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**Infective Endocarditis in Neonates at Charlotte Maxeke Johannesburg Academic Hospital:
A Retrospective Study (January 2015-March 2021)**

Dr Laura Hogarth

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in
partial fulfilment of the requirements for the degree of Master of Medicine in Paediatrics

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DECLARATION

I Laura Hogarth, declare that this Research Report is my original work. It is being submitted for the Degree of Master of Medicine in the branch of Paediatrics at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

Declarations of interest: None



Dr Laura Hogarth

_____ 2nd _____ day of _____ October 2024 Signed at _____

DEDICATION

This work is dedicated to my parents that have walked this long journey with me. I will always be grateful for their unwavering support and encouragement.

To my extended family and friends that supported me along the way, thank you.

To the mentors and teachers that have provided endless encouragement and support, thank you.

Thank you for believing in me and making me believe in myself.

To Dr Hlophe, thank you for inspiring me.

LIST OF ABBREVIATIONS

A. baumannii – *Acinetobacter baumannii*

Burkholderia – *Burkholderia cepacia*

CN – Culture negative

CoNS - Coagulase-negative staphylococci

CTX – Cephalosporins

D/C – discharged

E. cloacae – *Enterobacter cloacae*

E. coli – *Escherichia coli*

ESBL – Extended spectrum beta-lactamase

HACEK - *Haemophilus* species, *Aggregatibacter* species, *Cardiobacterium hominis*, *Eikenella corrodens* and *Kingella* species

IE – Infective Endocarditis

IV – Intravenous

K. pneumoniae – *Klebsiella pneumoniae*

L – Lost to follow-up

MRSA - Methicillin-resistant *Staphylococcus aureus*

PDA – Patent ductus arteriosus

PFO – Patent foramen ovale

PPS – peripheral pulmonary stenosis

S. aureus – *Staphylococcus aureus*

TEE - Transoesophageal echocardiography

TF – Transferred

TTE - Transthoracic echocardiograph

VSD – Ventricular septal defect

ABSTRACT

BACKGROUND

Paediatric endocarditis is rare but has significant morbidity and mortality. Neonatal endocarditis is an area lacking research. Previously endocarditis was associated with congenital cardiac lesions but with advancing medical care children with structurally normal hearts are developing endocarditis. The diagnosis is made using the Modified Duke Criteria and requires a high level of suspicion in neonates.

METHODS

Clinical and microbiological data was collected from a tertiary hospital in Johannesburg from 01 January 2015 to 31 March 2021. Data analysis included using the Modified Duke Criteria to determine if the patient had definite or probable endocarditis and these data were included.

RESULTS

There were 38 cases of probable endocarditis and four definite endocarditis, this accounts for 0.98% of the paediatric patients that were referred for echo during the study period. Two cases were community-acquired endocarditis. One patient had a cyanotic cardiac lesion, and seven patients had acyanotic cardiac lesions. The predominant causative organism was gram-negative bacteria (38.1%) followed by fungal (28.6%), 23.8% cases were due to gram-positive organisms and 21.4% were culture negative cases. A 42-day course of antibiotics was completed in 11 patients prior to the outcome. Another 40% of the patients were on directed antibiotics at outcome. The all-cause case fatality rate was 42.9%.

CONCLUSION

Endocarditis is an important condition in paediatrics due to advancements in medical care. Gram-negative bacteria and fungal pathogens are important organisms in hospital acquired endocarditis. Data relating to neonatal endocarditis is lacking and this research suggests that the condition may be more common than currently thought to be. A high index of suspicion is required in septic neonates and a multidisciplinary approach to the management of these neonates is imperative.

KEYWORDS

Infective endocarditis/Neonates/Sepsis/Nosocomial Sepsis/Infection

PRESENTATIONS ARISING FROM THIS RESEARCH

This research has been accepted for an oral presentation at the South African Cardiology Conference in November 2024

This research was also presented at the University of the Witwatersrand Paediatric Research Day in December 2024

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TABLE OF CONTENTS

DECLARATION.....	ii
DEDICATION	iii
LIST OF ABBREVIATIONS.....	iv
ABSTRACT.....	v
PRESENTATIONS ARISING FROM THIS RESEARCH	vi
ACKNOWLEDGEMENTS	vii
LIST OF FIGURES.....	ix
LIST OF TABLES	x
SUBMISSIBLE ARTICLE	1
REFERENCES	9
TABLES AND FIGURES	11
FIGURE 1	11
FIGURE 2	12
FIGURE 2A	12
FIGURE 2B	12
FIGURE 2C	13
FIGURE 2D	13
TABLE 1	11
TABLE 2	17
SUPPLEMENTARY MATERIAL	18
TABLE 3	18
TABLE 4	19
TABLE 5	20
APPENDIX A: SOCIAL MEDIA POST	23
APPENDIX B: ETHICS CLEARANCE.....	24
APPENDIX C: TURN-IT-IN REPORT	25
APPENDIX D: PLAGIARISM DECLARATION CERTIFICATE	28
APPENDIX E: AUTHOR GUIDELINES.....	29

LIST OF FIGURES

Figure 1: Flow of Patients into the study.....	13
Figure 2.....	14
Figure 2A: Enterobacterales Antibiotic Susceptibility.....	14
Figure 2B: Non-fermenter Gram-negative Antibiotic Susceptibility.....	14
Figure 2C: Staphylococcal Cloxacillin Susceptibility.....	15
Figure 2D: Antifungal Susceptibilities.....	15

LIST OF TABLES

Table 1: Demographics and clinical features of the patients included in the study.....	14
Table 2: Details of the cardiac lesions found on echocardiogram.	17
Table 3: Definitions of terms used in the Duke Criteria for the Diagnosis of Infective Endocarditis. ...	18
Table 4: Duke Criteria for Diagnosis of Infective Endocarditis.	19
Table 5: Details of Pathogens, antibiotics and outcomes of the patients included in the study.	20

Infective Endocarditis in Neonates at Charlotte Maxeke Johannesburg Academic Hospital: A Retrospective Study (January 2015-March 2021)

INTRODUCTION

Paediatric endocarditis is considered a rare but serious condition⁽¹⁾ that is associated with significant morbidity and mortality⁽²⁾. Due to medical advancements, developments in critical care, improved management of congenital heart defects, and hospital-acquired infections, the epidemiology of endocarditis in paediatrics is continuously evolving⁽²⁾. With these ongoing medical breakthroughs the incidence of endocarditis in paediatric patients has increased⁽³⁾. Diagnosis of infective endocarditis is made using the Modified Duke Criteria, but the diagnosis is challenging in paediatric patients⁽³⁾. The pathogenesis of endocarditis is evolving with gram negative bacilli, *Candida* species and *Staphylococcus* species becoming more significant in recent times^(4,5). Worldwide there is limited neonatal data and often the diagnoses were made in post-mortem examinations⁽³⁾.

Mortality data available for neonates is lacking. Data available is based on paediatric studies. In industrialised countries research showed that the introduction of antibiotics caused a marked reduction in the mortality rate of paediatric patients, but subsequently mortality rates remained consistent⁽⁶⁾. Mortality rates of paediatric endocarditis in high income nations currently range from 10.7% to 15%^(7,8). The latest data from Johannesburg and the Western Cape found paediatric mortality rates of 23.5% and 20% respectively^(1,9). Although there was a significant improvement, the mortality rates are still higher than in high income countries⁽⁷⁾. Independent risk factors for mortality are: congenital heart disease, patients under one-year, vegetations larger than 20mm, *Staphylococcus aureus* infection, heart failure, bi-ventricular vegetations and exposure to broad-spectrum antibiotics⁽⁸⁾.

Treatment of neonatal endocarditis requires a prolonged course of antibiotics; antibiotics need to be administered for four to eight weeks⁽¹⁰⁾. The duration of the antibiotics is determined by the micro-organism that is cultured and if the affected valve is a native or a prosthetic valve⁽¹⁰⁾. Bactericidal antibiotics are preferred as they have been shown to have reduced relapses and fewer treatment failures⁽¹⁰⁾. Prolonged use of Amphotericin B is the preferred treatment for fungal endocarditis⁽¹⁰⁾. Intravenous rather than intramuscular treatment is the preferred route of administration for paediatric patients⁽¹⁰⁾. *Staphylococcus aureus* infections are often associated with central lines and part of the standard of care is the removal of the lines⁽¹⁰⁾.

The present study aimed to describe the clinical profile of neonates with infective endocarditis in a tertiary referral centre in Gauteng from January 2015 to March 2021, including the causative organisms and associated antimicrobial susceptibility patterns, treatment practices and mortality rates.

MATERIALS AND METHODS

A retrospective review of the neonates diagnosed with endocarditis at a tertiary hospital in Johannesburg from 01 January 2015 to 31 March 2021 was performed. At discharge neonatal records are captured on a protected web-based system, Research electronic data capture⁽¹¹⁾. The paediatric cardiology database⁽¹²⁾ is used to store the patient data and echocardiogram reports of the patients seen by the department. These databases were searched using the terms “vegetation”, “infective endocarditis” and “endocarditis”. The inclusion criteria were neonates that met the Duke Modified Criteria for “definite” and “probable” endocarditis (Supplementary material Table 3 and Table 4). Neonates were defined based on the corrected gestational age for premature infants. Those that did not meet the criteria or had inadequate records were excluded (Figure 1). Patient demographics, birth details (gestational age, birthweight, and APGAR scores), details of human immunodeficiency virus (HIV) exposure and HIV infection status was collected. Clinical data regarding murmurs, temperature spikes, respiratory support, surfactant administration, echocardiogram findings, use of central lines, antimicrobial usage, blood culture results, total parenteral nutrition usage, prior surgeries and patient outcomes were collected.

DATA ANALYSIS

Data were collected and captured on a Microsoft Excel worksheet. The data was analysed using STATA 13.0 and R. Descriptive statistics were done. Categorical data were reported as numbers and percentages. The continuous data were reported as averages, medians and interquartile ranges for data that was not normally distributed. The study sample was divided into those that lived and those that died; the categorical data were analysed using the chi-squared test and the Kruskal-Wallis test was used to compare the medians. Cox regression was used for the survival analysis. P-value<0.05 was considered significant.

RESULTS

There were 4,265 paediatric echocardiograms done during the study period and 42 (21.3%) neonates were diagnosed with endocarditis. (Figure 1). The occurrence of endocarditis in this sample of patients who underwent echocardiograms is 0.98%. Using the Modified Duke Criteria to classify the patients, four neonates had definite and 38 had probable endocarditis. On average seven neonates were diagnosed with endocarditis yearly (range 3-8).

The demographic information is summarised in Table 1. Most (37/42, 88%) of the neonates were premature, one patient that was transferred in from another hospital and had no documented gestational age. Low birthweight neonates made up a large proportion of the study sample (39/42, 92.9%). Twelve neonates were HIV exposed, 3/12 (25%) had high-risk exposure (based on national guidelines at the time of the child’s birth), no patients tested HIV PCR positive during the study period. The median age at diagnosis was 29 days(IQR:15-47). At the time of diagnosis 23/42 (54.8%) neonates were under 37 weeks. Temperature spikes were documented in 10/42 (23.8%) of the cases, and 10/42 (23.8%) patients had a murmur. A large cohort of the group required ventilation (29/42, 69%); 18 (62.1%) of the ventilated patients received at least one dose of surfactant.

Table 1 details the culture results of the pathogens causing endocarditis. Identifiable pathogens were found in 33/42 (78.5%) of the cases of endocarditis and 9/42 (21.4%) were classified as culture negative endocarditis. Of the positive cultures, 4/33 (12.1%) had cultures with a mixed growth. The most common pathogens were gram-negative bacilli (N=16). The second largest group was fungal pathogens (N=12) followed by *Staphylococcal* species (N=10). Two of the neonates had community acquired endocarditis with methicillin-sensitive *Staphylococcus aureus*.

The median time between the culture being drawn and the endocarditis being diagnosed on echocardiogram was 11.5 days (IQR:7.5-19.5). The median time from culture to diagnosis for gram negative bacteria, staphylococcus species and fungal species was 12.5 days (IQR:8-20), 9.5 days (IQR:7-19) and 10.5 days (IQR:6.5-13), respectively. The time to diagnosis of endocarditis in the mixed culture group was longer with a mean time of 23 days (Range:21-40).

Results of the echocardiograms are in Table 2. In this cohort 41/42 (97.6%) of patients had a cardiac lesion, only 8/42 (19.0%) were clinically significant. One (2.4%) infant had a cyanotic cardiac lesion, 7/42 (16.7%) patients had a clinically significant acyanotic cardiac lesion and 33/42 (78.6%) patients that had a physiological acyanotic cardiac lesion. Right-sided involvement was most common with 83.3% (N=35) of the total cases whereas only 9.5% (N=4) had left-sided lesions and 7.1% (N=3) had lesions involving both the right and the left side of the heart. The area between the right atrium and superior vena cava was the most affected area on the right side (17/35, 48.6%), one patient that had both right and left-sided involvement also had a lesion involving the right atrium and superior vena cava junction. The pulmonary valve (N=8) and the tricuspid valve (N=6) were the most affected valves. One patient had lesions involving both the pulmonary valve and the tricuspid valve. Majority (34/42, 80.1%) of the masses were <10mm, 7/42 (16.7%) were 10-20mm and 1/42 (2.4%) had a mass >20mm. The mass resolved or reduced in size in 22/42 (52.4%). The statistical analysis indicated that that the resolution or reduction in size of the mass was associated with survival of the patient (p=0.006).

Of the patients with hospital acquired endocarditis 29/40 (72.5%) had at least one central line prior to diagnosis. Lines were present pre-diagnosis in 24/35 (68.6%) of patients with right-sided lesions, 2/3 (66.7%) left-sided lesions and 3/3 (100%) of the patients with mixed lesions had a line pre-diagnosis. Lines were present pre-diagnosis in 14/18 (77.8%) of the patients that had lesions in the junction between the right atrium and superior vena cava. Lines were indwelling for ≥10 days in 22/29 (75.8%) of the patients, 12/29 (41.4%) had lines in for ≥14 days. Total parenteral nutrition was given to 30/42 (71.4%) neonates. There was a total of 736 documented days of total parenteral nutrition documented between all the patients (average of 24.5 days).

All the patients had received antibiotics with majority of the patients being exposed to multiple episodes of antibiotics prior to the diagnosis of endocarditis. The unit protocol changed between 2015 and 2016, ampicillin replaced benzylpenicillin as the first line antibiotic on admission to the unit. Based on the unit's antibiogram meropenem and vancomycin were used as second line antibiotics, which resulted in majority of the patients being exposed to broad spectrum antibiotics prior to the diagnosis. Amphotericin B was used in the unit when fungal

infections were suspected while waiting for culture results. The data were reviewed to determine how many antimicrobial exposures there were prior to the diagnosis of endocarditis and until the outcome. Antibiotic exposure was counted if the medication was prescribed and administered. If the antibiotic was stopped, then restarted this was counted as a new antibiotic episode. Overall, in the 42 patients there were 308 antibiotic episodes pre-diagnosis and 408 antibiotic episodes at outcome.

The details of the culture and antimicrobial susceptibility results are detailed in Figure 2. 6/12 (50%) of the Enterobacterales were extended-spectrum beta-lactamase producers and 5/12 (41.7%) were sensitive to cephalosporins. Of note there were two extensively-drug resistant *Acinetobacter baumannii* isolates requiring treatment with colistin. Five of the patients (58.3%) grew a *Candida* species that was not susceptible to fluconazole. In 2020 5/8 (62.5%) of the cases were associated with positive fungal cultures. Compared to the other study years this was a significant increase in the number of cases of endocarditis associated with fungal cultures. The majority 6/10 (60%) of the Staphylococcus species were methicillin resistant.

A 42-day antibiotic course was completed in 11/42 (26.2%) patients; one of these patients died. There were an additional 17/42 (40%) of patients on directed antibiotics at outcome. Five patients completed at ≥ 14 days of directed antibiotics prior to outcome. Outcomes showed an all-cause case fatality rate of 42.9% (18/42), 14/42 (33.3%) of the patients were discharged and 10/42 (23.8%) were transferred to another unit or hospital to complete antibiotics. Of the patients that were discharged or transferred 68% (17/25) were lost to follow-up, due to this high loss to follow-up a long-term survival analysis could not be done. Two of the patients that died had been redirected to palliative care. One patient had surgery on the mass in another institution after being transferred out. One patient had surgery for a patent ductus arteriosus in a private facility after discharge. Duration of admission was statistically significant between the patients that survived versus the patients that died ($p=0.01$), with the duration of admission being longer for the patients that survived.

DISCUSSION

Although it is rare endocarditis in paediatrics is important to research due to the significant morbidity and mortality⁽³⁾. Neonatal endocarditis is evolving due to improved care of neonates and the increased use of indwelling catheters⁽⁴⁾. Even though the condition is becoming more prevalent there is limited published data available, with no published local data specific to neonatal endocarditis. Neonatal endocarditis was noted to be more prevalent in our unit which prompted this research. This is a unique study that concentrated on neonatal endocarditis, and there is a paucity of data specific to this group of patients.

There was a slight female predominance (1.1:1). Mean age at diagnosis was 29 days, which is significantly younger than other paediatric studies, but our population was unique in this regard. At diagnosis majority of the neonates were <37 weeks gestation and 39 patients were low birthweight, both of which could predispose to sepsis⁽¹³⁾.

The diagnosis of neonatal endocarditis is challenging⁽³⁾. Previously neonatal endocarditis was diagnosed in postmortem examinations⁽³⁾, with improved diagnostic tools, experience and knowledge the condition is being diagnosed more frequently⁽³⁾. The diagnosis requires high clinical suspicion as neonates do not present with typical features⁽¹³⁾. Reports indicate that neonates with endocarditis can present with non-specific features of septicaemia or possibly just a temperature spike^(3,13). Murmurs can be a presenting feature but the location of the lesion may impact this⁽¹³⁾. Our data was comparable to this as there were very few patients with typical features of endocarditis. We looked for clinical features that are included in the Duke Criteria and the only clinical features found in this study were temperature spikes and murmurs. Data of urine dipsticks was not collected so we cannot comment on the correlation between endocarditis in neonates and glomerulonephritis.

Studies in paediatric populations indicate that the presence of a cyanotic heart lesion is a risk factor for the development of endocarditis⁽⁵⁾. We had very few neonates with significant cardiac lesions and only one with a cyanotic lesion, these findings are in keeping with research on neonatal endocarditis and hospital-acquired endocarditis that found that congenital heart disease was not a major factor in the development of endocarditis in neonates specifically^(13,14). Local data was difficult to extrapolate as it was not specific to neonates, Ooka⁽⁹⁾ documented 22 premature babies and 59.1% had a congenital heart lesion. Our data had a smaller proportion with only 19% having cardiac lesions, which is in keeping with global data showing as few as one-third of neonates with endocarditis have a congenital heart lesions⁽¹⁰⁾.

Right-sided lesions were the most common, which was not an uncommon finding in other neonatal research^(13,15). Left-sided lesions are generally reported in older patients and associated with cardiac surgeries^(1,5). The predominant area affected by vegetations was junction between the right atrium and the superior vena cava. The possibility of these lesions being thrombi was considered, but only 4 cases were culture negative and had a vegetation in the junction between the right atrium and the superior vena cava. This did not show any tendency toward these lesions being thrombi rather than infected lesions. None of the patients had tissue cultures of the masses so confirmation of infection of masses was not possible. Research indicates that patients with central lines are also more likely to develop a right-sided mass⁽¹⁰⁾, this is because lines can cause endocardial damage that predisposes the neonate to endocarditis⁽¹³⁾. Our data correlated with this as majority of the patients with a right sided lesion had a line prior to diagnosis. Studies suggest that duration of lines and the use of total parenteral nutrition increase the risk of developing endocarditis, but our study did not find these to be a statistically significant factor.

Globally there has been a shift in the causative organisms for endocarditis⁽¹⁴⁾. There is also a notable difference in organisms for community versus hospital-acquired endocarditis, the latter accounting for 95.2% of our study population⁽¹⁴⁾. Early studies of endocarditis in the Western Cape found *Staphylococcus aureus*, *Staphylococcus epidermidis* and Viridans group streptococci had equal importance in the pathogenesis of endocarditis⁽¹⁶⁾. In the same time period reports from hospitals in Johannesburg found a variety of causative organisms in paediatric endocarditis⁽¹⁶⁾, with *Staphylococcus aureus* being the most common organism in the patients specifically presenting

from Soweto⁽¹⁷⁾. Ooka's⁽⁹⁾ study in 2018 was based in Soweto and found that *Staphylococcus* species were cultured in 37.8% of the patients, again *Staphylococcus aureus* was the most common organism in that area⁽⁹⁾. In 2019 Willoughby et al.⁽¹⁾ found that *Staphylococcus aureus* had become the most significant organism in the paediatric patients with endocarditis in the Western Cape⁽¹⁾. These findings suggest that *Staphylococcus aureus* has been an important organism in endocarditis in South Africa.

Gram-negative bacteria were the most common pathogen in this study, *Klebsiella pneumoniae* accounted for most of this group. Most fungal infections were due to *Candida parapsilosis* and 70% of the staphylococcal species were *Staphylococcus aureus*. This is not in keeping with the latest study done in the unit in 2018/2019 that found gram-positive organisms to be the predominant aetiology of sepsis related to neonates in this unit⁽¹⁸⁾. Coagulase-negative staphylococci and *Staphylococcus aureus* comprised 45.9% and 10.4% of isolates from bloodstream infections, respectively. *Staphylococcus aureus* as the most common gram-positive-organism could be explained by the nature of our patient selection, previous local data found that *Staphylococcus aureus* was an important organism in endocarditis in paediatric patients⁽⁹⁾. *Staphylococcus aureus* is known to commonly cause metastatic infection in patients with prolonged bacteraemia, and an echocardiogram to exclude endocarditis in all patients with *Staphylococcus aureus* bacteraemia is regarded as standard of care⁽¹⁹⁾. Gram-negative bacilli accounted for 31.9% of all bloodstream isolates. The reason for the unique finding of predominantly gram-negative infection in our neonates is perhaps due to a change in the microbiome of the unit since 2019. In addition, a proportion of the Coagulase-negative staphylococci isolates in the recent study may reflect blood culture contamination with normal skin flora. Data on neonates without endocarditis was not collected so it is not possible to report on whether the predominance of gram-negative isolates is specific to neonates with endocarditis or a representation of common isolates causing infection in the unit.

There are neonatal specific studies, but previous studies reviewing fungal infection in paediatric patients in the unit found that *Candida parapsilosis* was the most common cause of candidaemia.⁽²⁰⁾ This is in keeping with our data that found the most common fungal pathogen in this cohort was *Candida parapsilosis*. Neonates, especially premature neonates, are known to have a functionally immature immune system with increased susceptibility of developing fungal infections⁽²⁰⁾. This in combination with the use of central lines and total parenteral nutrition as well as broad-spectrum antibiotic use in the unit will contribute to a high rate of fungal infections.⁽²⁰⁾ There was a spike of fungal infections in our cohort 2020 this coincided with the COVID pandemic, the reason for this spike is not clear and this spike was followed by a reduction in cases on endocarditis associated with fungal cultures the following year. A review of the unit's cultures during that time to see if there was an increase in fungal infections overall would help to understand this surge in frequency of fungal infections.

There is a group of patients who meet the criteria for endocarditis but are classified as culture-negative endocarditis.⁽⁴⁾ Culture-negative endocarditis is more common following antibiotic exposure and with organisms that grow poorly in vitro, but the incidence of culture negative endocarditis is reducing worldwide due to improved

laboratory techniques.⁽⁸⁾ Our culture negative rate was 21.4%, this could be impacted by the frequent exposure to antibiotics in our cohort but this correlates with the incidence in both local and global paediatric data.^(8,9)

The antimicrobial resistance profile of the pathogens in this study population is alarming; there are multiple resistant organisms. In the group of gram-negative bacteria there were cases of extended-spectrum beta-lactamases and multi-drug-resistant organisms requiring colistin as treatment. Similar findings have been demonstrated in previous research done in the same unit. The latest research from 2018/2019, found that 88.9% of the *Klebsiella pneumoniae* cultured were extended-spectrum beta-lactamase producers and 81% of the *Acinetobacter baumannii* isolates were carbapenem-resistant.⁽¹⁸⁾ Methicillin-resistant staphylococcus was the most common gram-positive pathogen. With global data indicating that methicillin-resistant staphylococcus is becoming more prevalent⁽⁸⁾ this finding is expected. Unit specific data also indicated a rise in the methicillin-resistant staphylococcus at a rate of 62.5% in 2018/2019.⁽¹⁸⁾ Majority of the fungal pathogens in our study were fluconazole resistant. The antibiotics that were prescribed for nosocomial infection (carbapenems, vancomycin, amphotericin B) in the unit during the study period were appropriate considering the antibiotic susceptibility pattern that this study demonstrated. Neonatal infection is a significant problem in the unit and previous studies in the unit indicate an increasing incidence of nosocomial infection.⁽¹⁸⁾ These data can suggest that the high rate of nosocomial infection could be a factor related to the high numbers of neonatal endocarditis in the unit.

The mean time between the culture being taken and the endocarditis being diagnosed is slightly longer in staphylococcus species but shorter in gram-negative pathogens and fungal infections. The time delay is expected as neonates do not present with the same clinical findings as older children, they often have non-specific signs of sepsis.⁽²⁰⁾ Unless the child has other indications for an echocardiogram such as cyanosis, a murmur or a screening echocardiogram is requested for a congenital abnormality then it would be reasonable that the echocardiogram is only requested with culture results or when cultures repeatedly grow the same organism. This time frame to diagnosis is similar to other studies.⁽²¹⁾

Prolonged courses of antibiotics are recommended for endocarditis, ranging from at least two weeks up to eight weeks, depending on the pathogen and the site.⁽³⁾ The unit in our study required patients to complete 42-days of antibiotics for endocarditis, only 26.2% of the patients completed the course prior to outcome. This study data set was too small to determine if there was a correlation between outcome and duration of antibiotics received. Duration of admission was significantly longer in the group of patients that survived to outcome. This can be expected as more patients that completed antibiotics were in the group that survived to outcome. Completion of the full six-week course of intravenous antibiotics would result in a prolonged hospital stay.

Outcomes indicate an alarmingly high all case fatality rate of 42.9%. No statistically significant poor prognostic factors (Table 1) were identified in this cohort. Of note, patients with a fungal infection were two-times more likely to die. Research indicates that fungal endocarditis is one of the most severe forms of endocarditis and has a bad

prognosis.⁽²²⁾ The study cohort had many confounding factors that could have contributed to the high mortality rate, majority of them were premature and had a low birthweight, required ventilation and had surgical conditions. Half of the patients that died had gastrointestinal surgery prior to the diagnosis of endocarditis, this could influence the high mortality rate as the surgeries were mostly laparotomies which have been associated with poor outcomes in this neonatal unit.⁽¹¹⁾ There was a very high loss to follow-up.

CONCLUSION

Endocarditis is an important condition in paediatrics due to advancements in medical care. Gram-negative bacteria and fungal pathogens are important organisms in hospital acquired endocarditis. A high index of suspicion is required in septic neonates and a multidisciplinary approach to the management of these neonates is imperative.

LIMITATIONS

The retrospective nature limits this study, and the high loss to follow-up impairs the ability to determine long-term outcomes. As the data was retrospective some cases of endocarditis may have been missed as not all patients get an echocardiogram unless referred to cardiology. The small sample size limited the statistical analysis. In addition, this is a single centre study; a larger review that includes neonatal units from across South Africa should be undertaken to provide more comprehensive and robust data on neonatal endocarditis.

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FINANCIAL SUPPORT

None

CONFLICTS OF INTEREST

None

ETHICAL STANDARDS

The study was approved by the Human Research Ethics Committee of the University of the Witwatersrand (Reference number:M220350).

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TABLES AND FIGURES

FIGURE 1

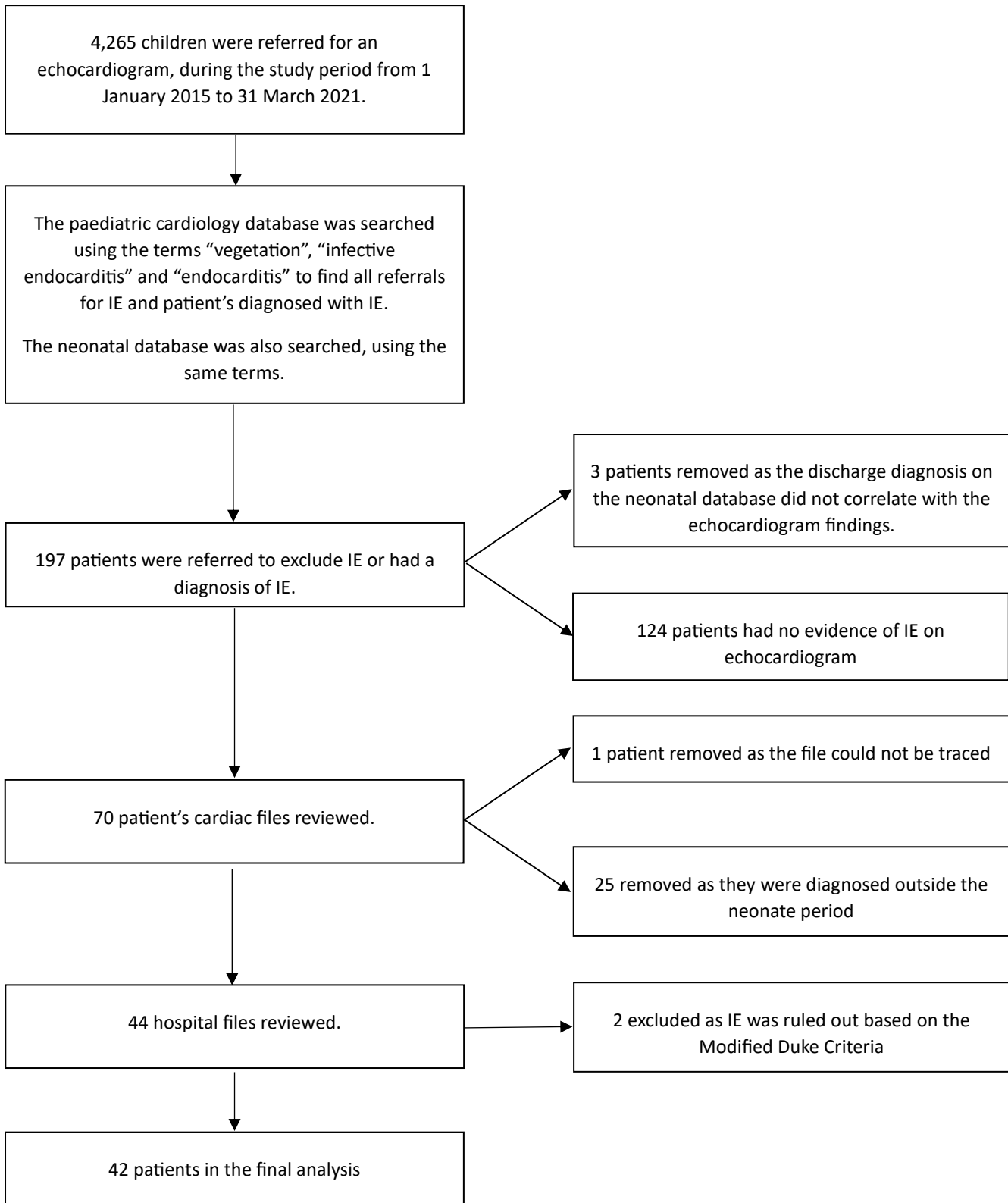


Figure 1: Flow of Patients into the Study

IE – Infective endocarditis

FIGURE 2

FIGURE 2A

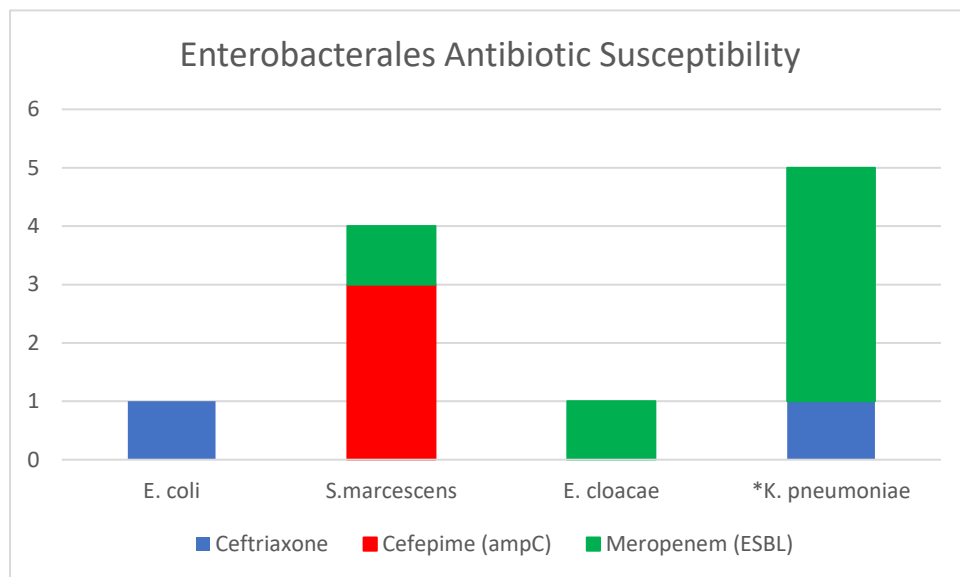


Figure 2A: Enterobacterales Antibiotic Susceptibility

E. coli – *Escherichia coli*, *S. marcescens* – *Serratia marcescens*, *E. cloacae* – *Enterobacter cloacae*, *K. pneumoniae* – *Klebsiella pneumoniae*, ampC - Ambler class C beta-lactamase, ESBL – Extended spectrum beta-lactamase
 *Antibiotic susceptibility of one *K. pneumoniae* is unknown.

FIGURE 2B

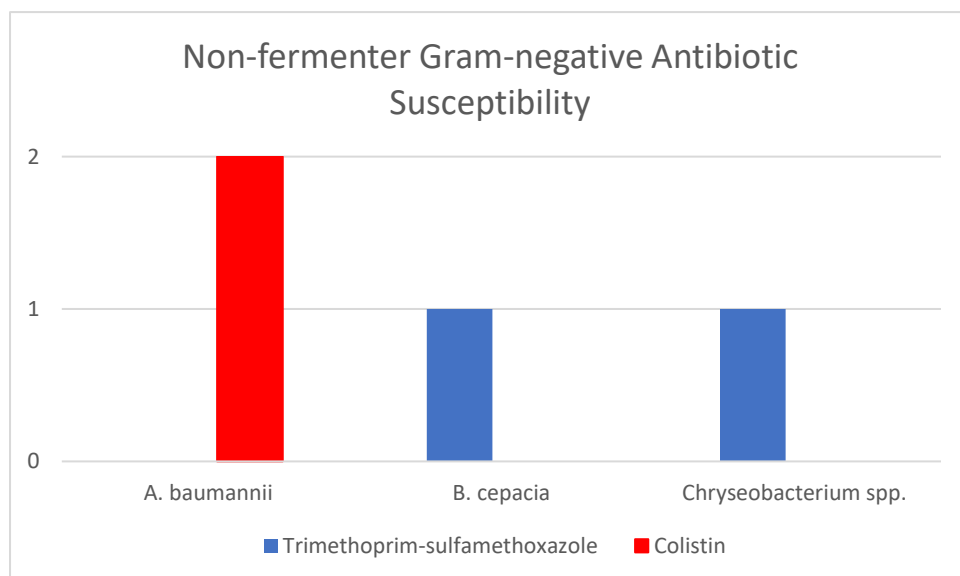


Figure 2B: Non-fermenter Gram-negative Antibiotic Susceptibility

A. baumannii – *Acinetobacter baumannii*, *B. cepacia* – *Burkholderia cepacia*, *Chryseobacterium* spp. – *Chryseobacterium* species

FIGURE 2C

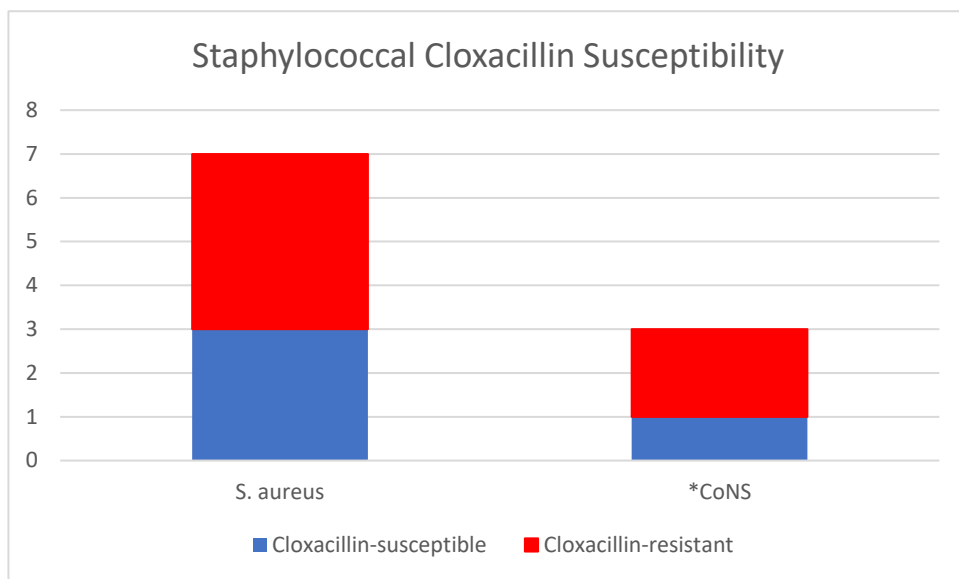


Figure 2C: Staphylococcal Cloxacillin Susceptibility

S. aureus – *Staphylococcus aureus*, CoNS - Coagulase-negative staphylococci

*Antibiotic sensitivity of one CoNS is unknown.

FIGURE 2D

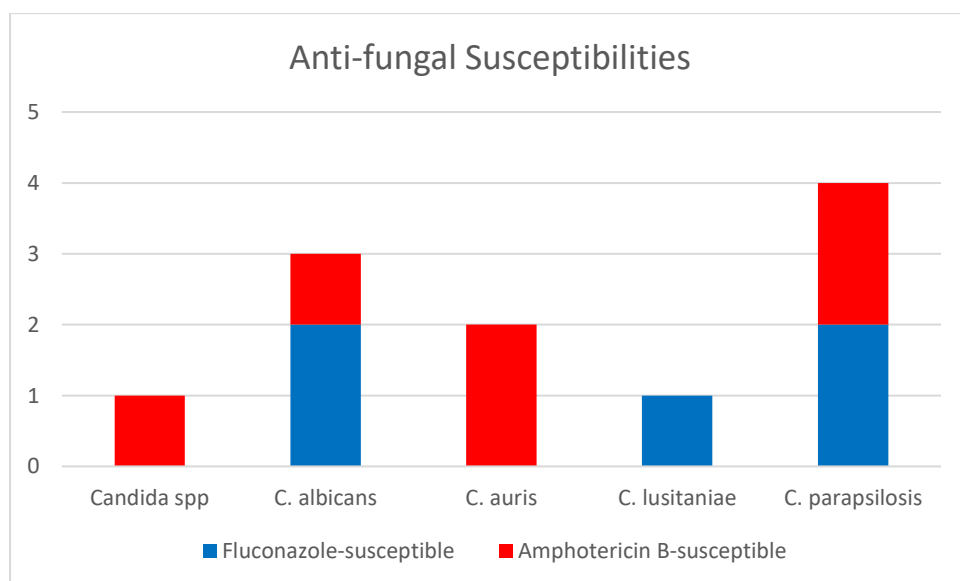


Figure 2D: Anti-fungal Susceptibility

Candida spp. – *Candida* species, *C. albicans* – *Candida albicans*, *C. lusitaniae* – *Candida lusitaniae*, *C. parapsilosis* – *Candida parapsilosis*

* Anti-fungal susceptibility of one *Candida* spp. is unknown.

TABLE 1 - DEMOGRAPHICS AND CLINICAL FEATURES OF THE PATIENTS INCLUDED IN THE STUDY

	Survived (N)	Died (N)	p-value
Sex			
Female (N=22)	15	7	0,13
Male (N=20)	9	11	
Gestational Age at Birth (weeks)			
≤37 (N=37)	20	17	0,11
>37 (N=4)	4	0	
Unknown (N=1)	0	1	
Birthweight (grams)			
≤999 (N=10)	5	5	0,64
1000-1499 (N=16)	9	7	
1500-2499 (N=13)	7	6	
≥ 2500 (N=2)	2	0	
Unknown (N=1)	1	0	
HIV			
Exposed (N=12)	6	6	0,68
Unexposed (N=26)	15	11	
Positive (N=0)	0	0	
Unknown (N=4)	3	1	
Clinically Significant Cardiac Lesion			
Yes (N=8)	5	3	0,73
No (N=34)	19	15	
Location of Lesion			
Right Side (N=35)	20	15	1,00
Left Side (N=4)	2	2	
Right and Left Side (N=3)	2	1	
Mass Size			
<10mm (N=34)	19	15	0.38
10mm - 20mm (N=7)	5	2	
>20mm (N=1)	0	1	
Central lines			
>10 days (N=22)	10	12	0,42
>14 days (N=12)	6	6	0,42

Mass smaller or resolved			
Yes (N=22)	17	5	0.006
No (N=20)	7	13	
Pathogens			
Gram Negative (N=16)			
Enterobacterales			
<i>Klebsiella pneumoniae</i>	5	1	
<i>Serratia marcescens</i>		4	
<i>Escherichia coli</i>	1		
<i>Enterobacter cloacae</i>	1		
Non-Fermenters			
<i>Acinetobacter baumannii</i>	2		
Chryseobacterium species	1		
<i>Burkholderia cepacia</i>		1	
Gram Positive (N=10)			
<i>Staphylococcus aureus</i>	5	2	
Coagulase-negative staphylococci	2	1	
Fungal (N=12)			
<i>Candida parapsilosis</i>	1	3	
<i>Candida auris</i>	1	1	
<i>Candida albicans</i>	2	1	
<i>Candida lusitaniae</i>		1	
<i>Candida</i> species	2		
Culture Negative (N=9)			
	6	3	
Gastrointestinal Surgery			
Yes (N=19)	9	10	0,25
No (N=24)	16	8	
Total Parenteral Nutrition			
Yes (N=30)	16	14	0,3
No (N=9)	5	4	
Days to Diagnosis of Infective Endocarditis			
Median (IQR)	37,5 (19-66)	31,5 (14-64)	-
Days from Positive Culture to Echocardiogram			
Median (IQR)	8 (-7-40)	12 (-4-52)	-

Duration of Admission			
Median (IQR)	73 (45-107)	39,5 (22-90)	0.01

TABLE 2 - DETAILS OF THE CARDIAC LESIONS FOUND ON ECHOCARDIOGRAM

Cardiac Lesions	N
Total (N=42)	
Normal Heart (N=1)	
	1
Physiological Lesions (N=33)	
PDA+PFO	8
PFO	9
PDA	3
PPS	1
PPS+PFO	8
PPS+PDA+PFO	4
Acynotic Lesions (N=7)	
PDA	3
VSD	3
Co-arctation	1
Cyanotic Lesions (N=1)	
Pentralogy of Fallot	1

PDA – Patent ductus arteriosus, PFO – Patent foramen ovale, PPS – peripheral pulmonary stenosis, VSD – Ventricular septal defect

SUPPLEMENTARY MATERIAL

TABLE 3 - DEFINITIONS OF TERMS USED IN THE DUKE CRITERIA FOR THE DIAGNOSIS OF INFECTIVE ENDOCARDITIS.⁽²²⁾

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,*<i>Streptococcus bovis</i>, or HACEK group - or ii. Community-acquired <i>Staphylococcus aureus</i> 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 h apart - or ii. All of 3 or a majority of ≥ 4 blood cultures, irrespective of the timing iii. 1 Positive blood culture for <i>Coxiella burnetii</i> or antiphase-I immunoglobulin G antibody titer $>1:800$
2. Evidence of endocardial involvement
A. Positive echocardiogram (TEE recommended in prosthetic valves, rated at least possible IE by clinical criteria, or complicated IE; TTE as the first test in other patients) 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 pre-existing murmur not sufficient)

Minor criteria

1. Predisposition: predisposing heart condition or IV drug use
2. Fever: temperature $\geq 38.0^{\circ}\text{C}$
3. Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial haemorrhage, conjunctival haemorrhages, and Janeway lesions
4. Immunologic phenomena: glomerulonephritis, Osler nodes, Roth's spots, and rheumatoid factor
5. Microbiological evidence: positive blood culture but does not meet a major criterion as noted above 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

HACEK indicates *Haemophilus* species, *Aggregatibacter* species, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella species*; IE, infective endocarditis, IV, intravenous; TEE, transoesophageal echocardiography and TTE, transthoracic echocardiography

*Includes nutritionally variant strains (*Abiotrophia* species). Excludes single positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis.

TABLE 4 - TABLE 1: DUKE CRITERIA FOR DIAGNOSIS OF INFECTIVE ENDOCARDITIS⁽²³⁾

Definite IE

Pathological criteria

- Microorganisms: demonstrated by culture or histology in a vegetation, a vegetation that has embolized, or an intracardiac abscess
- or
- Pathological lesions: vegetation or intracardiac abscess present, confirmed by histology showing active endocarditis

Clinical criteria as defined in Table 1

- 2 major criteria
- or
- 1 major criterion and 3 minor criteria
- or
- 5 minor criteria

Possible IE

Findings consistent with IE that fall short of “definite” but not “rejected”

Rejected

Firm alternative diagnosis for manifestations of endocarditis

or

Resolution of manifestations of endocarditis with antibiotic therapy for ≤ 4 d

or

No pathological evidence of IE at surgery or autopsy, after antibiotic therapy for ≤ 4 d

IE, indicates infective endocarditis

TABLE 5 - DETAILS OF PATHOGENS, ANTIBIOTICS AND OUTCOMES OF THE PATIENTS INCLUDED IN THE STUDY.

Culture Result		Antibiotic Susceptibility									Completed ≥ 14 days of antibiotics	Completed 42 days of antibiotics	Receiving directed antibiotics at outcome	Overall outcome	Care out
		Amikacin	Carbapenem	Vancomycin	Cephalosporin	Cloxacillin	Sulfamethoxazole- trimethoprim	Fluconazole	Amphotericin B	Colistin					
1	<i>Klebsiella pneumoniae</i>		+									+		D/C	
2	<i>Candida parapsilosis</i>							+						Died	
3	MRSA, <i>Klebsiella pneumoniae</i>		+	+										Died	
4	<i>Serratia marcescens</i>		+											Died	
5	CN											+		D/C	
6	<i>Staphylococcus aureus</i>					+						+		TF	D
7	CN													D/C	
8	<i>Klebsiella pneumoniae</i>		+										+	Died	
9	<i>Klebsiella pneumoniae</i>		+										+	Died	
10	<i>Serratia marcescens</i>				+									D/C	
11	MRSA, <i>Candida parapsilosis</i>			+					+		+			D/C	D
12	<i>Escherichia coli</i>				+						+			D/C	
13	MRSA			+									+	Died	
															20

31	<i>Candida auris</i>							+			+								TF
32	Chryseobacterium species							+										+	TF
33	<i>Klebsiella pneumoniae</i> , <i>Candida albicans</i> , <i>Enterobacter cloacae</i>	+		+							+			+					D/C
34	<i>Candida parapsilosis</i>										+							+	Died
35	CN																	+	D/C
36	<i>Serratia marcescens</i>							+										+	Died
37	<i>Candida albicans</i>										+							+	TF
38	<i>Serratia marcescens</i>							+										+	Died
39	CN																	+	D/C
40	CN																		Died
41	MRSA																+		D/C
42	<i>Klebsiella pneumoniae</i> , <i>Candida</i> species													+				+	D/C

D/C – discharged, TF – Transferred, L – Lost to follow-up, CN – Culture negative, MRSA - Methicillin-resistant *Staphylococcus aureus*, CoNS - Coagulase-negative staphylococci

*If CN and completed 42 days of antibiotics included as completed, three patients CN and on broad spectrum antibiotics at death, one patient CN and on Amphotericin B at death

*Three patients have unknown antibiotics at outcome (all died)

APPENDIX A: SOCIAL MEDIA POST

Neonatal endocarditis, research from South Africa. A high number of cases with the main causative pathogen being gram-negative bacilli. Concerningly high all-cause case fatality rate.

@CardiologyYoung

#Pedscards #Neonates #Infectiveendocarditis #Neonatalinfectiveendocarditis #Nosocomialsepsis

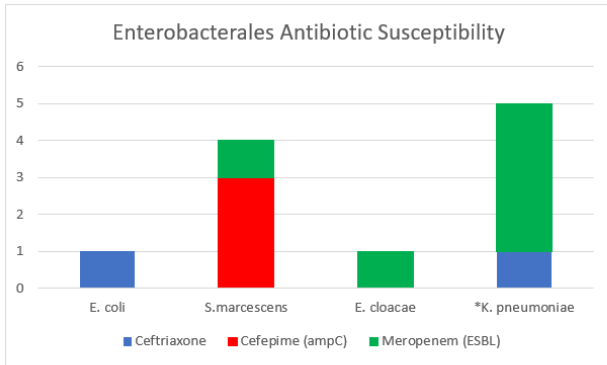


Figure 2A: Enterobacterales Antibiotic Susceptibility

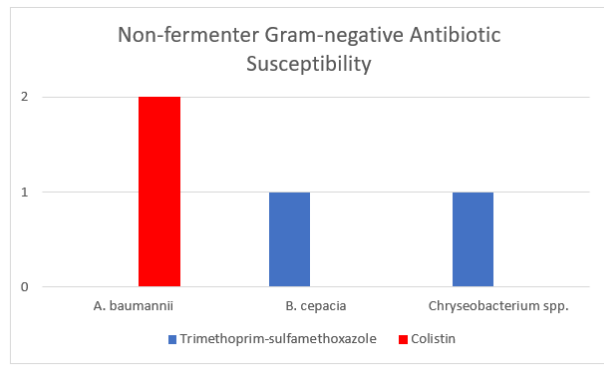


Figure 2B: Non-fermenter Gram-negative Antibiotic Susceptibility

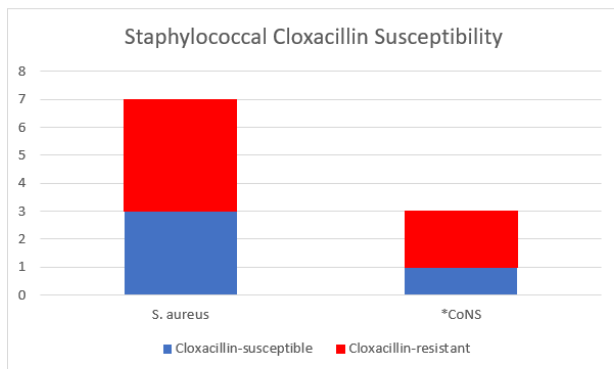


Figure 2C: Staphylococcal Cloxacillin Susceptibility

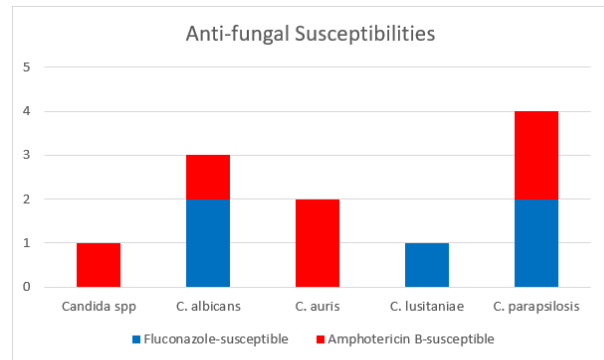


Figure 2D: Anti-fungal Susceptibility

APPENDIX B: ETHICS CLEARANCE



R49 Dr LG Hogarth

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL) CLEARANCE CERTIFICATE NO. M220350

NAME:
(Principal Investigator)

Dr LG Hogarth

DEPARTMENT:

School of Clinical Medicine
Department of Paediatrics and Child Health
Medical School
University

PROJECT TITLE:

*Infective Endocarditis in neonates at Charlotte Maxeke
Johannesburg Academic Hospital: a retrospective study
(January 2015 - March 2021)*

DATE CONSIDERED:

2022/03/25

DECISION:

Approved unconditionally

CONDITIONS:

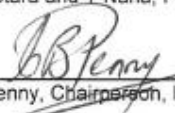
NOTE:

If contact information regarding student study participants is required,
please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>

SUPERVISOR:

Drs F Motara and T Nana; Professor D Ballot

APPROVED BY:


Dr CB Penny, Chairperson, HREC (Medical)

DATE OF APPROVAL:

2022/06/10

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report.** When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **March** and therefore reports and re-certification will be due in the month of **March** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).



Signature of Principal Investigator

10 June 2022

Date

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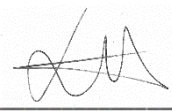
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Date: 2 October 2024

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