 count	Viral Load	ARV Treatment

Pathology					RHD VS NON RHD	PROSTHETIC VS NATIVE	Vegitations
Aortic valve	Mitral valve	Tricuspid valve	Pulmonary valve	Others			

HYPERTENSION	DM	SMOKING	CAD FAMILY HISTORY	DYSLIPIDEMIA	RENAL DISEASE	PULMONARY DISEASE	HEART RHYTHM

IMMUNOSUPPRESSIVE THERAPY	NEUROLOGICAL DISEASE	Endocarditis Risk	EuroScore II	Blood Culture	ORGANISMS

infective endocarditis diagnosis (MD)criteria	Operative Priority	Reoperation	Indication for surgery	AORTIC VALVE	MITRAL VALVE	TRICUSPID VALVE

PULMONARY VALVE	AORTA	OPERATIVE COMPLICATION	INFECTION	NEUROLOGIC	PULMONARY	RENAL	VASCULAR	OTHER

Death	discharge date	DHA MORTALITY	DEATH DATES	IN HOSPITAL MORTALITY	LONG TERM MORTALITY	CAUSE OF DEATH	F/U IN MONTHS	LAST SEEN

Appendix - F: Instructions to authors

European Journal of Cardio-Thoracic Surgery

Manuscript Format and Style

Manuscripts should be prepared using a word-processing package.

- • Font type: Arial or Calibri
- • Font size: 11 or 12 points
- • Double-spacing for the main text
- • Pages and lines should be numbered consecutively

Order of the manuscript contents Manuscripts should be organized as follows: (a) Title page; (b) Visual abstract; (c) Abstract and Keywords; (d) Text with the following sections: Introduction, Materials and Methods (or Patients and Methods), Results, Discussion, Conclusion, Acknowledgement (optional), Funding statement, Conflict of interest statement; Author contribution statement; (e) Figure (and Video) legends; (f) Tables; (g) References.

Specifications for each article type Each article type must include a title page and 3-6 keywords. *Important:* the total number of words specified below comprises words on the title page, abstract, keywords, main text, figure and video legends, tables, and references. All manuscripts must adhere to the following specifications.

Original Article

- Authors: At the discretion of the Editor-in-Chief
- Abstract (structured): 250 words (sections should be: Objectives, Methods, Results and Conclusions)
- Figures/tables combined: 8 (preferably no more than 6 parts/graphs – at the discretion of the Editor-in-Chief)
- Videos: 2 (total playback time: 5 min)
- References: 30
- Total number of words: 5000

.

The manuscript should be organized as follows:

Title page

Title

Should be brief and descriptive (100 characters) - no abbreviations are allowed, even if well known.

Authors

List all authors by full first name, initial of or full middle name and family name. Qualifications are not required. Ensure the author names correspond (in spelling and order of appearance) with the metadata of the system. Remember that all authors must have substantially contributed to the article - see criteria in the authorship section above.

For equal contributions include the statement that 'X and Y contributed equally to this work' below the author list of the manuscript.

Institution(s) Include the name of all institutions with the location (department, institution, city, country) to which the work should be attributed (in English). Use superscript numbers to connect authors and their department or institution.

Corresponding author
The full name, full postal address, telephone number and the e-mail address should be typed at the bottom of the title page.

Meeting presentation
If the manuscript was (or will be) presented at a meeting, include the meeting name, venue, and the date on which it was (or will be) read; also indicate if you have submitted an Abstract of this manuscript for the EACTS or ESTS annual meeting and whether it has been accepted (if known).

Word counts
The total number of words of the whole article (including title page, abstract, main text, legends, tables, and references) must be specified on the title page.

Visual abstract
Include the key question (max. 120 characters), key findings (max. 120 characters) and takehome message (max. 140 characters). The maximum number of characters include spaces.

Clinical registration number
Include name of registry and registration number. See section above.

Abstract

An abstract should be a concise summary of the manuscript. Reference citations are not allowed. The abstract should be factual and free of abbreviations, except for SI units of measurement. A structured abstract must have four sections:

1. *Objectives:* should describe the problem addressed in the study and its purpose.
2. *Methods:* should explain how the study was performed (basic procedures with study materials and observational and analytical methods).
3. *Results:* should describe the main findings with specific data and their statistical significance, if possible.
4. *Conclusions:* should contain the main conclusion of the study.

Keywords
Following the abstract, 3-6 keywords should be given for subject indexing.

Main text

Abbreviations and acronyms
For Original Articles, Meta-Analyses and Reviews, abbreviations and acronyms used in the text should be gathered in a list and included at the beginning of the article before the introduction.

Use of abbreviations renders the text difficult to read so they should be limited to SI units of measurement and to those widely used in the text of the article. Full definitions should be given at first mention in the text, and in the tables and figures. Abbreviations should not be included in headings.

Introduction
Should state the purpose of the investigation and give a short review of pertinent literature.

Materials and methods (or patients and methods)
Should be described in detail with appropriate information about patients or experimental animals.
For all articles reporting on human subjects and animals, the first paragraph should comprise a short statement confirming approval of the study by the Institutional Review Board (IRB) or Ethics Committee (EC) of the institution(s) where the work was carried out. The name of the institution, the date and ID number of the IRB approval must be included. Whether written patients informed consent was obtained or waived by the IRB or EC should also be disclosed.

Generic names of drugs and equipment should be used throughout the manuscript, with brand names (proprietary name) and the name and location (city, state, country) of the manufacturer in brackets when first mentioned in the text.

Results
Results should be reported concisely and regarded as an important part of the manuscript. They should be presented either in tables and figures, and briefly commented on in the text, or in the text alone. Repetition of results should be avoided! For statistical analysis, follow the Statistical and data reporting guidelines. The full set of raw data must be available at any time should reviewers or editors request these for more in-depth review during the review process and/or after publication.

Discussion
The discussion is an interpretation of the results and their significance with reference to pertinent work by other authors. It should be clear and concise. The importance of the study and its limitations should be discussed.

Acknowledgement
This section can be used to acknowledge contributions from other individuals who do not meet the ICMJE criteria for authorship (e.g. those who provided administrative support, writing assistance, language editing).

Author contributions statement
Contributor Roles Taxonomy (CRediT from CASRAI) roles of authors will be published for all accepted articles; hence it is paramount that these are selected carefully and accurately upon submission of the revised manuscript. See here for a description of the CrediT roles.

Funding statement See Funding and conflict of interest section below.

Conflict of interest statement
See Funding and conflict of interest section below.

Figure (and video) legends
A list with legends for each figure (and each video) must be included.

Tables
All tables must be included in the manuscript file, as part of the text, not as images. All tables should start on separate pages and be accompanied by a title, and footnotes (use superscript a,b,c….) where necessary. The tables should be numbered consecutively using Arabic numerals. Abbreviations and their full definitions should be listed in alphabetical order at the bottom of the table. Avoid overcrowding the tables and the excessive use of words. The format of tables should be in keeping with that normally used by the journal. Please ascertain that the data given in tables are correct. All tables must be cited in the text.

References
Authors are responsible for checking the accuracy of all references. If you use EndNote or Reference Manager to facilitate referencing citations (not required for submission), this journal's style is available for use. References should be numbered in order of appearance in the text (in Arabic numerals in parentheses) and must be listed numerically in the reference list. Journal titles and author initials should be abbreviated and punctuated according to PubMed. If an automatic referencing system has been used in the preparation of the paper, the references must not be left embedded in the final text file submitted. The citation of journals, books, multi-author books and articles published online should conform to the following examples:

Journals
[1] Sousa-Uva M, Head SJ, Milojevic M, Collet JP, Landoni G, Castella M *et al.* 2017 EACTS Guidelines on perioperative medication in adult cardiac surgery. Eur J Cardiothorac Surg 2018; 53:5-33.

Books
[2] Cooley DA. Techniques in cardiac surgery. Philadelphia: Saunders, 1984:167-76.

Multi-author books
[3] Rastan AJ, Borger MA, Haensig M, Kempfert J, Mohr FW. Recent developments in transcatheter aortic valve implantation in Moorjani N, Ohri SK, Wechsler A (eds). Cardiac Surgery: Recent Advances and Techniques. CRC press 2013.

Online-only publications (please give the doi wherever possible)
[4] Durko A, Mahtab E, Romeo J, Bogers A. Skeletonized internal mammary artery harvest with diathermy and cold dissection. *Multimed Man Cardiothorac Surg* 2017 Dec 12; doi: 10.1510/mmcts.2017.023

or

[5] National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology:

Cancer-associated Venous Thromboembolic Disease; Version 2.2018. 2018 https://www.nccn.org/professionals/physician_gls/pdf/vte.pdf (10 July 2019, date last accessed). For references with more than six authors, the first 6 authors should be listed, followed by et al. Personal communications (Jones, personal communication) must be authorized in writing by those involved, and unpublished data should be cited in the text as (unpublished data). References to manuscripts submitted, but not yet accepted, should be cited in the text as (Jones and Smith, manuscript in preparation) and should not be included in the list of references. Authors are encouraged to cite web URLs in parentheses at the appropriate mention in the text.

Figures and Videos

All figures and videos require a legend and must be cited in the text.

Figures

Each figure should contain no more than 4 parts for Original Articles, Meta-Analyses and Reviews. For Case report, Surgical Technique, and Images-in-Cardiothoracic Surgery, 6 parts in total are allowed.

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1. Literature Review

1.1 Background

1.2 Epidemiology

1.2.1 Infective endocarditis

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