

The changing landscape of infective endocarditis in South Africa

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Dedicated to my mother, Ivonne de Villiers

who always encouraged and supported my academic interests, teaching me the value of science and learning from a young age. “The only way we will understand the world is by asking questions and then trying to answer them.”

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Declaration

I, **Marthinus Coenraad de Villiers**, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Signed by candidate

Date: 04 February 2019

Abstract

Background. Little is known about the current clinical profile and outcomes of patients with infective endocarditis (IE) in South Africa.

Methods. We conducted a retrospective review of the records of patients admitted to Groote Schuur Hospital between 2009 and 2016 fulfilling universal criteria for definite or possible IE, in search of demographic, clinical, microbiological, echocardiographic, treatment and outcome information.

Results. 105 patients fulfilled the modified Duke criteria for IE. The median age of the cohort was 39 years (IQR 29–51), with a male preponderance (61.9%). The majority of patients (72.4%) had left-sided native valve endocarditis, 14% had right-sided disease, and 13.3% had prosthetic valve endocarditis. A third of the cohort had rheumatic heart disease. Although 41.1% of patients with left-sided disease had negative blood cultures, the three most common organisms cultured in this subgroup were *Staphylococcus aureus* (18.9%), *Streptococcus spp.* (16.7%) and *Enterococcus spp.* (6.7%). Participants with right-sided endocarditis were younger (29 years (IQR 27-37)), were predominantly intravenous drug users (IVDU; 73.3%) and the majority cultured positive for *S. aureus* (73.3%) with frequent septic pulmonary complications (40.0%). The overall in-hospital mortality was 16.2%, with no deaths in the group with right-sided endocarditis. Predictors of death in our patients were heart failure (OR 8.16, CI 1.77-37.70; p=0.007) and an age > 45 years (OR 4.73, CI 1.11-20.14; p=0.036). Valve surgery was associated with a reduction in mortality (OR 0.09, CI 0.02-0.43; p=0.003).

Conclusions. Infective endocarditis in a typical teaching tertiary care centre in South Africa remains an important clinical problem. In this setting, it continues to affect mainly young people with post-inflammatory valve disease and congenital heart disease. IE is associated with an in-hospital mortality that remains high. Intravenous drug-associated endocarditis caused by *S. aureus* is an important IE subset, comprising approximately 10% of all cases, a fact which was not reported 15 years ago, and culture-negative endocarditis remains highly prevalent. Heart failure in IE carries significant risk of death and needs a more intensive level of care in hospital. Finally, cardiac surgery was associated with reduced mortality, with the largest impact in those patients with heart failure.

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Contributions

Marthinus Coenraad de Villiers developed study protocol, collected and analysed data and wrote the manuscript.

Charle André Viljoen and Mpiko Ntsekhe contributed to study design, data analysis and reviewing and editing manuscript.

Kathryn Manning contributed to data analysis.

Clinton van der Westhuizen, Azhar Seedat, Max Rath and Mariette Graham contributed to data collection.

Abbreviations

CHF – Congestive Heart Failure

IE – Infective Endocarditis

IV – Intravenous

IVDU – Intravenous Drug Use

IQR – Inter Quartile Range

OR – Odds Ratio

RHD – Rheumatic Heart Disease

SAMJ – South African Medical Journal

Chapter 1: Accepted for publication (SAMJ) manuscript

The changing landscape of infective endocarditis in South Africa

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Abstract

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Conclusions. Infective endocarditis in a typical teaching tertiary care centre in South Africa remains an important clinical problem. In this setting, it continues to affect mainly young people with post-inflammatory valve disease and congenital heart disease. IE is associated with an in-hospital mortality that remains high. Intravenous drug-associated endocarditis caused by *S. aureus* is an important IE subset, comprising approximately 10% of all cases, a fact which was not reported 15 years ago, and culture-negative endocarditis remains highly prevalent. Heart failure in IE carries significant risk of death and needs a more intensive level of care in hospital. Finally, cardiac surgery was associated with reduced mortality, with the largest impact in those patients with heart failure.

Background

Despite advances in diagnostic imaging, antimicrobial treatment and cardiac surgery, infective endocarditis (IE), as defined by the modified Duke criteria,^[1] remains a potentially fatal condition with an annual in-hospital mortality rate of approximately 20%.^[2,3]

Observational data from the developed world indicate that the profile of IE has changed significantly over the last four decades. Infective endocarditis has become a disease that predominantly affects older and/or diabetic patients with infections on degenerative native valves or prosthetic valves. Rheumatic heart disease (RHD) has all but disappeared as a predisposing risk factor.^[4-6] The classic clinical signs of IE are now infrequent, with patients often presenting with only fever and/or a heart murmur.^[4] Furthermore, endocarditis caused by oral organisms (such as *Streptococcus viridans*) and culture-negative endocarditis, have each declined significantly as a proportion of IE in the developed world.^[4] Nosocomial infections from long-term indwelling catheters and intravenous lines are increasing in incidence and *Staphylococcus aureus*, coagulase negative *S. aureus* and *Enterococcus spp.* are the dominant organisms.^[7] In spite of this evolution in the patient and clinical profile of IE, in-hospital mortality, morbidity and complication rates remain high. Specifically, congestive cardiac failure (CHF), stroke and intra-cardiac abscesses with conduction abnormalities are reported at a frequency of approximately 60%, 30% and 1 to 15%, respectively.^[8-11]

Besides a recent focus on intravenous (IV) drug use related IE^[12], there is little contemporary data on IE from South or sub-Saharan Africa, with the most recent information on the subject published in 2003.^[13] Specifically, there is a dearth of information on patient profiles, risk factors, predisposing cardiac conditions, and the spectrum of causative microbiological organisms. Furthermore, little is known about the prevalence and predictors of complications, the proportion of patients with IE who undergo surgery and the in-hospital mortality rates in sub-Saharan Africa. This knowledge is vital for increasing the survival of IE patients as well as improving their overall care by optimizing local clinical practice.

This study was therefore conducted to address these gaps in our local knowledge, providing a contemporary and descriptive overview of IE in a representative South African tertiary centre.

Methods

This was a retrospective review of patient records. Patients older than 17 years with complete data who fulfilled the modified Duke criteria for infective endocarditis^[14] and were commenced on treatment for possible or definite infective endocarditis at Groote Schuur Hospital in Cape Town in 2009 to 2016 were included. After approval by the University of Cape Town's Human Research Ethics Committee (HREC Ref: 517/2016), 181 potential cases were identified by screening the hospital's electronic database for all hospital admissions and referrals to cardiology. Data collection included the collection of demographic, clinical, microbiological, echocardiographic, laboratory and outcome data on all identified cases.

Six independent investigators (MCD, CAV, CV, AS, MR and MG) used a standardized data collection form, from where data was entered into REDCap (Research Electronic Data Capture, a secure online database manager hosted at the University of Cape Town). All the collected data was verified. Collected data was exported from the REDCap database to Stata software, version 14.1 (Stata Corp, College Station, TX), for statistical analysis. Descriptive statistics were used to summarize demographic, clinical and microbiological variables. Univariable and multivariable logistic regression was used to determine the association between clinically relevant variables and in-patient mortality in patients with left-sided IE. Variables were selected *a priori* and were excluded if data was sparse. Those considered for regression analysis were age, sex, comorbidities (including HIV status), serum creatinine, white cell count, organism cultured, echocardiographic complications, clinical complications and valve replacement surgery performed. Variables were retained in multivariable model if the p-value was <0.25 or if an association has been demonstrated in previous studies.^[15,16] Unadjusted and adjusted odds ratios (OR) were presented with a 95% CI.

Results

One hundred and five cases were included in the study (figure 1), with 64.8% (68) and 35.8% (37) of patients fulfilling the modified Duke criteria for definite and possible IE respectively. In all cases, the responsible clinicians felt it appropriate to commence treatment for endocarditis. There was a steady increase in the number of cases seen over the period from 2009 to 2016, with a peak in 2014 (Supplementary file 1).

The median age of this cohort was 39 years (IQR 29 – 51), with a slight male preponderance (61.9%). The majority of patients had left-sided native valve endocarditis (72.4%) while the remainder was evenly split between prosthetic valve endocarditis (PVE, 13.3%) and right-sided endocarditis (14.3%).

The most common underlying cardiac conditions were RHD (34.3%), mechanical or tissue prosthetic valves (13.3%; most of whom had had valve surgery for RHD) and congenital heart disease (10.5%). Five patients (4.7%) had a prior history of infective endocarditis and one patient had device-associated endocarditis (permanent pacemaker). Amongst those who were tested for HIV (87/105 patients), 23.0% were seropositive. Ten patients (9.5%) had diabetes mellitus, while other comorbidities such as chronic kidney disease, chronic liver disease and cancer were uncommon (3 patients respectively). One patient had a permanent intravenous (IV) port. A detailed description of the clinical characteristics, special investigations and laboratory results can be found in *table 1*. The most frequent presenting signs and symptoms were: fever (63.8%), dyspnoea (61.0%), a temperature > 38.5°C (58.1%) and weight loss (24.8%). Most patients (85.7%) had a new or changed murmur on clinical examination. More than a quarter (27.6%) had an acute neurological deficit and 18.1% were noted to have splinter haemorrhages (Table 2).

All patients had a transthoracic echocardiogram. Where vegetations were detected, the mitral (52.9%) and aortic valve (37.6%) were the most frequently affected. Two-thirds (68.4%) of those with aortic valve involvement had severe aortic regurgitation, whereas 54.1% of those with mitral involvement and 36.4% of those with tricuspid involvement had severe regurgitation.

The median number of blood cultures done per patient was 3 (IQR 2.5-4.5). Blood cultures were persistently positive after 48 hours in 21.0% of patients in this study (13.2% of left-sided native endocarditis, 42.9% of prosthetic valve endocarditis and 40.0% of right-sided endocarditis; $p = 0.006$). Based on the attending clinician's evaluation, the most frequent sources of infection were thought to be the skin (66.7%), oral cavity (25.9%) and gastrointestinal tract (7.9%). Of patients with left-sided disease, 41.1% had negative blood cultures (fig 2a), and the three most common organisms cultured in this subgroup were *Staphylococcus aureus* (18.9%), *Streptococcus spp.* (16.7% (*S. viridans* 10.0%, other 6.7%)) and *Enterococcus spp.* (6.7%).

Right-sided disease was different to left-sided disease: Those patients with tricuspid and pulmonary valve endocarditis were younger (median age 29.1; IQR 27-37) and had a greater male predominance (73.3%); IV drug use was a common risk behaviour (73.3%); and *S. aureus* was the most common organism cultured (73.3%), while 13.3% were culture negative (fig 2b).

In-hospital course and outcome

Heart failure was the most common in-hospital complication (42.9%), followed by embolic complications (36.1%), acute kidney injury (21.9%) and pneumonia (8.6%). In-hospital mortality was observed only in those with left-sided native and prosthetic valve endocarditis and was found to be 18.9% in that subgroup. Heart failure (adjusted OR 8.16, CI 1.77-37.7; $p=0.007$) and age greater than 45 years (adjusted OR 4.73, 1.11-20.14; $p=0.036$) were significantly associated with an increased in-hospital mortality in this study, however data sparsity reduced the precision of these estimates. HIV, diabetes and infection with *S. aureus* did not appear to influence mortality. The most common complications for right-sided disease were septic pulmonary emboli (40.0%) and acute kidney injury (40.0%).

All patients were treated with antibiotics and 44 (42.3%) underwent valve surgery. Heart failure was the most common indication for surgery (66.7%, $p=0.001$). Surgery was associated with a reduced risk of death (OR 0.09, CI 0.02-0.43; $p=0.003$). Only one patient with right-sided endocarditis underwent surgery, i.e. tricuspid valve repair due to severe tricuspid regurgitation.

Discussion

We have presented a retrospective review of the hospital records of patients admitted to a South African urban tertiary referral centre with a diagnosis of infective endocarditis. The study, which covered the period between 2009 and 2016, is the first of its kind since the early 2000s and describes the demographic, clinical and microbiological profile of patients with the disease, discusses treatment strategies and provides information about the in-hospital outcomes and their predictors.

The main findings of this study demonstrate that: IE in urban South Africa remains a disease of relatively young people (median age 39yrs) with rheumatic or congenital heart disease (44.8%); culture-negative endocarditis remains a prevalent problem; the proportion of IE due to community-acquired *S. aureus* appears to be growing; and that there is evidence that IVDU-associated right-sided endocarditis is now an important problem. Furthermore, we found that heart failure was the most common complication of IE, was the most important predictor of death and was the main reason patients are referred for cardiac surgery, an intervention which was associated with reduced mortality rates. Finally, HIV, diabetes, alcohol use and chronic kidney disease were not important predictors of a poor outcome.

Although no major conclusions can be made from a retrospective review, or from comparisons with other studies, it is interesting to compare our findings with data from recent international registries^[4,17–20] and a similar but older South African study.^[13] When compared with our findings, these registries suggest that there are major differences in the age profile (>70yrs vs <40yrs), clinical profile (degenerative valve disease vs RHD) and microbiological profile of the studied IE patients, with apparently fewer cases of culture-negative and oral organism-related IE seen in the developed world.

Additionally, in comparison to findings from the South African study,^[13] the main observed differences revolved around the microbiological profile, proportion of IVDU-associated right-sided disease and the prevalence of underlying congenital heart disease. Whereas in 2003, community-associated *S. aureus* was noted infrequently, it was found in 26% of our overall cohort and was the dominant cause of infection in participants with IVDU-associated IE. This is in line with a recently published study from Johannesburg which found *S. aureus* to be present in 61% of recreational drug users who developed IE.^[12] The same study reported a higher burden of right sided endocarditis at their centre. This could possibly be explained by recent data on drug abuse in South Africa which showed higher rates of IV drug use in Gauteng than in the Western Cape.^[21] On the other hand, viridans group streptococci, which were previously dominant, may be diminishing in frequency. The high rate of culture-negative IE in our cohort was in line with the previous study and other middle- and low-income country data, as demonstrated in a systematic review by Njuguna et al.^[22] High rates of the empiric administration of antibiotics prior to blood culture collection is often provided as the main reason for high culture-negative IE rates. In those patients with culture-negative IE in our study, 24.8% of patients received antibiotics prior to blood culture collection. Culture negative rates are significantly lower in higher income countries (10%).^[4]

Mortality in our cohort (16.2%) was lower than what has previously been reported in other middle- and low-income countries (19-46%).^[22] A possible explanation for this relatively lower than expected mortality was the liberal use of cardiac surgery for those with international guideline-based recommendations, such as heart failure.^[23] Approximately 48% of participants with left-sided IE underwent surgery, a figure which was much higher than that reported in other low- and middle-income country registries, where about 15% receive valve replacement for the same indication.^[22,24]

To the best of our knowledge, this is the largest cohort of IE patients in sub-Saharan Africa to date and provides important information and insight into the disease in a South African context. There are a number of important limitations of this study, including: that it was a single-centre, retrospective study; that the number of participants was relatively small; that the subgroup sizes were relatively small and unequal; that it is likely that not all patients with IE over the given period of interest were captured; and that some patient records may have been incomplete and their ICD-9 and ICD-10 information may not have always been accurate. As a result of these and other limitations inherent in the design and conduct of such a study, caution needs to be taken with the conclusions one draws as well as with the generalizability of the findings.

Conclusions

Infective endocarditis in a typical teaching tertiary care centre in South Africa remains an important clinical problem. In this setting, it continues to affect mainly young people with post-inflammatory valve disease and congenital disease and is associated with an in-hospital mortality that is quite high at almost 20%. Intravenous drug-associated endocarditis caused by *S. aureus* is an important IE subset, comprising approximately 10% of all cases, a fact which was not reported 15 years ago, and culture-negative endocarditis remains highly prevalent. Heart failure in IE carries significant risk of death and needs a more intensive level of care in hospital. Finally, cardiac surgery which reduced mortality and it was most impactful in those patients with heart failure. These findings suggest that prospective cohorts of IE are needed to keep track of changing trends and profiles in order to provide clinicians with more robust information to inform their clinical practice and thereby improve patient outcomes.

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Author contributions. MCD developed study protocol, collected and analysed data and wrote the manuscript. CAV and MN contributed to study design, data analysis and reviewing and editing manuscript. KM contributed to data analysis. CV, AS, MR and MG contributed to data collection.

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Appendices to manuscript (List of table and figures)

1. Table 1 – Demographic, comorbidities, clinical characteristics and mortality of patients with left- and right-sided infective endocarditis.
2. Table 2 - Presenting signs and symptoms of patients with left- and right-sided infective endocarditis.
3. Table 3 - Complications of patients with infective endocarditis.
4. Table 4 - Clinically relevant risk factors associated with in-patient mortality in patients with left-sided infective endocarditis
5. Figure 1 – Number of patients included in study
6. Figure 2 – Microbiological profile of (a) left-sided and (b) right-sided endocarditis
7. Supplementary file 1 – Yearly number of patients included

Table 1. Demographic, comorbidities, clinical characteristics and mortality of patients with left- and right-sided infective endocarditis.

	Total n = 105 n, (%)	Left-sided disease n = 90 n, (%)	Right-sided disease n = 15 n, (%)
Sex - Male	65 (61.9)	54 (60.0)	11 (73.3)
Age (median, IQR)	39 (29-51)	42.7 (31-53)	29.1 (27-37)
Congenital heart disease	11 (10.5)	9 (10.0)	2 (13.3)
RHD	36 (34.3)	36 (40.0)	0 (0.0)
Previous IE	5 (4.8)	5 (5.6)	0 (0.0)
Prosthetic valves	14 (13.3)	14 (15.6)	0 (0.0)
None	31 (29.5)	20 (22.2)	11 (73.3)
HIV	20/87 (23.0)	20/75 (26.6)	0/12 (0.0)
IV drug use	15 (14.2)	4 (4.5)	11 (73.3)
Diabetes Mellitus	10 (9.5)	9 (10.0)	1 (6.7)
Ethanol use	23 (21.9)	23 (21.9)	0 (0.0)
Native valve IE	91 (86.7)	76 (84.4)	15 (100.0)
Prosthetic valve IE	14 (13.3)	14 (15.6)	0 (0.0)
Duke criteria definite	68 (64.8)	53 (58.9)	15 (100.0)
Echocardiography			
LVEF (% , IQR)	60 (53-66)	59.5 (53-65)	64 (58-70.5)
Vegetations present	85 (81.0)	71 (78.9)	14 (93.3)
Aortic regurgitation	39 (37.1)	38 (42.2)	1 (6.7)
Mitral regurgitation	62 (59.1)	60 (66.7)	2 (13.3)
Pulmonary regurgitation	9 (8.6)	8 (8.9)	1 (6.7)
Tricuspid regurgitation	34 (32.4)	23 (21.9)	11 (73.3)
Laboratory values			
WCC (median, IQR)	12.7 (8.3-15.7)	11.5 (7.7-15.4)	14.95 (13.8-18.5)
HB (median, IQR)	10.1 (8.5-11.4)	10.3 (8.8-11.4)	9.15 (7-11.6)
Creatinine (median, IQR)	89.5 (67-120)	87 (67-110)	121.5 (62-209)
Diuretic use	62/100 (59.1)	58/86 (64.5)	4/14 (28.6)
Valvular surgery performed	44 (42.3)	43 (47.8)	1 (6.7)
In-patient mortality	17 (16.2)	17 (18.9)	0 (0.0)

Abbreviations. LVEF, Left ventricular ejection fraction. IQR, Interquartile range.

Table 2. Presenting signs and symptoms of patients with left- and right-sided infective endocarditis.

	Total n = 105 n, (%)	Left-sided disease n = 90 n, (%)	Right-sided disease n = 15 n, (%)
Fever	67 (63.8)	54 (60)	13 (86.7)
Dyspnoea	64 (61.0)	57 (61.5)	7 (46.7)
Poor appetite	13 (12.4)	12 (13.3)	1 (6.7)
Weight loss	26 (24.8)	22 (24.4)	4 (26.7)
Neurological deficit	29 (27.6)	28 (31.1)	1 (6.7)
Arthralgia	11 (10.5)	8 (8.9)	3 (20.0)
Temperature >38.5°C	61 (58.1)	51 (56.7)	10 (66.7)
Clubbing	32 (30.5)	28 (31.1)	4 (26.7)
New or changed murmur	90 (85.7)	79 (87.8)	11 (73.3)
Slinter haemorrhages	19 (18.1)	17 (18.9)	2 (13.3)
Haematuria on urine test strip	44/64 (68.8) *	35/54 (64.8)	9/10 (90.0)

* data missing on 41 patients

Table 3. Complications of patients with infective endocarditis.

Complication	Total n = 105 n, (%)
Heart failure	45 (42.9)
Embolic	38 (36.1)
Ischaemic stroke	15 (14.3)
Mycotic aneurysm	8 (7.6)
Septic pulmonary emboli	6 (5.7)
Pulmonary infarct	2 (1.9)
Splenic infarct	2 (1.9)
Cerebral abscess	2 (1.9)
Intracranial haemorrhage	3 (2.9)
Acute kidney injury	23 (21.9)
Pneumonia	9 (8.6)
Septic shock	7 (6.7)

Table 4. Univariable and multivariable logistic regression analysis of clinically relevant risk factors associated with in-patient mortality in patients with left-sided endocarditis

	Univariable regression analysis		Multivariable regression analysis	
	Unadjusted OR (95% CI)	<i>p</i> value	Adjusted OR (95% CI)	<i>p</i> value
Age >45	3.73 (1.26-11.09)	0.018	4.73 (1.11-20.14)	0.036
Diabetes Mellitus	2.39 (0.53-10.73)	0.225	0.85 (0.12-6.15)	0.870
<i>Staphylococcus Aureus</i>	1.42 (0.40-5.06)	0.589	2.04 (0.41-10.23)	0.386
Heart Failure	1.83 (0.63-5.34)	0.269	8.16 (1.77-37.70)	0.007
Valvular Surgery Performed	0.18 (0.05-0.67)	0.011	0.09 (0.02-0.43)	0.001

Abbreviations. OR, odds ratios

Note: Analysis was restricted to patients with left sided IE as risk profiles differ between right- and left-sided IE. There was insufficient data to conduct similar analysis in right sided cohort.

Figure 1. Number of patients included in study

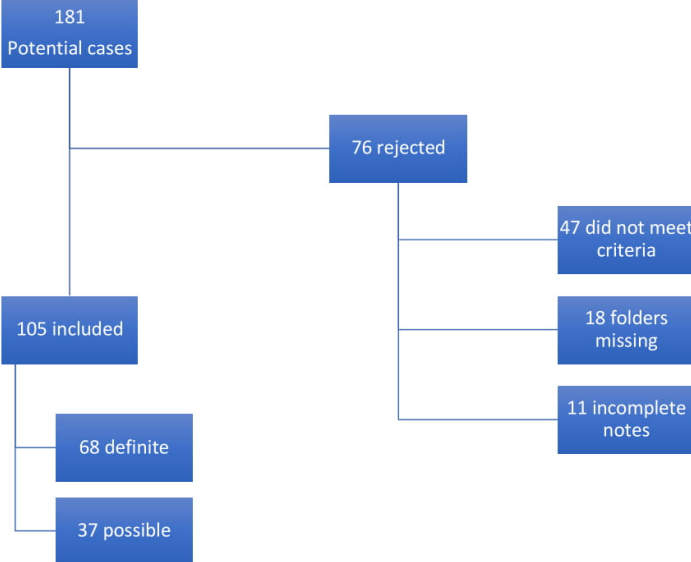


Figure 2. Microbiological profile of left-sided (a) and right-sided endocarditis (b)
Fig 2(a). Left-sided endocarditis

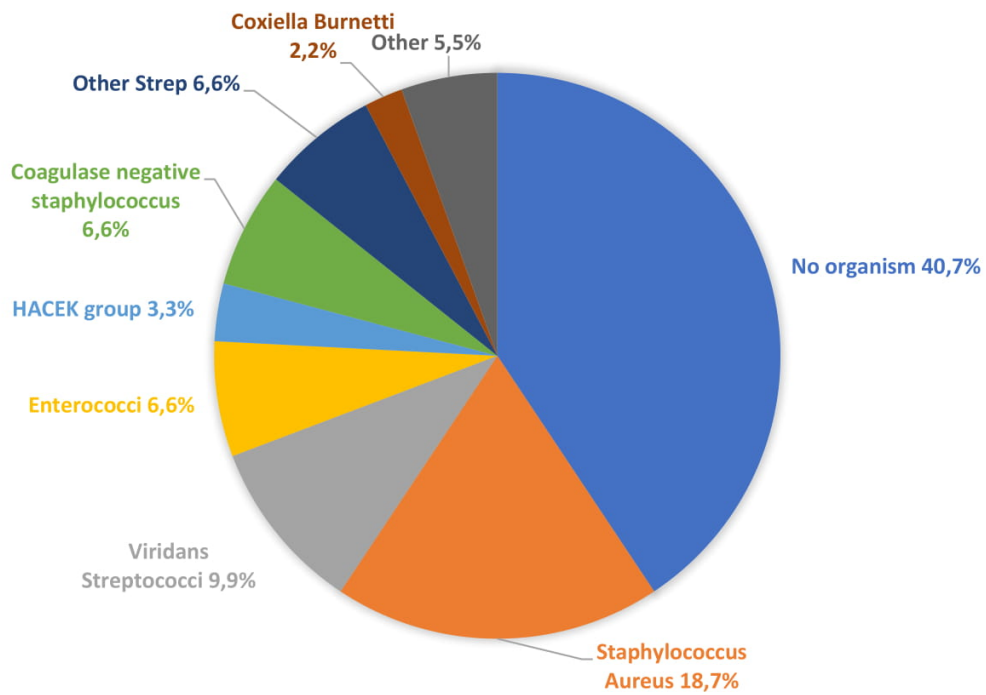
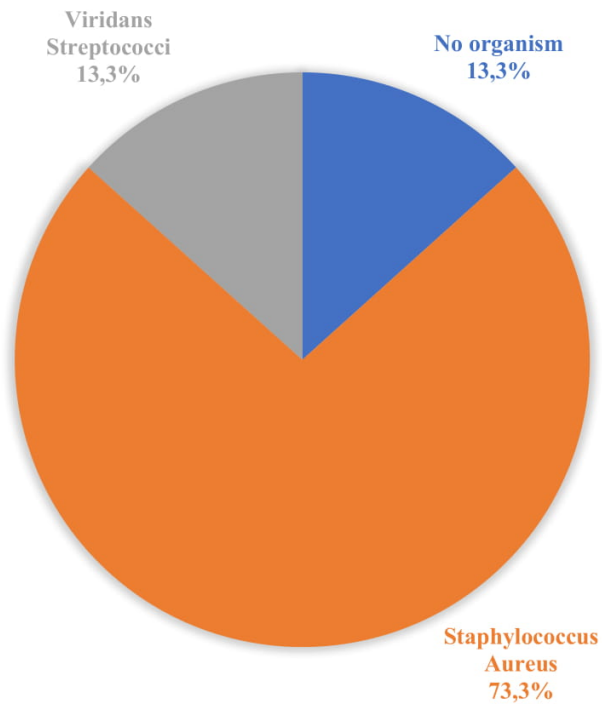
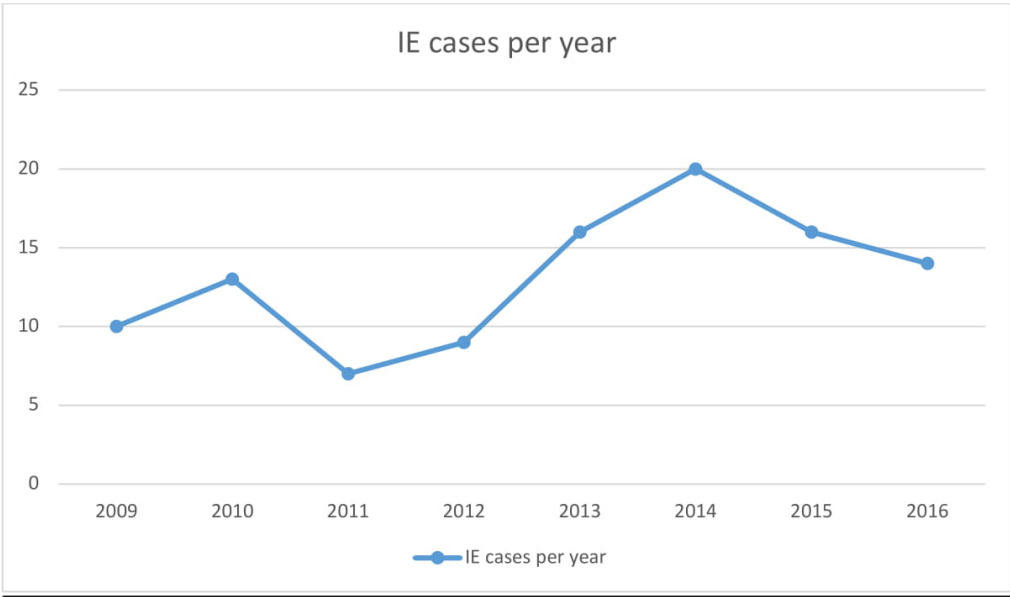


Fig 2(b). Right-sided endocarditis



Supplementary file 1. Yearly number of patients included



Research Protocol

Retrospective analysis of infective endocarditis at Groote Schuur Hospital

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Background and Rationale

Infective endocarditis (IE), as defined by the modified Duke criteria, (1) is a potentially fatal condition. (2,3) In the developed world, the classic clinical signs of IE are becoming less common, with patients often only presenting with fever and/or heart murmur. (3) Over and above the diagnostic challenges and difficulties, IE remains a difficult condition to manage. (4) Observational data from the developed world indicates that the profile of IE has changed significantly over the last four decades. It is now a disease which affects predominantly geriatric or diabetic patients with degenerative (70%) or prosthetic valves (30%) with rheumatic heart disease all but disappearing as a predisposing risk factor. Nosocomial infections from long term indwelling catheters and intravenous lines are increasing in incidence with staph aureus, coagulase negative staph and enterococcus becoming the dominant organisms while infections with traditional oral organisms have declined significantly. Congestive cardiac failure, stroke, intra-cardiac abscess, conduction abnormalities remain major complications of IE. Congestive cardiac failure is the most common indication for early cardiac surgery, which is the therapeutic strategy of choice in 50% of patients. (5) Despite this evolution in profile, IE carries a significant in-hospital mortality of between 15% and 30%, which has changed little over the past four decades. (4,6-8)

There is little contemporary data available on IE from South or sub-Saharan Africa (9). Specifically, there is sparse information about the patient profiles, patient related risk factors, the spectrum of heart disease, the spectrum of microbiological organisms, complications and their predictors, the proportion of patients with IE who undergo surgery, and in hospital mortality rate of the condition. This knowledge is vital for improving the health care of patients, the clinical practice of care-givers and improving the overall outcomes and survival of patients.

Purpose of the study

- **Aim of study**

The aim of this retrospective review of the records is to provide a contemporary descriptive overview of infective endocarditis as experienced in a large referral hospital in sub-Saharan Africa

- **Objectives:**

- Describe the patient profile including demographics and risk factors
- Describe the spectrum of predisposing structural heart disease
- Describe the proportion of those who meet criteria for definite, probable and possible IE amongst those treated for IE
- Describe the microbiological spectrum
- Determine the complications rates with a focus on:
 - Cardiac failure
 - Heart block and intracardiac abscesses
 - Neurological complication (mycotic aneurysms, meningitis, strokes)
 - Acute kidney injury
 - Peripheral emboli
- Proportion of patients treated with Cardiac Surgery
 - Determine the predictors of surgery
- The in-hospital mortality rate

Methodology

Study design

This study will be a retrospective review of the medical records of patients diagnosed and treated as infective endocarditis at Groote Schuur Hospital between 2007 and 2016. The analysis will be done by doing a folder review of medical and surgical notes, prescription charts and reports of special investigations.

Characteristics of the study population

Inclusion criteria

This study aims to include all adult patients (>17years) admitted to Groote Schuur Hospital for treatment of infective endocarditis between 2007 and 2016.

Exclusion criteria

Patients to be excluded from this study:

- Patients with incomplete or missing clinical records

Study methods and procedures for data collection

Patients who meet the inclusion criteria for the study will be identified through the following sources:

1. ECCR (Electronic Continuity of Care Records) - electronic database of discharge summaries at Groote Schuur Hospital. We will use keyword searches, i.e. infective endocarditis, and the ICD-10 code, to identify patients, dating back to 2012
2. Clinicom system - ICD 10 code (I33.0) will be used to search for patients
3. Database created by SSM project 77, "Retrospective analysis of the spectrum of disease seen during Cardiology consultations at GSH" (HREC ref no 348/2016)
4. Handwritten discharge summaries from the department of Medicine, dating back to 2007
5. The record of in-patients referrals to Cardiology, kept in E17 Cardiac Clinic
6. Cardiothoracic "filemaker" internal database for patients who have undergone

surgery

7. Death notification document as obtained through A5 death administration
8. Microbiology lab records of patients with blood cultures or PCR positive for organisms typically associated with infective endocarditis
9. The internal records of the Division of Cardiology
10. Patient folders from records department of Groote Schuur Hospital
11. Relevant data pertaining to the patients from
 - a. NHLS laboratory online results
 - b. PACS radiography system
 - c. Echocardiography data from records in the echo department in ward E17 (paper based and via centrality)

Sample size

We anticipate that there are at least 15 cases of IE per year, thus will acquire 150 patient records.

A paper based data collection sheet will be used to collate data from the above sources. An example of the data collection sheet is included as Appendix 1.

Data will be entered as categorical or nominal values. The data collection sheet will be electronically uploaded to *RedCap*, from where data extraction will be done to Microsoft Excel and SPSS.

To protect patient confidentiality, access to *RedCap* is password protected and will only be able to be accessed by the principal investigator. Only the principal investigator, supervisors and statistician will have access to the data on *RedCap*, MS Excel and SPSS. Patient confidentiality and anonymity will be maintained by identifying patients by their folder numbers.

The principal investigator will have a team to assist with data collection, comprising of:

1. Dr Azhar Seedat
Persal number: 56383011
Intern at Groote Schuur Hospital

2. Dr Mariette Graham
Persal number: 22773231
Intern at Groote Schuur Hospital
3. Dr Max Rath
Persal number: 56382456
Intern at Groote Schuur Hospital
4. Dr Clinton van der Westhuizen
Persal number: 55365914
Medical Officer in the Department of Medicine at Karl Bremer Hospital

The following data will be collected (see appendix 1 for detail)

1. Demographics, as documented in patient folders and clinical notes
2. Co-morbidities, as documented in clinical notes
3. Heart Valves Infected (native or prosthetic), as documented in clinical notes or echocardiogram reports
4. Diagnostic criteria for infective endocarditis
 - a. Major
 - i. Microbiology, as documented in clinical notes or NHLS results on DISA or LABTRACK
 - ii. Echocardiogram
 - b. Minor
 - i. Predisposing heart lesions, as per clinical notes
 - ii. Clinical presentation, as documented in clinical notes

iii. Laboratory investigations, as per NHLS results on DISA or LABTRACK

5. Infective source found, as documented in clinical notes
6. Complications, as documented in clinical notes, echocardiogram, electrocardiogram and computerised tomography scanning
7. Therapy, as documented on prescription charts
8. Admission to wards or high care units
9. Length of hospital stay

Data safety and monitoring

To maintain confidentiality and anonymity, patients will be identified only by their hospital numbers in the electronic database used in the study. Only the data as outlined will be collected and analysed.

Data analysis

Data will be stored and extracted with a database built in Redcap. Data analysis will be performed in Stata (version 13.1, College Station, TX, USA).

Descriptive statistics will be used to present a profile of the total sample namely type of IE, risk factors, microbiological characteristics, screening procedures, medical complications and surgical interventions. Continuous variables will be described using means \pm standard deviations (SD) or medians with interquartile range (IQR) depending on their distributions, while categorical variables will be expressed as frequencies and percentages.

Primary analysis will assess whether there are any associations between profile measures, and mortality or morbidity. Parametric tests (Two-sample T-test for continuous or Chi-square test for categorical variables) or non-parametric tests (Mann-Whitney U test for continuous or Fisher's Exact test for categorical variables) will be used where appropriate. Univariate and multivariable logistic regression will be used to identify risk factors for mortality in patients with IE, and provide crude and adjusted odds ratios accordingly. The incidence rate for death will be calculated by the number of cases divided by disease-free person-time of observation. Where applicable, a $p < 0.05$ will be considered statistically significant and 95% confidence intervals used to determine the precision of estimates.

Budget

No budget is required.

Timeline

May - July 2016:	Protocol finalization and HREC approval
August 2016 - July 2017:	Data Collection
August 2017:	Data Analysis
September 2017 - February 2018:	Literature review and prepare dissertation

Benefits of study

This study aims to

- Improve understanding of infective endocarditis in our setting
- Identify areas where our care of infective endocarditis could be improved

Ethical considerations

- Risk:
 - This is a low risk study.
 - There is no risk involved for patients participating in this study.
- Privacy and confidentiality:
 - Patient confidentiality will be maintained at all times.
- Reimbursement for participation:
 - There will be no reimbursement for participants in this study

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9. Koegelenberg CFN, Doubell AF, Orth H, Reuter H. Infective endocarditis in the Western Cape Province of South Africa: A three-year prospective study. *QJM - Mon J Assoc Physicians*. 2003;96(3):217-25.

Appendices to protocol

Appendix 1 - Data to be collected

1. Demographics
 - a. Age
 - b. Gender

2. Co-morbidities - As documented in clinical notes
 - a. Previous infective endocarditis
 - b. Rheumatic heart disease
 - c. Congenital heart disease
 - d. HIV
 - e. Diabetes
 - f. Chronic liver disease
 - g. Chronic Kidney Disease
 - h. Dialysis
 - i. Cancer

3. Foreign material - As documented in clinical notes
 - a. Dialysis catheters
 - b. Intravenous ports
 - c. Urethral catheter
 - d. Pacemaker

4. Habits - As documented in clinical notes
 - a. History of recreational IV drug use
 - b. Smoking
 - c. Alcohol

5. Heart Valves Infected - As documented in clinical notes

- a. Native
- b. Tissue prosthesis
- c. Mechanical prosthesis
- d. TAVI

6. Localisation - As documented in clinical notes

- a. Left native
- b. Left prosthesis
- c. Right
- d. Device

7. Clinical Presentation - As documented in clinical notes

- a. Initial symptom
 - i. Fever
 - ii. Poor appetite
 - iii. Weight loss
 - iv. SOB (NYHA)
 - v. Neurological deficit
 - vi. Arthralgia

- b. Clinical signs
 - i. Fever
 - ii. Murmurs
 - iii. Clubbing
 - iv. Splinter haemorrhages
 - v. Janeway lesions
 - vi. Osler nodes
 - vii. Roth spots
 - viii. Splenomegaly

- c. Urinary dipstick
 - i. If done
 - ii. Presence of hematuria

8. Microbiology

- a. Blood cultures
 - i. Number done
 - ii. Number positive
 - iii. Organisms cultured

9. Echocardiogram

- a. Echocardiogram modality (Trans-thoracic or trans-esophageal)
- b. Valve dysfunction - Defined as at least moderate on echo
 - i. Aortic
 - ii. Mitral
 - iii. Pulmonary
 - iv. Tricuspid
- c. Vegetation on valve - As documented on echo report
 - i. Aortic
 - ii. Mitral
 - iii. Pulmonary
 - iv. Tricuspid
- d. Size of vegetations - Size in cm on echo report
- e. Left ventricular function - Ejection fraction as documented on echocardiogram
- f. Complications
 - i. Abscess
 - ii. Dehiscence of prosthetic valves

10. ECG findings - As documented in clinical notes

- a. Heart rate
- b. Rhythm
 - i. Sinus
 - ii. AF
 - iii. Heart block

- c. PR interval

11. Baseline laboratory investigations - Values on presentation to GSH

- a. WCC
- b. Hb
- c. Plt
- d. Creatinine
- e. CRP
- f. ESR
- g. CD4 count
- h. Albumin
- i. Complement C3 C4

12. Infective source found - As documented in clinical notes

- a. Dental
- b. GIT
- c. Skin
- d. Unknown
- e. Other

13. Complications - As documented in clinical notes

- a. Heart failure
- b. Heart block
- c. Prosthetic valve dehiscence

- d. Embolism
 - i. Pulmonary infarcts
 - ii. Splenic infarcts
 - iii. Cerebral abscess
 - iv. Mycotic aneurysms
 - v. Septic arthritis
- e. Intracranial haemorrhage

- f. Septic shock
- g. Renal failure
- h. Death

14. Therapy

- a. Medical
 - i. 1. Antibiotics
 - a. Which antibiotics used
 - b. Duration of treatment
 - ii. 2. Diuretics
 - iii. 3. Pacing
 - a. Temporary
 - b. Permanent
- b. Surgical
 - i. If replacement or repair done
 - ii. Duration since diagnosis to surgery

15. Admission

- a. Medical wards
- b. CCU
- c. Cardiothoracic ward

16. Length of hospital stay

- a. Date of admission
- b. Date of discharge / death
- c. Date referred to Cardiology
- d. Date of surgery (if done during admission)

End of appendix 1

Data collection tool

Retrospective Analysis infective endocarditis				Duke	Definite	Possible	Maj: Min:
Surname				Folder no			
First Name				Date admission			
Date of Birth				Date discharge/death			
Gender		M	F	Date referred cardio			
Co-morbids		CLD	Prev IE	CKD	Dialysis	Cancer	Other:
		HIV	RHD	Diabetes	CongHD	Pregnancy	
Foreign Material		Dial Cath	IV port	Habits	Hx IV drug	Smoking	ETOH
Heart Valves Infected		U-Cath	Pacemaker	Localisation lesion		Left Native	Left pros
Native	Tissue pros	Mech pros	TAVI			Right	Device
Clinical presentation		Symptoms	Fever	Poor appetite	Weight loss	SOB NYHA:	
Signs	Fever >38.0	Clubbing	Neuro def:			Arthralgia	
	Murmur:	PrN/Chg/Old	Splint haem	Janeway	Osler	Roth	Spleen
Urine dip	Not done	Haem	No Haem	Bloodcult	Organism:	No done:	
BC + after 48h	Yes	No			No. positive:		
Echo	Not done	TTE	TOE	Abx before BC done	Yes	No	
Valve dysf	AR (Mild/Mod/Sev)	PR (Mild/Mod/Sev)	Vegetations and size		AO	MV	
None	MR (Mild/Mod/Sev)	TR (Mild/Mod/Sev)	mn	None	PV	TV	
LVEF:	Complications (echo)		None	Yes (Define):			
ECG	HR:	PR:	Rhythm:	Sinus	AF	Heart Block	Other:
LAB	WCC:	Hb:	Plt:	Creat:	CRP:	ESR:	CD4:
HIV:	Alb:	C3:	C4:	Infective source		Dental	GIT
Complications		HF	Pneumonia	Other:		Skin	Unknown
Heart Block (1/2/3)	Spleen infarct		Pulm infarct	Cerebral abscess		Septic	
Intracranial haemorrhage	Sept shock	Renal failure		Mycotic Aneurysm		Arthritis	
Abx + dates							
1.	2.		3.		4.		
	5.			6.			
Diuretic	Yes	No	Unknown	Pacing	None	Temp	Permanent
Surgery	None	Repair AO/MV/PV/TV		Admission	Medical	CCU	CT surg
Date:	Replace AO/MV/PV/TV		Other:		CT ICU	O+G	
AB Reg	Emp Nat	Emp Pros	Direct	Outcome	Demise	DC	Down ref
Investigator Name:					Form	Complete	Incomplete
Signature:							
Date Data Collected:							

Ethics and hospital approval



UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee



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Website: www.health.uct.ac.za/fhs/research/humanethics/forms

18 July 2016

HREC REF: 517/2016

Prof M Ntsekhe

Cardiac Clinic
E-17
NGSH

Dear Prof Ntsekhe

PROJECT TITLE: VERSION 1.0- RETROSPECTIVE ANALYSIS OF INFECTIVE ENDOCARDITIS AT GROOTE SCHUUR HOSPITAL (MMeD-candidate-Dr M de Villiers)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 July 2017.

Data collection must occur from 30/06/2016 retrospectively.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

We acknowledge that the student, Dr Martin de Villiers will also be involved in this study.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval before the research may occur.

Yours sincerely

Signature Removed

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.

HREC 517/2016

GROOTE SCHUUR HOSPITAL

Enquiries: Dr Bernadette Eick

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Professor M. Ntsekhe
Cardiology Department
E17 - NEW MAIN BUILDING

E-mail: mc.devilliers@hotmail.com / mpiko.ntsekhe@uct.ac.za

Dear Professor Ntsekhe

RESEARCH PROJECT: Version 1.0 Retrospective Analysis of Infective Endocarditis at Groote Schuur Hospital (MMed. Dr Martin de Villiers)

Your recent letter to the hospital refers.

You are hereby granted permission to proceed with your research which is valid until **30 July 2017**.

Please note the following:

- a) Your research may not interfere with normal patient care.
- b) Hospital staff may not be asked to assist with the research.
- c) No additional costs to the hospital should be incurred i.e. Lab, consumables or stationary may be used.
- d) **No patient folders may be removed from the premises or be inaccessible.**
- e) Please introduce yourself to the person in charge of an area before commencing.
- f) Please discuss the study with the HOD before commencing.
- g) Please provide the research assistant/field worker with a copy of this letter as verification of approval.
- h) Confidentiality must be maintained at all times.
- i) Should you require additional research time beyond the stipulated expiry date, please apply for an extension.
- j) **On completion of research, please submit a copy of the publication or report.**

I would like to wish you every success with the project.

Yours sincerely

Signature Removed

DR BERNADETTE EICK
CHIEF OPERATIONAL OFFICER

Date: 28 July 2016

BE/vms

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Reviewers comments with reply (SAMJ)

Manuscript revision – reply to reviewer comments
Reference: SAMJ13888 - The changing landscape of infective endocarditis in South Africa
General impression of this manuscript
<p>Reviewer #1: Please see comments to the authors- as document attached. I think this is a well conducted retrospective review of records of patients admitted with infective endocarditis. There is only one paper from this region published more than 10 years ago. The manuscript is well written, the tables and figures are relevant and informative, the discussion is comprehensive. I think this manuscript is relevant for the South African SAMJ reader as it alerts to the fact that we now see an increasing number of right sided infective endocarditis, that despite patients presenting with heart failure the outcome can be improved if patients are referred early for surgery. As 24% of the cases received antibiotics prior to having blood cultures awareness can be raised take blood cultures earlier. I think this article fits well into a general medical journal.</p>
Thank you for the suggestions and the constructive feedback.
<p>Reviewer #2: Yes, this article is relevant under South African context. It offers important information on the current clinical spectrum of infective endocarditis in a single center and adds to the existing body of knowledge. There are similar studies in South Africa. The article is overall reasonably presented. The conclusions are fair and are clearly stated. It will sensitize the general practitioner to infective endocarditis and hence improve diagnosis and management. It is fit for SAMJ.</p>
Thank you for reviewing our manuscript and the positive feedback.
Methods and analysis presented in this manuscript
<p>Reviewer #1: the research question is well addressed; sample adequate and well described (table 1 and 2).</p>
We appreciate the positive feedback.
<p>Reviewer #2: The research question is well stated. The sample for left sided endocarditis is sufficient but not for right sided infective endocarditis whereby a larger sample is needed to make any meaningful interpretation of results. The methods are well described. Table 1 compares the characteristics of left and right sided endocarditis. However, this comparison is statistically questionable due to the significant difference in the sample size between the right and left sided endocarditis.</p>
Thanks for the feedback. We agree that a p value for the differences observed between baseline variables between right and left sided endocarditis is meaningless given the numbers and have removed the p values from table 1 and table 2.

Results, Discussion and Conclusions presented in this manuscript
Reviewer #1: Please see comments above and comments to the authors. I would have the one figure as a supplementary figure.
Thank you for the comment, see response to comment no.2 on next page.
Reviewer #2: The population is adequately described. The results are well presented. Except Table one comparison as mentioned above the rest are credible. Tables are useful. The pie chart (figure 3b) can be deleted as the sample size for right sided endocarditis was small. This information can be written in words under results.
Thank you for pointing out this limitation, as discussed above. As left sided and right sided endocarditis have different microbiological profiles, we believe that a visual representation highlighting these differences would be beneficial for the reader.
Discussion
Reviewer #1: The results are well discussed. I had just one suggestion for the conclusion of the abstract.
Thank you for this excellent suggestion. We have addressed this in the abstract.
Reviewer #2: The results are well discussed. A more detailed direct comparison in a table format of the current study with the study conducted in 2003 by Koegelenberg CFN would have enhanced the quality of the paper. Yes, the limitations are discussed reasonable well. Yes, the relevance of the study is discussed.
Thank you for the valuable suggestion. The differences in study design and statistical analysis in the Koegelenberg study and our study, a direct comparison in a table format leaves incomplete data. However, we have described the major differences in the text on page 7: <i>"...in comparison to findings from the South African study,[13] the main observed differences revolved around the microbiological profile, proportion of IVDU-associated right-sided disease and the prevalence of underlying congenital heart disease. Whereas in 2003, community-associated S. aureus was noted infrequently, it was found in 26% of our overall cohort and was the dominant cause of infection in participants with IVDU-associated IE."</i>
Conclusion
Reviewer #1: Yes- I just had a minor suggestion how to make the conclusion stronger
Thank you for the suggestion, please see next page for full reply under comment 1.
Reviewer #2: Yes, the implications are summarised. The conclusion about IV drug abuse right sided infective endocarditis pertaining to this study may not be entirely reflective of the real burden of this disease as this group formed minority of the patients. Recommendation for future research is made.
Thank you for this important comment. We agree that the burden of right sided endocarditis in South Africa might be greater than what we saw at our centre, however our study shows an increase in right sided IE from what was previously shown in the Western Cape. Please also refer to reply of comment no. 6 below.

Reviewer #1: Comments to Authors and Editor

The changing landscape to infective endocarditis in South Africa The authors need to be congratulated to a well conducted retrospective review of records of patients admitted with infective endocarditis.

The manuscript is well written, the tables and figures are relevant and informative, the discussion is comprehensive. I think this manuscript is relevant for the South African SAMJ reader as it alerts to the fact that we now see an increasing number of right sided infective endocarditis, that despite patients presenting with heart failure the outcome can be improved if patients are referred early for surgery. As 24% of the cases received antibiotics prior to having blood cultures awareness can be raised take blood cultures earlier. I have only a few minor suggestions:

1) Conclusion of main manuscript and abstract should be aligned. 48% of patients with left-sided endocarditis underwent surgery versus 15% in reports from other LMICs (Ref 21 & 23). As this clearly impacted on (relatively good) outcome I would highlight this more in the abstract. I also suggest highlighting the fact that patients presenting with heart failure and infective endocarditis need intensive and high-level care. The OR of death is 8.1 in multivariable regression analysis.

Thank you for this important correction. We have aligned the conclusion of the main manuscript with the abstract and included above suggestions to highlight the fact that heart failure carries higher mortality and needs increased level of hospital care.

See page 2:

"Infective endocarditis in a typical teaching tertiary care centre in South Africa remains an important clinical problem. In this setting, it continues to affect mainly young people with post-inflammatory valve disease and congenital disease and is associated with an in-hospital mortality that is quite high at almost 20%. Intravenous drug-associated endocarditis caused by S. aureus is an important IE subset, comprising approximately 10% of all cases, a fact which was not reported 15 years ago, and culture-negative endocarditis remains highly prevalent. Heart failure in IE carries significant risk of death and needs a more intensive level of care in hospital. Finally, cardiac surgery which reduced mortality and it was most impactful in those patients with heart failure."

2) Figures: Figure 3 is very nice. If there is not enough space for all the figures and tables I would make figure 2 supplementary.

As suggested, we changed figure 2 to supplementary file 1.

See page 5:

"There was a steady increase in the number of cases seen over the period from 2009 to 2016, with a peak in 2014 (Supplementary file 1)."

3) Comorbidities: More than 20% of the patients reported ethanol abuse. Was this a predictor of poor outcome? I could not find this information in the manuscript.

Thanks for pointing this out. We analysed ethanol use in the univariable regression analysis and did not find it to have a statistically significant impact on death amongst those with left sided endocarditis (OR 1.79 with CI 0.58-5.58, P=0.311). We have added this finding in the discussion section. However, as a limitation of retrospective studies, the amount of ethanol use not consistently documented in the majority of patients, and we could therefore not use this in our analyses. It would be important to quantify ethanol use in prospective studies of IE to have a more accurate analysis of risk of death in the setting of IE.

See page 7:

"Finally, HIV, diabetes, alcohol use and chronic kidney disease were not important predictors of a poor outcome."

Reviewer #2: The study is relevant as it provides contemporary information relating to infective endocarditis in a single centre in South Africa and will hopefully stimulate renewed interest in the field in other hospitals in the Country. The retrospective nature of the study is an important limitation.

1) Can the Authors provide a more detailed echocardiographic description of these patients echocardiographic exam such as ventricular function, dimensions, presence or absence of pericardial effusion, pulmonary hypertension?, the mean vegetation size.

Thank you for this comment. As mentioned, retrospective studies are limited by the extent of information that can be extracted. We collected the following echocardiographic data: LV function, presence of vegetations and associated dysfunction of valve because that was what was noted in all the reports. LV dimensions and vegetation size were unfortunately not always documented, and we could therefore not include these values in our analysis. It is also important to note that while we felt the additional echo detail may have enhanced the descriptive study, we felt that we were still able to meet the main aims and objectives of the study. We are conducting a prospective registry where more the requested details are being captured. As suggested, we have included the LV systolic function in the descriptive analysis of table 1.

2) Table one provides a comparison of the characteristic of right and left sided endocarditis. However, is this comparison valid with such a drastic difference in sample size between the two groups?

We agree that a comparison is not valid given the large differences in size and have removed the p values. We do however feel it important to provide the absolute numbers and interquartile ranges

Please see changes to table 1 and table 2 (p-values removed)

3) A third of the patient were HIV positive, what were their CD4 count and viral load? Should this information have not been included in the multivariate analysis?

On univariable regression analysis CD4 count was not associated with death, and was therefore included in multivariable regression analysis. Viral load was infrequently measured in this cohort at the time of admission for IE and could therefore not be used for any analysis.

4) How many of the patient with Right sided endocarditis presented with features of pulmonary embolism. One of the complication for right sided infective endocarditis was pneumonia, were these not simply cases of septic pulmonary emboli misdiagnosed as pneumonia?

The term pneumonia is what was captured from the source documents. However, we agree that septic emboli to the lungs are a much more common complication of right sided IE than pneumonia and therefore are likely to be the complication which was being describe. The term pneumonia in this context is confusing have therefore changed the notation in the text. In the right-sided endocarditis sub-group there were 6 patients who complicated with septic pulmonary emboli (documented as pneumonia from source) and the descriptions has been changed accordingly in the text and in table 3.

See page 6:

“The most common complications for right-sided disease were septic pulmonary emboli (40.0%) and acute kidney injury (40.0%).”

“Heart failure was the most common in-hospital complication (42.9%), followed by embolic complications (36.1%), acute kidney injury (21.9%) and pneumonia (8.6%).”

Also see table 3 adjusted accordingly.

5) Which Congenital heart lesion was a predisposing factor for IE in this cohort?

Unfortunately the notes did not always specify the extent of congenital heart disease and we did not include this information in the scope of this study as it does not change the aims and objectives originally described.

6) The majority of the cases were that of left sided infective endocarditis. Only 11 cases were intravenous drug related right sided infective endocarditis over a period of 6 years. This is an interesting finding as it contrasts with the current study on IV drug use related infective endocarditis from Chris Hani Baragwanath Hospital, where in a period of two years close to 80 patients were diagnosed with IV drug related infective endocarditis (majority had right sided infective endocarditis). Is there an explanation for these contrasting results within the same Country? Does this merely reflect the larger number of patients seen at Chris Hani Baragwanath Hospital?

That is a very interesting finding indeed. IV drug use rates are traditionally lower in the Western Cape. In our setting there are low rates of IV heroin use but high rates of smoked drug abuse (eg. tik). In contrast, Gauteng has much higher IV drug abuse rates. We have included this in our discussion section with reference to recent statistical data.

See page 7:

"...recently published study from Johannesburg which found S. aureus to be present in 61% of recreational drug users who developed IE.[12] The same study reported a higher burden of right sided endocarditis at their centre. This could possibly be explained by recent data on drug abuse in South Africa which showed higher rates of IV drug use in Gauteng than in the Western Cape.[21]"

7) There was no mortality reported in the right sided infective endocarditis group and it seems they all responded to antibiotic therapy except for one patient. What was the reason for surgery in that particular patient? Additionally the small sample size in the IV drug related right sided endocarditis group does not reflect the true profile and outcomes of this unique group of patients in a resource limited South African setting.

We agree that we have small cohort of right sided endocarditis and that a larger cohort in a prospective study would be needed to validate our results. The one patient in the right sided IE group who underwent surgery, had a tricuspid valve repair due to severe tricuspid regurgitation.

See page 6

"Only one patient with right-sided endocarditis underwent surgery, i.e. tricuspid valve repair due to severe tricuspid regurgitation."

8) How many of these patients required additional imaging (in the form of transesophageal echocardiogram, PET scan) to make an assessment of infective endocarditis? As this diagnosis can sometimes be challenging.

At the time of the study duration we did not have access to PET Scanning. All the patients who had surgery underwent intra-op TEE prior to their operation but detailed TEE findings were not always available which is why we did not include this in the descriptive analysis.

Acceptance letter for publication (SAMJ)

From: "SAMJ" <em@editorialmanager.com>

Subject: Your Submission

Date: 04 February 2019 at 10:43:55 SAST

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The changing landscape of infective endocarditis in South Africa

South African Medical Journal

Dear Dr De Villiers,

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Please note that as per the author guidelines, page-fee charges have been implemented since March 2017 for all research articles. Please find payment form attached herewith. As soon as proof of payment and the completed form have been received, we will send your article into production. (Please note that we are unable to process American Express card payments). Please send proof of payment to claudian@hmpg.co.za

Thank you for submitting your work to the journal.

Best wishes

Bridget Farham, PhD

Editor

South African Medical Journal

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