Candida bloodstream infection among children hospitalized in three public-sector hospitals in the Metro West region of Cape Town, South Africa

By

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ABSTRACT

Introduction

Candida bloodstream infection (BSI) causes appreciable mortality in children. There are few studies describing the epidemiology of *Candida* BSI in children living in the Western Cape province of South Africa.

Methods

A retrospective descriptive study was conducted at three public sector hospitals in Cape Town from January 2015 to December 2019. Demographic, clinical, antifungal management and patient outcome data were obtained by medical record review.

Candida species and antifungal susceptibility results were extracted from the National Health Laboratory Service microbiology database

Results

Of the 97 *Candida* BSI episodes identified during the study period, 48/97 (49.5%) were *C. albicans*, 49/97 (50.5%) non-*C. albicans* species. The overall incidence risk was 0.84 *Candida* BSI episodes per 1000 admissions at Red Cross War Memorial Children's Hospital. Of the 77 *Candida* BSI episodes with available clinical information, median age (interquartile range) at the time of BSI was 6.8 (1.3-24.7) months, 46.8% were associated with moderate or severe underweight-for-age and vasopressor therapy was administered to 22 (28.6%) participants. Fluconazole resistance was documented among 25% and 0% of non-*C. albicans* and *C. albicans* isolates respectively. All *Candida* isolates tested were susceptible to amphotericin B and the echinocandins. The mortality rate within 30 days of BSI diagnosis was 17.3% (13/75). On multivariable analysis, concomitant bacterial infection during *Candida* BSI was associated with 30-day mortality, adjusted OR 5.7, 95% confidence interval: 1.4-24.0.

Conclusion

The study adds to the limited number of studies describing paediatric *Candida* BSI in sub-Saharan Africa. Concomitant bacterial infection was associated with 30-day mortality.

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I am extremely grateful to my supervisors, Prof. Brian Eley and Dr. James Nuttall for their invaluable advice, continuous support, and patience during this study. Their immense knowledge and great experience have encouraged me in my academic research and daily life. I would like to thank Dr. Hafsah Tootla & Dr. Amanda Khumalo and the entire team at the National Health Laboratory Service Groote Schuur laboratory. I also acknowledge Dr Wisdom Basera for assisting with statistical analysis.

I would like to express my sincere gratitude to the African Paediatric Fellowship Program for providing financial and technical support, without which this research would not have been possible.

To conclude, I cannot forget to thank the patients of Red Cross War Memorial Children's Hospital, Groote Schuur Hospital & Mowbray Maternity Hospital, their parents, and caregivers whose medical history and records were used in this study.

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ABBREVIATIONS

aOR - adjusted odds ratio

BSI- bloodstream infection

CDW - Central Data Warehouse

CVP - central venous pressure

CI - confidence interval

CLSI - Clinical and Laboratory Standards Institute

GSH - Groote Schuur Hospital

GA - gestational age

HAI - healthcare- associated infection

HIV - Human Immunodeficiency Virus

HREC - Human Research Ethics Committee

ICU - intensive care unit

IQR - interquartile range

IPOA - infection present on admission

LBW - low birth weight

MMH - Mowbray Maternity Hospital

NHLS - National Health Laboratory Service

OR - odds ratio

RCWMCH - Red Cross War Memorial Children's Hospital

SA - South Africa

SD - standard deviation

SAJID - Southern African Journal of Infectious Diseases

Sp. - species (singular tense)

Spp. - species (pleural tense)

TPN - total parenteral nutrition

VLBW - very low birth weight

WAZ - weight-for-age Z score

WHO - World Health Organization

CHAPTER 1: INTRODUCTION

1.1 Context

Candida species (spp.) are normal microflora of the oral cavity, vagina and gastrointestinal tract but may also cause different clinical forms of infection, ranging from superficial mucocutaneous candidiasis to fatal bloodstream infection (BSI).[1,2] *Candida* spp. remain the leading cause of invasive fungal disease among paediatric patients and in some settings in the United States and Europe are the fourth most common pathogens detected in healthcare-associated BSI.[3,4] The reported candidaemia incidence in paediatric patients ranges between 0.21 and 10.5 cases per 1000 admissions.[5,6] An increasing frequency has been observed in some settings and is explained by the growth of populations at high risk of candidaemia.[7,8]

Invasive candidiasis has also been reported in children in South Africa with BSI.[9,10,11,12,13] In multicentre, laboratory-based surveillance among hospitalized children in South Africa from 2012 to 2017, the overall incidence risk of paediatric candidaemia at tertiary-level, public-sector hospitals was 5.3 cases per 1000 admissions and ranged from 0.39 to 119.1 per 1000 admissions.[14] A retrospective study on BSI at Red Cross War Memorial Children's Hospital (RCWMCH), Cape Town, in 2011 and 2012 identified candidaemia in 6.1% of all BSIs.[12] An Egyptian study documented a higher prevalence of 17.3% among all BSIs.[15] In another study from China, the incidence of candidaemia was 106.9 per 1000 very low birth weight (VLBW) neonates.[16]

Risk factors for candidaemia in paediatric patients include antibiotic exposure, corticosteroid therapy, the presence of a central venous catheter (CVC), neutropaenia, prior fungal colonisation, and prolonged stay in an intensive care unit (ICU).[17,18] In non-neonatal paediatric candidiasis, underlying chronic conditions, especially, haematological/oncological malignancy, cardiopulmonary disorder, neurological disorder & gastrointestinal disorder accounted for most of the susceptible hosts.[19,20] Additional risk factors are present during the neonatal period including prematurity, low birth weight (LBW) and related co-morbidities including total parenteral nutrition (TPN) and underlying chronic lung disease.[17,21,19]

Globally, the most prevalent cause of candidaemia has shifted from *Candida albicans* (*C. albicans*) to non-*C. albicans spp.* such as *C. tropicalis*, *C. parapsilosis*, and *C. glabrata*. The frequency of non-*C. albicans spp.* varies according to geographical location and age.[22,23,24,25] In Latin America, it has been reported that the frequency of *C. parapsilosis* increased from 14% to 23.4% within a decade.[24] Recent paediatric studies from Egypt and China also demonstrated that non-*C. albicans spp.* collectively account for the greatest number of cases, although *C. albicans* was the most common species.[15,16] A multicentre paediatric *Candida* BSI study conducted in South Africa showed *C. parapsilosis* to be the most prevalent cause accounting for 46% of *Candida* BSI followed by *C. albicans* in 33% of cases, while *C. glabrata*, *C. auris* and *C.*

tropicalis were responsible for fewer *Candida* BSI events.[14] Another study reported that children ≤2 years of age were at increased risk for developing candidaemia due to *C. parapsilosis*.[26] Similarly, a study at the neonatal unit of Charlotte Maxeke Johannesburg Academic Hospital, South Africa showed that *C. parapsilosis* was the most common *Candida* species isolated followed by *C. albicans.*[27]

The shift to non-*C. albicans* candidaemia is associated with reduced susceptibility to fluconazole, a first-line antifungal agent in many settings. In one study, fluconazole resistance was lower among *C. albicans* isolates than non-*C. albicans* isolates, 4.3% versus 16.6%.[28] Another study showed that the majority of *C. glabrata* isolates were resistant to fluconazole as were a significant number of *C. tropicalis* and all the *C. krusei* isolates.[29] An Egyptian study found that fluconazole-resistant *C. albicans* and non-*C. albicans spp.* accounted for 38.9% and 44% of the total number of *Candida spp.* tested, respectively. In that study, susceptibility of all *Candida* isolates tested against caspofungin, amphotericin B and itraconazole was 99%, 97%, 73% respectively[15] A study from Johannesburg also reported more fluconazole resistance among *C. parapsilosis* isolates compared to *C. albicans* isolates.[27] Furthermore, in a South African multicentre study, 35% of all *Candida* isolates were resistant to fluconazole and fluconazole resistance was higher among *C. parapsilosis* isolates than other *Candida spp.* Only three of 3061 isolates tested were resistant to echinocandins and all *Candida* isolates were susceptible to amphotericin B.[14]

High mortality has been associated with *Candida* BSI. A South Africa study of neonates with fungal BSI recorded a mortality rate of 45.8%. In that study death was significantly associated with LBW and necrotizing enterocolitis.[27] An Egyptian study reported mortality of 64% among children diagnosed with *Candida* BSI, most deaths were associated with non-*C. albicans* BSI.[15] As with previous studies, a recent South African study showed that the overall crude 30-day inpatient mortality for patients with *Candida* BSI is high (38%) and even higher among neonates (43%) and adolescents (43%).[14] In another study, treatment in an ICU, the presence of an indwelling CVC, failure to remove an indwelling CVC, and mechanical ventilation during invasive *Candida spp.* infection were associated with mortality.[28]

A limited number of studies have described the epidemiology of candidaemia in children in sub-Saharan Africa. The results of a large multicentre laboratory-based surveillance study of culture-confirmed candidaemia in children in South Africa were recently published. Sixty-four percent of the isolates included in that study were from Gauteng Province. Furthermore, risk factor analysis for 30-day mortality among neonates with candidaemia, showed that *C. parapsilosis* BSI was a significant risk factor.[14] The present study was undertaken to describe the recent burden of *Candida* BSI, the clinical presentation, species distribution, antifungal susceptibility, and outcome of *Candida* BSI among children less than 15 years of age admitted to three public sector hospitals in Cape Town, and thus provide specific information about this important

infection in the Western Cape province of South Africa including recommendations on empirical antifungal therapy for *Candida* BSI and infection prevention practices.

1.2 Ethical Considerations

The study was submitted for approval to the Departmental Research Committee, Department of Paediatrics and Child Health, University of Cape Town; Human Research Ethics Committee (HREC), Faculty of Health Sciences, University of Cape Town, HREC approval number 159/2020 (Appendix 1); and the Research Committee at Red Cross War Memorial Children's Hospital (Appendix 2). The study was done in accordance with the Declaration of Helsinki.

The data was collected retrospectively; thus, the HREC waived the need for informed consent. The data sheets included hospital folder numbers of study subjects which enabled the researchers to check information from the hospital folders after data collection had been completed. Each hospital folder number was linked to a study number. Study numbers but not hospital folder numbers were entered into an electronic database for anonymous analysis and reporting, refer data collection sheet, Appendix 3.

Risk to participants

There were no risks to the patients included in the study. Data was collected retrospectively and analysed anonymously.

Benefits to the patient

There were no direct benefits to the patients included in this study

1.3 Journal for Publication- Southern African Journal of Infectious Diseases

Southern African Journal of Infectious Diseases (SAJID) is a peer-reviewed, open-access journal that publishes original clinical and laboratory-based research, brief reports, reviews, case reports, book reviews, and guidelines. In 2021, the impact factor was 0.3. The interest areas of the SAJID *are* epidemiology, laboratory diagnosis, treatment, and control of infectious diseases, with emphasis placed on the southern African region, particularly those of importance to the Federation of Infectious Diseases Societies of Southern Africa (FIDSSA) and this motivated my interest in choosing the journal. Original articles do not exceed 3500 words in length. The word count is from the introduction through to the end of the conclusion, excluding the structured abstract and references; refer to Appendix 4 for the complete author guidelines.

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CHAPTER TWO: PUBLICATION-READY MANUSCRIPT

TITLE PAGE

Candida bloodstream infection among children hospitalized in three public-sector hospitals in the Metro West region of Cape Town, South Africa

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Abstract

Introduction

Candida bloodstream infection (BSI) causes appreciable mortality in children. There are few studies describing the epidemiology of *Candida* BSI in children living in the Western Cape province of South Africa.

Methods

A retrospective descriptive study was conducted at three public sector hospitals in Cape Town from January 2015 to December 2019. Demographic, clinical, antifungal management and patient outcome data were obtained by medical record review. *Candida* species and antifungal susceptibility results were extracted from the National Health Laboratory Service microbiology database

Results

Of the 97 *Candida* BSI episodes identified during the study period, 48/97 (49.5%) were *C. albicans*, 49/97 (50.5%) non-*C. albicans* species. The overall incidence risk was 0.84 *Candida* BSI episodes per 1000 admissions at Red Cross War Memorial Children's Hospital. Of the 77 *Candida* BSI episodes with available clinical information, median age (interquartile range) at the time of BSI was 6.8 (1.3-24.7) months, 46.8% were associated with moderate or severe underweight-for-age and vasopressor therapy was administered to 22 (28.6%) participants. Fluconazole resistance was documented among 25% and 0% of non-*C. albicans* and *C. albicans* isolates respectively. All *Candida* isolates tested were susceptible to amphotericin B and the echinocandins. The mortality rate within 30 days of BSI diagnosis was 17.3% (13/75). On multivariable analysis, concomitant bacterial infection during *Candida* BSI was associated with 30-day mortality, adjusted OR 5.7, 95% confidence interval: 1.4-24.0.

Conclusion

The study adds to the limited number of studies describing paediatric *Candida* BSI in sub-Saharan Africa. Concomitant bacterial infection was associated with 30-day mortality.

Candida species (spp.) are a leading cause of fatal bloodstream infection (BSI) in paediatric and neonatal patients globally.[1,2] The reported candidaemia incidence in paediatric patients ranges between 0.21 and 10.5 cases per 1000 admissions.[3,4] In multicentre, laboratory-based surveillance among hospitalized children in South Africa from 2012 to 2017, the overall incidence risk of paediatric candidemia at tertiary-level, public-sector hospitals was 5.3 cases per 1000 admissions and ranged from 0.39 to 119.1 per 1000 admissions.[5] A retrospective study on BSI at Red Cross War Memorial Children's Hospital (RCWMCH), Cape Town, in 2011 and 2012, identified candidaemia in 6.1% of all BSIs.[6] An Egyptian study documented a higher prevalence of 17.3% among all BSIs.[7] In another study from China, the incidence of neonatal candidemia was 106.9 per 1000 very low birth weight (VLBW) infant admissions.[8]

Risk factors for candidaemia in paediatric patients include antibiotic exposure, corticosteroid therapy, the presence of a central venous catheter (CVC), neutropaenia, prior fungal colonisation, and prolonged stay in an intensive care unit (ICU).[9,10] Additional risk factors are present during the neonatal period including prematurity, low birth weight (LBW), and related co-morbidities, including total parenteral nutrition (TPN) and underlying chronic lung disease.[9,11,12]

Globally the most prevalent cause of candidaemia has shifted from *Candida albicans (C. albicans)* to non-*C. albicans spp.*. The frequency of non-*C. albicans spp.* infections varies according to geographical location and age.[13,14,15,16] Recent paediatric studies from Egypt and China also demonstrated that non-*C. albicans spp.* collectively account for the greatest number of cases, although *C. albicans* was the most common single species.[7,8] A multicentre paediatric *Candida* BSI study conducted in South Africa, showed that between 2016 and 2017 *C. parapsilosis* was the most prevalent cause accounting for 46% of *Candida* BSI and *C. albicans* was the next most frequent isolate occurring in 33% of cases.[5] Similarly, a study at the neonatal unit of Charlotte Maxeke Johannesburg Academic Hospital, South Africa showed that *C. parapsilosis* was the most common *Candida sp.* isolated followed by *C. albicans.*[17]

The shift to non-*C. albicans* candidaemia is associated with reduced susceptibility to fluconazole, a first-line antifungal agent in many settings. In one study, fluconazole resistance was lower among *C. albicans* isolates than non-*C. albicans* isolates, 4.3% versus 16.6%.[18] An Egyptian study found that while fluconazole resistance to *C. albicans* and non-*C. albicans spp.* accounted for 38.9% and 44% of the total number of *Candida spp.* tested, respectively, caspofungin, amphotericin B and itraconazole had activities of 99%, 97%, 73% respectively against all *Candida* isolates tested.[7] A study from Johannesburg reported more fluconazole resistance among *C. parapsilosis* isolates compared to *C. albicans* isolates.[17] Similarly, in a South African multicentre study, 35% of all *Candida* isolates were resistant to fluconazole. Fluconazole resistance was higher among *C. parapsilosis* isolates than other *Candida spp.* By contrast, only three of 3061 isolates tested were resistant to echinocandins and all *Candida* isolates were susceptible to amphotericin B.[5]

High mortality has been associated with *Candida* BSI. A South African study of neonates with fungal BSI recorded a mortality rate of 45.8%. In that study death was significantly associated with LBW and necrotizing enterocolitis.[17] An Egyptian study reported mortality of 64% among children diagnosed with *Candida* BSI, most deaths were associated with non-*C. albicans* BSI.[7] As with previous studies, a recent South African study showed that the overall crude 30-day inpatient mortality for patients with *Candida* BSI is high (38%) and even higher among neonates (43%) and adolescents (43%).[5] In another study, treatment in an ICU, the presence of an indwelling CVC, failure to remove an indwelling CVC, and mechanical ventilation during invasive *Candida* infection were associated with mortality.[18]

A limited number of studies have described the epidemiology of candidaemia in children in sub-Saharan Africa. The results of a large multicentre laboratory-based surveillance of culture-confirmed candidaemia in children in South Africa were recently published. Sixty-four percent of the isolates included in that study were from Gauteng Province. Furthermore, risk factor analysis for 30-day mortality among neonates with candidaemia, showed that *C. parapsilosis* BSI was a significant risk factor.[5] The present study was undertaken to describe the recent burden of *Candida* BSI, the clinical presentation, species distribution, antifungal susceptibility, and outcome of *Candida* BSI among children less than 15 years of age admitted to three public sector hospitals in Cape Town, providing contemporary information about this important infection in the Western Cape including recommendations on empirical antifungal therapy for *Candida* BSI and infection prevention practices.

Methods

Study design, setting and inclusion criteria

This retrospective descriptive study was conducted at RCWMCH, Groote Schuur Hospital (GSH), and Mowbray Maternity Hospital (MMH). The RCWMCH serves as a tertiary referral centre for children in the Western Cape Province and surrounding provinces. GSH is a major tertiary referral centre for adult patients but also provides neonatal and paediatric inpatient services, including a 75-bed neonatal ICU. MMH is a dedicated maternal and neonatal regional hospital with a 73-bed nursery. The study was done among children less than 15 years of age, including neonates, infants and older children with culture-confirmed *Candida* BSI, diagnosed between 1 January 2015 and 31 December 2019. The study population at RCWMCH included children less than 15 years of age from all service areas, including the general wards, paediatric ICU, medical sub-specialty and surgical wards. The paediatric ICU manages a wide spectrum of critically ill children including children with general surgical diseases, burns, cardiac, oncology, pulmonology, neurological, neurosurgical and renal diseases, and children after surgery or solid organ transplantation. Patients from GSH were mainly neonates and a few older children.
All *Candida* BSI episodes diagnosed at RCWMCH were used in the incidence risk calculations.

We restricted our incidence risk calculation to RCWMCH as we did not have admission data for GSH and MMH and most of the cases were from RCWMCH.

Patients with sufficient information and available clinical records were used to complete the clinical and microbiology descriptions. Patients with incomplete or unavailable clinical records were excluded from this component of the analysis.

Data collection

The academic and research unit managing the Central Data Warehouse (CDW) in the information technology department of the National Health Laboratory Service (NHLS) in Johannesburg, South Africa retrieved the list of children admitted to RCWMCH, GSH and MMH with laboratory-confirmed *Candida* BSI for the period, January 2015 to December 2019. This list was used to obtain the microbiology results of every *Candida* BSI during the study period.

Paper-based medical records of patients with *Candida* BSI episodes were reviewed at RCWMCH, GSH and MMH, and relevant data extracted and manually transferred to standardised data collection forms. All the data are collected only by the study investigator, MNG. The microbiological results obtained from the NHLS were added to the data collection forms.

Microbiological procedures

Blood culture specimens from the three hospitals were sent to the GSH NHLS microbiology laboratory where they were processed. The laboratory uses the BacT/ALERT automated blood culture system (BioMérieux, Marcy-l'Etoile, France). Signal-positive blood culture broth was Gram-stained. Broth with yeasts observed using light microscopy, was inoculated onto 2% horse blood agar and Sabouraud Dextrose agar and incubated aerobically at 37°C. Yeasts cultured between 24 and 48 hours were identified with susceptibility testing performed using the Vitek 2 automated system (BioMérieux, Marcy-l'Etoile, France) YST identification and AST-YS08 cards respectively. Susceptibility test results were interpreted according to annually published Clinical and Laboratory Standards Institute guidelines.[19]

Study definitions

Candida BSI was defined as isolation of any *Candida spp.* from blood culture either collected peripherally or via a central venous catheter (CVC).

Candida BSI was classified as (1) infection present on admission (IPOA) if the *Candida sp.* was cultured from a blood culture obtained on the day of admission to RCWMCH, GSH and MMH (calendar day 1), 2 days before admission or the calendar day after admission (calendar day 2),

or (2) healthcare-associated infection if the *Candida sp.* was isolated from a blood culture obtained on or after the 3rd calendar day of admission to RCWMCH, GSH and MMH.[20]

Severe neutropaenia was defined as a polymorphonuclear neutrophil count ≤500 cells/mm^3.

Pre-term birth: a gestational age (GA) <37 completed weeks at birth

Concomitant bacteraemia: Isolation of a bacterial isolate from the blood culture specimen in which the *Candida sp.* was isolated

HIV status was defined as follows: (1) HIV-infected: a child < 18 months old with a positive HIV DNA PCR result confirmed by either a quantitative HIV RNA PCR or repeat HIV DNA PCR test, or a child ≥ 18 months old with 2 positive serological test results (HIV ELISA or HIV Rapid test) or a positive HIV DNA PCR result confirmed by either a quantitative HIV RNA PCR or repeat HIV DNA PCR test, (2) HIV-uninfected: a child with a negative HIV serological or HIV DNA PCR result and (3) unknown HIV status: a child with unknown maternal HIV status and who was not tested for HIV infection.[21]

Moderate and severe underweight for age (UWFA) were defined as weight-for-age z score (WAZ) between −2 and −3 standard deviations (SD) below the mean World Health Organisation (WHO) growth reference standards, and a WAZ < −3 SD, respectively.[22] In determining weight-for-age z score, age correction was done for premature infants**.**

Disseminated intravascular Coagulopathy*:* A prothrombin time of ≥2 seconds, an activated partial thromboplastin time of ≥60 seconds or a fibrinogen level of <2 μmol/L.[23]

Renal dysfunction*: a* serum creatinine concentration above the normal age-related range.[24,25]

Liver dysfunction*:* a ≥2-fold increase of serum aspartate aminotransferase and/or serum alanine aminotransferase concentration and/or a total bilirubin in a child more than 28 days old of >70 μmol/L.[25,26]

Statistical analysis

The data were analysed with Statistical Package for the Social Sciences (SPSS; SPSS Inc., Chicago, IL, USA) version 27 for Microsoft Windows. The incidence risk of *Candida* BSI was calculated per 1000 hospital admissions. Continuous variables were expressed as medians (interquartile range, IQR) since the continuous data were skewed. Proportions and percentages were used to describe categorical variables. The Wilcoxon rank-sum test for independent variables was used to compare the continuous data stratified by type of *Candida* BSI.

The association between categorical variables was done using Pearson's Chi-square test ($\chi 2$) or Fisher's Exact test if one or more of the expected values is less than five or the large sample size assumption is not met. P-values ≤ 0.05 were considered statistically significant.

Univariable and multivariable logistic regression were used to identify factors independently associated with 30 days *Candida* BSI-associated mortality. The multivariable logistic regression model was built by stepwise backward selection, incorporating variables which on univariable analysis had a p value<0.2. The multivariable logistic regression model results were expressed as adjusted odds ratios (aORs) and 95% confidence intervals (95% CIs). The 30-day mortality from *Candida* BSI versus non-*C. albicans* BSI was analysed using Kaplan Meir curve and compared between the two using the log rank test.

Ethical considerations

The study was approved by the Human Research Ethics Committee (HREC), Faculty of Health Sciences, University of Cape Town, reference number: HREC REF 159/2020 (Appendix 1) and the RCWMCH research committee (Appendix 2). Furthermore, the study was completed in accordance with the Declaration of Helsinki. Since the data was collected retrospectively, the HREC waived the need for informed consent. Patient details were anonymised before data analysis.

Results

Study participants

During the study period, there were 97 *Candida* BSI episodes, 85 at RCWMCH, 11 at GSH and one at MMH. The 85 *Candida* BSI episodes at RCWMCH were used to estimate the risk of *Candida* BSI at that hospital. There was insufficient clinical information on twenty episodes of *Candida* BSI thus 77 (79.4%) *Candida* BSI episodes were used in the subsequent analyses (Figure 1).

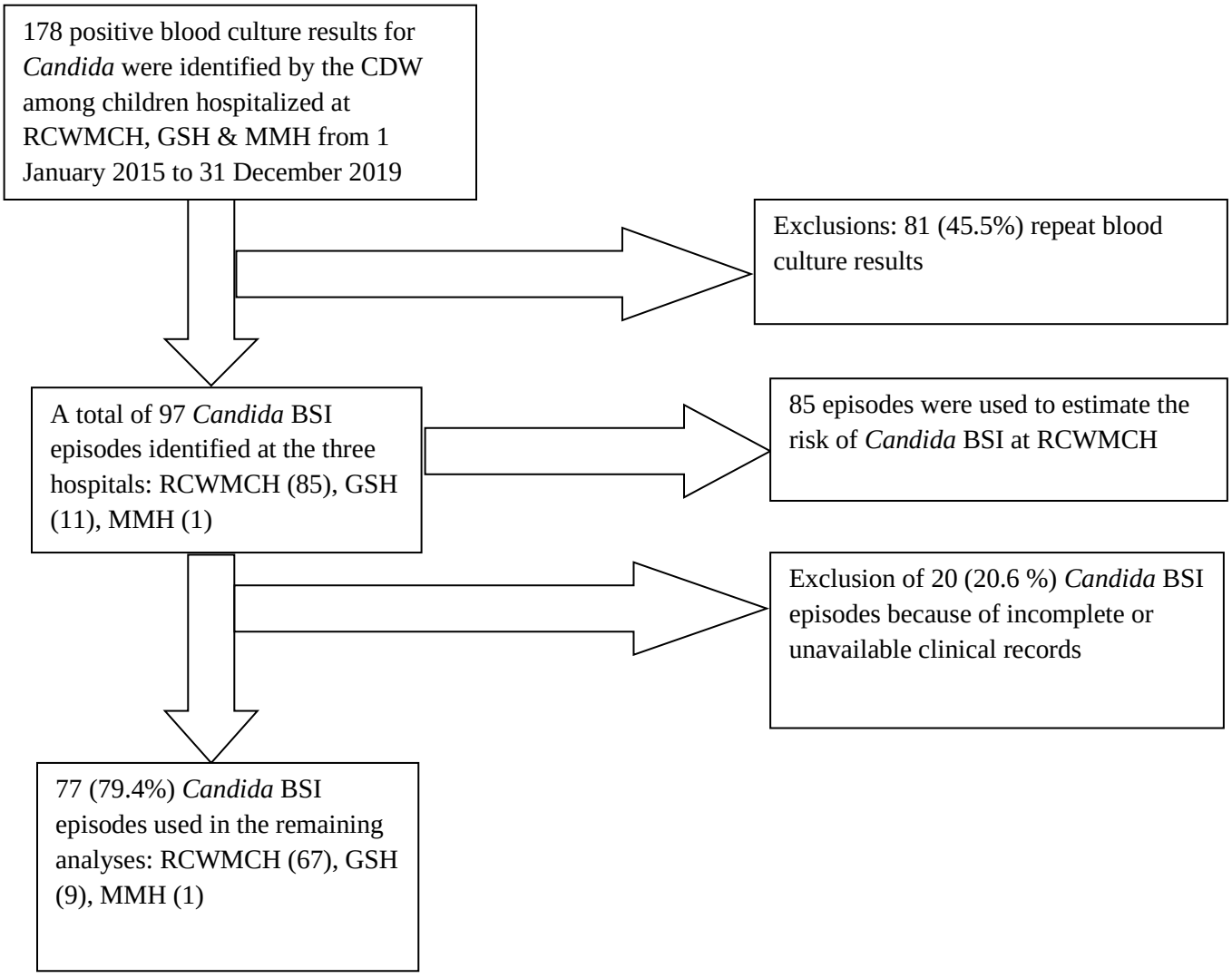

Figure 1: Selection of *Candida* bloodstream infection episodes for data analysis. CDW, Central Data Warehouse; *Candida* BSI, *Candida* bloodstream infection; RCWMCH, Red Cross War Memorial Children's Hospital; GSH, Groote Schuur Hospital; MMH, Mowbray Maternity Hospital

Risk of *Candida* bloodstream infection at RCWMCH

The overall incidence risk throughout the study period was 0.84 episodes / 1000 hospital admissions for all *Candida* BSI episodes, 0.47 episodes / 1000 hospital admissions for all non-*C. albicans* BSI episodes and 0.38 episodes / 1000 hospital admissions for all *C. albicans* BSI episodes. With the exception of 2018, the overall annual incidence risk increased progressively throughout the study period (Figure 2). This increase as well as the decline in 2018 were mainly attributed to changes in the incidence risk of non-*C. albicans* over time (Figure 2).

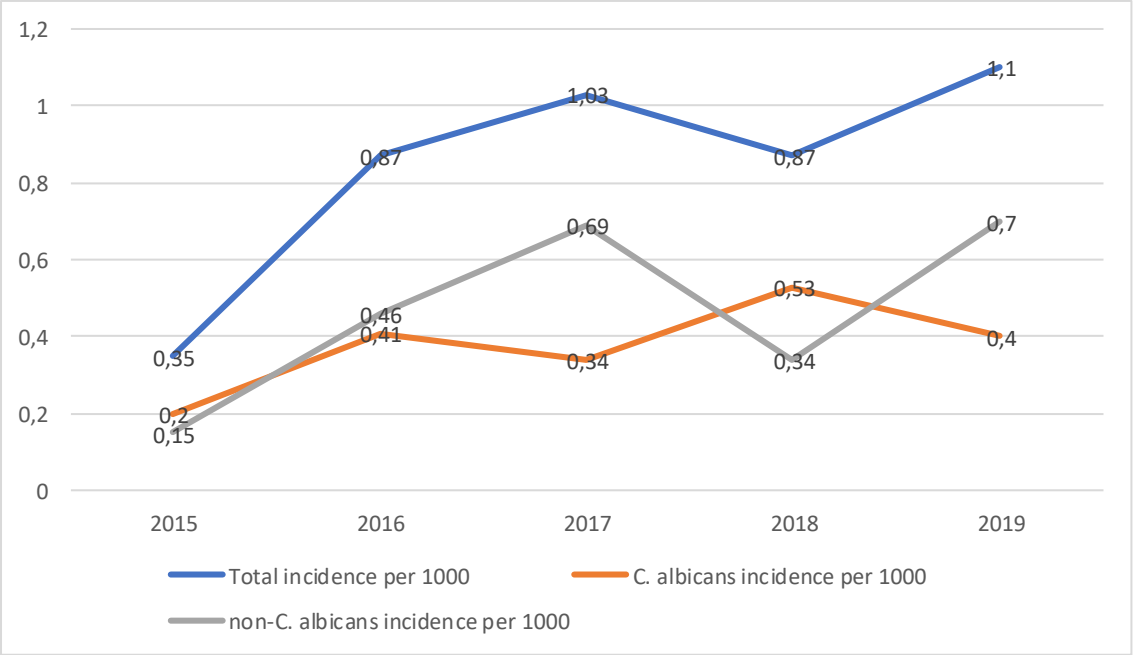

Figure 2: Annual change in incidence risk per 1000 admissions of *Candida* BSI episodes at Red Cross War Memorial Children's Hospital, 2015-2019

Baseline characteristics

Table 1 describes demographic and clinical characteristics of 77 *Candida* BSI episodes in 77 study participants. The median age at the time of *Candida* BSI was 6.8 months, IQR 1.3–24.7. Close to 50% of the episodes occurred in participants who were moderately or severely underweight for age. Of the 52 participants (67.5%) whose HIV status was known at the time of their C*andida* BSI events, only two were HIV-infected. The proportion of participants who were in ICU during the *Candida* BSI was higher among those with *C. albicans* BSI episodes compared to those with non-*C. albicans* BSI episodes, 78.9% (30/38) *vs.* 48.7% (19/39), p=0.01. Furthermore, a higher proportion of non-*C. albicans* than *C. albicans* BSI episodes occurred in

participants with haematological conditions or cancer on immunosuppressive treatment 28.2% (11/39) *vs.* 5.3% (2/38), p=0.01.

Table 1: Characteristics of study participants at the time of *Candida* bloodstream infection

	Total N=77*	***C. albicans* BSI N=38***	**Non-*C. albicans* BSI N=39***	**P value****
Median age (IQR) in months	6.8 (1.3 - 24.4)	5.0 (1.2 – 18.7)	9.2 (1.5 – 57.5)	0.2
Age category				
< 1 month	14 (18.2)	8 (21)	6 (15.4)	0.5
1 - 12 months	29 (37.7)	15 (39.5)	14 (35.9)	
1 - 5 years	21 (27.3)	11 (29)	10 (25.6)	
> 5 years	13 (16.9)	4 (10.5)	9 (23.1)	
Gender				
Male	38 (49.5)	21 (55.3)	17 (43.6)	0.3
Female	39 (50.6)	17 (44.7)	22 (56.4)	
HIV status				
HIV-infected	2 (2.6)	2 (5.3)	0 (0)	0.2
HIV-uninfected	50 (64.9)	22 (57.9)	28 (71.8)	
Unknown	25 (32.5)	14 (36.8)	11 (28.2)	
Weight-for-age, Z score category				
Normal weight	41 (53.3)	19 (50.0)	22 (56.4)	0.5
Moderate underweight	6 (7.8)	2 (5.3)	4 (10.3)	
Severe underweight	30 (39)	17 (44.7)	13 (33.3)	
Gestational age of infants (<12 months of age) at birth				
Term	13/43 (30.2)	4/23 (17.4)	9/20 (45)	0.08
Preterm	24/43 (55.8)	14/23 (60.9)	10/20 (50)	
Unknown	6/43 (14)	5/23 (21.7)	1/20 (5)	
Recorded temperature (°C)				
< 35.5	1/66 (1.5)	0/31 (0)	1/35 (2.8)	0.1
35.5–37.9	29/66 (43.9)	17/31(54.8)	12/35 (34.3)	
≥ 38.0	36/66 (54.5)	14/31 (45.2)	22/35 (62.9)	
Exposure to selected IV antibiotics in the preceding 12 months ***	63 (81.8)	33 (86.8)	30 (76.9)	0.3
Corticosteroid therapy for more than a month	9 (11.7)	2 (5.3)	7 (17.9)	0.2
Presence of central venous or arterial catheter	57 (74)	30 (78.9)	27 (69.2)	0.3
Total parental nutrition	25 (32.5)	13 (34.2)	12 (30.7)	0.7
Necrotizing enterocolitis	11/43 (25.6)	8/23 (34.8)	3/20 (15)	
Haematological/cancer patients on immunosuppressive treatment	13 (16.9)	2 (5.3)	11 (28.2)	***0.01***
Haemodialysis	2 (2.6)	2 (5.3)	0 (0)	0.2
Present in ICU at the time of *Candida* BSI	49 (63.6)	30 (78.9)	19 (48.7)	***0.01***
Abdominal surgery during the previous 3 months	21 (27.3)	11 (29.0)	10 (25.6)	0.7
Cardiac surgery during the previous 3 months	7 (9.1)	1 (2.6)	6 (15.4)	0.1

*N denominator used unless otherwise stated

**Comparison of *C. albicans* and non-C. *albicans* BSI

Proportions reported as n/N (%)

p-values for categorical variables calculated using Pearson's Chi-square test or Fishers exact test and those for continuous variables calculated using Wilcoxon rank-sum test for independent variables

C. albicans, *Candida albicans*; non-*C. albicans*, non-*Candida albicans*; BSI - blood stream infection; °C - degrees Celsius; ICU - intensive care unit, IV - intravenous

***Carbapenems, vancomycin, aminoglycosides, penicillin, cephalosporins, piperacillin tazobactam, fluoroquinolones & clindamycin

Classification and clinical manifestations

Of the 77 *Candida* BSI episodes, 63 (81.8%) episodes were HAIs and 14 (18.2%) were IPOA. The median time between admission and the development of *Candida* BSI in study participants who experienced HAI was 12 days, IQR 7.0-21.0. A clinical site of infection was identified in 44.2% of the *Candida* BSI episodes. Urinary tract as a focus of infection (36.8% vs. 2.5%) and acute renal failure (36.8% vs. 2.5%) as a complication were more common in *C. albicans* BSI than non-*C. albicans* BSI, $p < 0.001$. Vasopressor therapy was administered in 22 (28.6%) episodes and concomitant bacterial BSI was documented in 29.9% of episodes (Table 2).

Pathogens causing concomitant bacterial BSI during *C. albicans* BSI episodes included *Staphylococcus aureus* (2 episodes), *Enterococcus faecium* (1 episode) *Pseudomonas aeruginosa* (2 episodes), *Acinetobacter baumannii* (2 episodes), *Klebsiella pneumoniae* (4 episodes) and *Escherichia coli* (1 episode). A similar spectrum of pathogens was isolated in non-*Candida albicans* BSI episodes with concomitant bacterial BSI, namely *Staphylococcus aureus* (3 episodes), *Enterococcus faecium* (3 episodes) *Pseudomonas aeruginosa* (1 episode), *Acinetobacter baumannii* (1 episode), *Klebsiella pneumoniae* (2 episodes) and *Enterobacter cloacae* (1 episode).

Table 2: Classification, site of infection and complications of *Candida* bloodstream infection

	Total N=77	***C. albicans* BSI N=38**	**Non-*C. albicans* BSI N=39**	**P value***
Classification of *Candida* bloodstream infection				
Infection present on admission	14 (18.2)	6 (15.8)	8 (20.5)	0.8
Healthcare-associated infection	63 (81.8)	32 (84.2)	31 (79.5)	0.8
Site of infection				
No definable focus of infection	43 (55.8)	17 (44.7)	26 (66.4)	0.07
Urinary tract	15 (19.5)	14 (36.8)	1 (2.5)	***<0.001***
Intravenous/arterial catheter	17 (22.1)	5 (13.2)	12 (30.7)	0.1
Abdomen	2 (2.6)	2 (5.2)	0 (0)	0.2
Complications				
Disseminated intravascular coagulopathy	9 (11.7)	3 (7.9)	6 (15.4)	0.5
Vasopressor therapy requirement	22 (28.6)	15 (39.5)	7 (17.9)	0.05
Acute renal failure	15 (19.5)	14 (36.8)	1 (2.5)	***<0.001***
Confusion	35 (45.5)	20 (52.6)	15 (38.5)	0.3
Liver dysfunction	15 (19.5)	7 (18.4)	8 (20.5)	1.0
Abdominal sepsis	14 (18.2)	8 (21.1)	6 (15.4)	0.6
Concomitant bacterial BSI	23 (29.9)	12 (31.5)	11 (28.2)	0.8

C. albicans, *Candida albicans*; non-*C. albicans*, non-*Candida albicans*; BSI, bloodstream infection

* Comparison of *C. albicans* and non-C. *albicans* BSI

Species distribution and antifungal susceptibility of the *Candida* isolates

During the study period, a total of 77 *Candida* species were isolated from the 77 children with complete and available clinical information. Of these, 38 (49.4%) were *C. albicans* isolates. Among the *non-C. albicans* isolates, the most frequent species isolated were *C. parapsilosis* (31.2%), *C. tropicalis* (7.8%), *and C. glabrata* (5.2%) (Table 3).

All *C. albicans* isolates and 75% (27/36) of non-*C. albicans* isolates were susceptible to fluconazole. All *Candida* isolates tested were susceptible to amphotericin B and echinocandins (Table 3).

Table 3: Distribution of *Candida* species and results of antifungal susceptibility testing among *Candida* bloodstream infection isolates

Candida species		**Antifungal susceptibility results**				
			Fluconazole	Amphotericin B	Echinocandins	Voriconazole
C. albicans (n=38)		No. isolates tested	38	38	35	38
		No. (%) Susceptible	38(100)	38 (100)	35 (100)	38 (100)
non-*C. albicans* (n=39)	Total	No. isolates tested	36	38	35	33
		No. (%) Susceptible	27(75)	38 (100)	35 (100)	31 (94)
	C. parapsilosis (24)	No. isolates tested	24	24	23	24
		No. (%) Susceptible	20 (83.3)	24 (100)	23 (100)	22 (91.7)
	C. glabrata (4)	No. isolates tested	2	4	3	0
		No. (%) Susceptible	0 (0)	4 (100)	3 (100)	0 (0)
	C. tropicalis (6)	No. isolates tested	6	6	6	6
		No. (%) Susceptible	6 (100)	6 (100)	6 (100)	6 (100)
	C. krusei (3)	No. isolates tested	3	3	2	3
		No. (%) Susceptible	0 (0)	3 (100)	2 (100)	3 (100)
	C. lusitaniae (1)	No. isolates tested	1	1	1	0
		No. (%) Susceptible	1 (100)	1 (100)	1 (100)	0 (0)
	C. magnolae (1)	No. isolates tested	0 (0)	0 (0)	0 (0)	0 (0)
		No. (%) Susceptible	0 (0)	0 (0)	0 (0)	0 (0)

No., number

Antifungal therapy

Of the 77 BSI episodes, 69 (89.6%) were treated with an antifungal agent. Of the eight episodes (10.4%) that were not treated at RCWMCH, MMH or GSH, two patients died and two were transferred to another hospital before the diagnosis of *Candida* BSI was established. Antifungal therapy was initiated a median of 1 day (IQR, 1-2) after the first diagnostic blood culture was performed. The median duration of all antifungal therapy per episode was 14 days (IQR, 13-20). In 58 of the 69 treated episodes (84.1%), at least one repeat blood culture was performed during the BSI episode. The median time (IQR) between initial blood culture and repeat blood culture was 2 (2-4) days. The repeat cultures were negative in 56 of these 58 episodes (96.6%). Thus, clearance of the identified *Candida* isolate was documented during antifungal therapy in 56/69 (81.2%) of the treated BSI episodes. Clearance was not documented in the two episodes in which repeat cultures were still positive as no further blood cultures were performed. The median time (IQR) until documentation of clearance from initiation of treatment was 4 (2-6.75) days. The median duration (IQR) of antifungal therapy from negative repeat culture was 13 (9.5-14.5) days.

After the antifungal susceptibility results became available, the initial antifungal agent was continued in 49 (71%) episodes and changed in 20 (29%) episodes due to resistance or de-escalation to agents with narrower spectrum of antifungal activity. In 5 of the 49 episodes (10.2%) in which initial antifungal therapy was continued, the susceptibility results indicated that de-escalation was possible but not implemented. Fluconazole was the most frequently used initial antifungal agent, 43/69 (62.3%), followed by amphotericin B, 21/69 (30.4%), and caspofungin, 5/69 (7.2%). After adjustments were made in response to the antifungal susceptibility results, the final treatment regimens were fluconazole, 51/69 (73.9%), amphotericin B 13/69 (18.8%) and caspofungin, 5/69 (7.2%).

Outcome

74.0 % (57/77) of *Candida* BSI episodes were successfully treated and the children were discharged from hospital after these episodes. During the study period, 14 (18.2%) children died during or after the *Candida* BSI episode but prior to hospital discharge (Supplementary Table 1). Thirteen of these deaths occurred within 30 days of *Candida* BSI diagnosis and were included in the survival analysis. The median time (IQR) to death of these 13 children was 9 (3–16) days. Table 4 describes risk factors associated with 30-day inpatient mortality in children with *Candida* BSI. On multivariable analysis, the presence of concomitant bacterial BSI during *Candida* BSI was significantly associated with 30-day inpatient mortality. Furthermore, Kaplan-Meier survival analysis showed that there was no difference in the time to death of patients with *C. albicans* compared to non-*C. albicans* BSI episodes, p=0.7 even though the later showed better survival times (Figure 3).

Supplementary Table 1: Outcome associated with *Candida* bloodstream infection

	Total N=77	***C. albicans* BSI N=38**	**Non-*C. albicans* BSI N=39**	**P value***
Recovered after antifungal therapy	57 (74.0)	31 (81.6)	26 (66.7)	0.1
Death within 30 days of *Candida* BSI	13 (16.9)	5 (13.2)	8 (20.5)	0.6
Death after 30 days of *Candida* BSI	1 (1.3)	1 (2.6)	0 (0)	1.0
Unknown, transferred to another hospital before antifungal therapy initiated	2 (2.6)	1 (2.6)	1 (2.5)	1.0
Not treated with antifungal therapy, remained well	4 (5.2)	0 (0)	4 (10.3)	0.1

C. albicans, Candida albicans; non-*C. albicans,* non-*Candida albicans*, BSI bloodstream infection

* Comparison of *C. albicans* and non-C. *albicans* BSI

Table 4: Risk factors associated with 30-day inpatient mortality in children with *Candida* bloodstream infection

Risk factors for mortality	**Patients who died with 30 days**	**Patients who survived**	**Univariable analysis**		**Multivariable analysis**	
	N= 13	**N= 62**	**OR (95% CI)**	**p-value**	**aOR (95% CI)**	**p-value**
Age less than 12 months	8/13 (61.5)	33/62 (53.2)	1.4 (0.4-4.8)	0.6		
Severe underweight (weight for age <-3 z score)	6/13 (46.2)	22/62 (35.5)	2.0 (0.5-7.2)	0.3		
Disseminated intravascular coagulopathy	5/13 (38.5)	4/62 (6.5)	9.1 (2.0-41.0)	***<0.001***	5.2 (0.9-30.7)	0.07
Required vasopressor therapy	8/13 (61.5)	14/62 (22.6)	5.5 (1.5-19.5)	***0.01***	2.8 (0.6-13.3)	0.2
Acute renal failure	3/13 (23.1)	12/62 (19.4)	1.3 (0.3-5.3)	0.8		
Hepatic dysfunction	5/13 (38.5)	9/62 (14.5)	3.7 (1.0-13.8)	***0.05***	2.5 (0.5-12.4)	0.3
White cell count <4000 cells/μL	3/13 (23.1)	12/62 (19.4)	1.4 (0.3-5.9)	0.7		
Presence of an immunosuppressive condition*	2/13 (15.4)	12/62 (19.4)	0.8 (0.1-3.9)	0.7		
Present in ICU during *Candida* BSI	9/13 (69.2)	38/62 (61.3)	1.4 (0.4-5.1)	0.6		
Presence of definable focus of infection	5/13 (38.5)	28/62 (45.2)	0.8 (0.2-2.6)	0.7		
Presence of concomitant bacterial BSI during *Candida* BSI	8/13 (61.5)	14/62 (22.6)	5.5 (1.5-19.5)	***0.01***	5.7 (1.4-24.0)	***0.02***
Non-Candida albicans BSI	8/13 (61.5)	30/62 (49.2)	1.7 (0.5-5.8)	0.4		

*Presence of immunosuppressive condition: study participants with haematological conditions or cancer patients on immunosuppressive treatment, HIV infection, corticosteroid therapy for more than a month

BSI, blood stream infection; ICU, intensive care unit; OR - Odds ratio; 95% CI, 95% confidence interval; aOR, adjusted Odds ratio

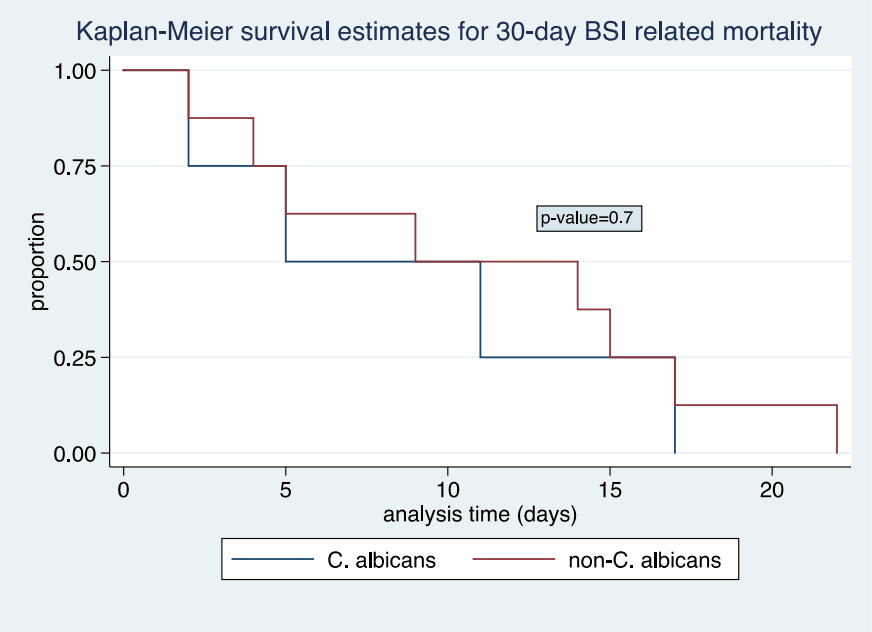

Figure 3: Survival estimates for the outcome of 30-day mortality stratified by the type of *Candida* bloodstream infection

Discussion

The exact incidence of *Candida* BSI in children in sub-Saharan Africa is not known due to a lack of systematic epidemiological data. In multicentre laboratory-based surveillance among hospitalized children at public-sector hospitals in South Africa, the overall incidence was 5.3 *Candida* BSI episodes per 1000 admissions and ranged from 0.39 to 119.1 per 1000 admissions.[5] The incidence risk in our study of 0.84 per 1000 hospital admissions is consistent with this report, although at the lower end of the range. It is also at the lower end of the range of incidence estimates reported by non-South African studies of 0.21-10.5 *Candida* BSI episodes per 1000 admissions.[3,4] Good infection prevention practice, less crowded wards, better infrastructure and staffing resources, and presence of antifungal stewardship programmes are possible factors that contribute to lower incidence.[27,28] Though our study's overall incidence risk is low, the annual incidence risk increased progressively throughout the study period. This might be because of increased use of central lines in children requiring intensive care, an increase in the number of children with other risk factors for invasive fungal infection and more frequent blood culture investigation over time.

Many of the children in our study had interventions and underlying medical conditions that most likely predisposed them to *Candida* BSI. These included prior antibiotics exposure, the presence of CVCs, parenteral nutrition, treatment in the ICU, and malignancy, and in neonates and infants, preterm birth and necrotising enterocolitis. Similar risk factors have been reported in other

studies, including the recent South African multicentre laboratory-based surveillance report.[5,9,10,11,12]

In our study, non-*C. albicans spp.* collectively accounted for the greater number of cases, although *C. albicans* was the most common single species accounting for nearly half of all *Candida* BSI episodes. Similarly, recent paediatric studies from Egypt and China showing a shift to non-*C. albicans*, reported that *C. albicans* was the predominant species.[7,8] A multicentre paediatric *Candida* BSI study showed that between 2016 and 2017, *C. parapsilosis* was the most prevalent species in South Africa although *C. albicans* remained predominated in less populous provinces.[5] In our study, *C. parapsilosis* was the most common non-*albicans Candida* species accounting for 31.2% of all *Candida* isolates.

Unlike previous studies, we found that all *C. albicans* isolates and 75% of non-*C. albicans* isolates were susceptible to fluconazole.[5,7] All ten *Candida* isolates from GSH and MMH were susceptible to fluconazole. In a South African multicentre study, over half of the *C. parapsilosis* isolates were resistant to fluconazole.[5] The contrasts with our findings, showing that only 16.7% of *C. parapsilosis* isolates were resistant to fluconazole. The lower fluconazole resistance rate might be due to reasonable infection control practice and hospital antifungal stewardship. All *Candida* isolates tested were susceptible to amphotericin B and echinocandin in our study. This is consistent with a large South Africa study, in which only three of 3061 *Candida* isolates tested were resistant to echinocandins and all isolates were susceptible to amphotericin B.[5] A study from Egypt also reported very high caspofungin and amphotericin B susceptibilities among all *Candida* isolates tested.[7]

In our study, mortality within 30 days of *Candida* BSI diagnosis was 17.3% of 75 patients with known outcomes. This is lower than that reported in an Egyptian study of children with *Candida* BSI (64%), a South African study of neonates with fungal BSI (45.8%) and a large multicentre study of hospitalized children with *Candida* BSI (38%).[7,17,5] The lower mortality documented in our study may be related to low fluconazole resistance, early initiation of antifungal therapy and the duration of antifungal therapy administered to our patients. In the Egyptian study, most deaths were associated with non-*C. albicans* BSI.[7] Although more children who died in our study had non-*C. albicans* BSI compared to those who survived, this difference was not statistically significant.

On multivariable analysis the presence of concomitant bacterial BSI during *Candida* BSI was the only significant risk factor associated with 30-day inpatient mortality. To our knowledge, previous paediatric studies have not identified this risk factor. However, given that bacterial BSI *per se* is associated with appreciable mortality, concomitant bacterial BSI is likely to significantly increase the mortality risk during *Candida* BSI as suggested by our findings.

Study strengths and limitations

The results underline an important antimicrobial stewardship principle, namely that low fluconazole resistance in *Candida* BSI at our institutions implies that fluconazole should still be used for the empiric treatment of *Candida* BSI, thus preserving the echinocandins for the treatment of fluconazole resistant isolates.

Due to the retrospective study design, bias was unavoidable due to limitations in the completeness and availability of laboratory and clinical data. Additionally, we did not have admissions data for GSH & MMH and thus restricted our incidence calculations to RCWMCH. Furthermore, the sample size was small and underpowered to fully explore 30-day mortality risk factors. Differences between our 30-day mortality rate and higher rates documented in other sub-Saharan African studies suggest that our results may not be generalizable to other hospitals. Despite these limitations, our findings provide valuable insights into the epidemiology and clinical manifestations of paediatric *Candida* BSI at our institutions.

Conclusion

Our study provides a description of *Candida* BSI in children in the Western Cape province of South Africa, indicating low incidence, low fluconazole resistance and relatively low mortality. The increasing annual incidence risk of *Candida* BSI documented in our study suggests that attention should be given to improving infection control practices, particularly in those children at risk of *Candida* BSI. Furthermore, children with risk factors for *Candida* BSI including the presence of a CVC, haematological malignancy, receipt of immunosuppressive therapy, management in the ICU and preterm delivery, and who develop suggestive clinical features should be investigated promptly and considered for empiric antifungal therapy. Concomitant bacterial infection during *Candida* BSI was the only independent risk factor associated with 30-day mortality in our study. Further research, particularly prospective studies, is required to provide a complete understanding of the impact of *Candida* BSI on the childhood population in sub-Saharan Africa.

Acknowledgements

We acknowledge Ms. Simone Twaku and the records department of RCWMCH, GSH & MMH for the provision of the medical files needed for retrospective review. We thank the NHLS and the CDW, housed in the information technology department of the NHLS in Johannesburg, for providing data on blood cultures and antimicrobial susceptibilities of patients from RCWMCH, GSH & MMH. We also acknowledge Mr. Ebrahim Jacobs, RCWMCH for providing denominator data for RCWMCH annual admissions

Competing interests

Authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

Authors' contributions

M. N. G. wrote the study protocol, extracted the clinical data from the medical files at RCWMCH, GSH and MMH, and the microbiology data from the NHLS database for microbiology, analysed the data, interpreted the results and wrote the initial draft of the manuscript. B. S. E. developed the concept and provided guidance on the title, objectives and the development of the protocol of the study and the study literature review, data analysis, and manuscript development. J. J. N. assisted with the study protocol and manuscript development. W. B. provided guidance on the statistical analysis, assisted with the regression and Kaplan-Meier analyses and manuscript writing. H. T. and A. K. supported manuscript writing, particularly for describing microbiology methods, and assisted with retrieval of patient list and microbiology results from the CDW and NHLS. L. T., S. S., R. M. and N. R. helped with the protocol development and the retrieval of the clinical records of patients in their respective units. All authors reviewed and approved the final draft.

Funding information

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Data availability statement

The data that supported the findings of this study are available from the corresponding author, M. N. G., upon request.

Disclaimer

The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of any affiliated agency of the authors.

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APPENDICES

1. FACULTY OF HEALTH SCIENCES ETHICS APPROVAL LETTER

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

Room G50 -G Floor
Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone (021) 650 1236
Email: hrec-enquiries@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

16 March 2020

HREC REF: 159/2020

Professor Brian Eley
Paediatrics & Child Health
Room 520, 5th Floor
ICH Building,
Red Cross War Memorial Children's Hospital
Klipfontein Road
Rondebosch

Dear Professor Brian Eley

PROJECT TITLE: CANDIDA BLOODSTREAM INFECTION AMONG CHILDREN HOSPITALIZED IN THREE PUBLIC-SECTOR HOSPITALS IN THE METRO WEST REGION OF CAPE TOWN, SOUTH AFRICA. MPHIL CANDIDATE DR M GEBREMICAEL

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

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 March 2021.

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

The HREC acknowledge that student: Dr Mulugeta Gebremicael *will also be involved in this study.*

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

Please quote the HREC REF in all your correspondence.

HREC 159/2020 SC

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines.
The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

HREC 159/2020 SC

2. APPROVAL LETTER FROM HOSPITAL RESEARCH COMMITTEE

Western Cape Government
Health

DR AN PARBHOO
Manager: Medical Services
Red Cross War Memorial Children's Hospital
Email: Anita.Parbhoo@westerncape.gov.za
Tel: +27 21 658 5430 Fax: +27 21 658 5006/5166

17 June 2020

Prof B Eley
Paediatric Infectious Diseases

Dear Prof Eley,

RESEARCH: RXH: RCC 233 / WC_202006_010

PROJECT TITLE: *Candida* bloodstream infection among children hospitalized in three public-sector hospitals in the Metro West region of Cape Town, South Africa

It is a pleasure to inform you that the hospital Research Review Committee has approved your application to conduct above-mentioned study in the Department at Red Cross War Memorial Children's Hospital.

Kindly note that this approval is subject to strict adherence to the HREC recommendations regarding research involving participants during COVID-19, dated 17 March 2020 (UCT HREC notice attached).

Yours sincerely,

DR AN PARBHOO
MANAGER: MEDICAL SERVICES

3. DATA COLLECTION SHEET

Biographical Information

1. Study No----------
2. Folder No----------
3. Date of Birth ----------
4. Age at admission (in months) ----------
5. Gestational age (for neonates) Term ☐ Pre-term ☐ Post-term ☐ NA ☐
6. Birth Weight (for neonates) NBW ☐ LBW ☐ VLBW ☐

   ELBW ☐ NA ☐
7. Gender Male ☐ Female ☐
8. Admission mass (kg)----------
9. Admission height/length (cm)----------
10. Nutritional status (Z score)
    A. WAZ score----------
    B. WHZ score----------
    C. HAZ score----------
    D. Presence of oedema Yes ☐ No ☐

Admission status at the hospital of current admission

11. Hospital of current admission

    RCWMCH ☐ MMH ☐ GSH ☐
12. Date of current admission to the hospital----------
13. Ward in which culture grown *Candida spp.* in the current admission----------
14. Duration of stay in the current admission (in days) ----------

15. History of Previous hospitalization in the hospital of current admission

Admission to current hospital in the past 28 days	Yes/No	Duration
No of admissions to the current hospital in the past 1 year	Date of admission	Duration of admission
1.		
2.		
Admission to ICU to the current hospital in the past 28 days	Yes/No	Duration
No of admission to ICU to the current hospital in the last 1 year	Date of admission	Duration of admission
1. 2.		

16. Admission to other health care facilities (other than hospital of current admission)

	Yes	No	Date of admission	Duration of admission
Admission during preceding 28 days				
Admission during preceding 1 year				

Clinical Characteristics

17. HIV infection

Patient tested for HIV	Yes	No	Unknown
HIV test	Rapid	PCR	Elisa
Date test done			
HIV exposed	Yes	No	Unknown
HIV infected	Yes	No	Unknown
	Date	Values	
CD4%/Abs (baseline)/(µl)			
CD4%/Abs (most recent)/(µl)			
Viral load (baseline)/(copies/ml)			
Viral load (most recent)/(copies/ml)			
Treatment with ART at the time of culture	Yes	No	Unknown
Date of ART initiation		Duration of ART	

Clinical features at time of *Candida* BSI diagnosis

18. Fever Yes ☐ No ☐
19. Severe sepsis and/or septic shock Yes ☐ No ☐
20. Disseminated intravascular coagulopathy Yes ☐ No ☐
21. Vasopressor therapy requirement Yes ☐ No ☐
22. Acute renal failure Yes ☐ No ☐

23. Confusion Yes ☐ No ☐

24. Respiratory distress Yes ☐ No ☐

25. Liver dysfunction Yes ☐ No ☐

26. Abdominal sepsis Yes ☐ No ☐

27. Other ----------(Specify)

Evidence supporting an invasive infection at time of *candida* BSI

Clinical diagnosis of infection	Recorded (Yes or No)	If yes- actual value
Fever		
White cell count		
C reactive protein		
Procalcitonin		
Platelet		

Underlying medical illness & risk factors

28. Corticosteroid therapy (›1 month) Yes ☐ No ☐

29. Presence of a central line Yes ☐ No ☐

30. Granulocytopenia Yes ☐ No ☐

31. Prior fungal colonization Yes ☐ No ☐

32. Low birth weight Yes ☐ No ☐ Unknow

33. Prematurity Yes ☐ No ☐

Unknown

34. Necrotizing enterocolitis Yes ☐ No ☐

35. Total parenteral nutrition Yes ☐ No ☐

36. Chronic lung disease Yes ☐ No ☐

37. Severe acute malnutrition Yes ☐ No ☐

38. Neurological sequelae Yes ☐ No ☐

39. Hemodialysis Yes ☐ No ☐

40. Hematological/cancer patients

on immunosuppressive treatment Yes ☐ No ☐

41. Stay in the ICU during invasive

Candida spp. Infection Yes ☐ No ☐

42. History of abdominal surgery

during the previous 3 months Yes ☐ No ☐

43. Maternal history of perinatal invasive

candida infection (for infants <7days of age) Yes ☐ No ☐ NA

44. If the answer is Yes to Q 44, describe site of infection, species of *Candida*& resistance profile of isolate:----------

45. Others----------

Diagnosis

46. Diagnosis during the current admission

Initial diagnosis	
Additional diagnosis	
Additional diagnosis	
Final diagnosis	
Focus of infection	

47. **Screening or investigation**

Type of screening	Date	Finding	Done
Echo			
KUB			
Eye exam			

48. **Other positive culture specimen**

Site / specimen	Date	Organism(s)	Sensitivity	Resistance

49. **History of antibiotic exposure before *Candida* BSI diagnosis in the last 1 year**

No of episodes of antibiotic exposure in the last 1 year	Date of start	Type of antibiotic	Name of specific drug	Duration of exposure
1.		1.Carbapenems 2.Cephalosporin 3.Fluoroquinolones 4.Aminoglycosides 5. Piperacillin-tazobactam 6. Other		
2.				

50. **History of antifungal exposure before *Candida* BSI diagnosis in the last 1 year**

No of episodes of antifungal exposure in the last 1 year	Date of start	Type of antifungal	Name of specific drug	Duration of exposure
1.		1.Azole group 2.Amphotericin B 3. Echinocandin		
2.				

51. Probiotics exposure at the time of *candida* BSI Yes ☐ ☐ No

Culture results in the current admission

52. Date blood culture was taken for *Candida* BSI----------

53. Time was taken from incubation to growth for *Candida* BSI----------

54. Organism isolated----------

55. History of recurrent *Candida* BSI Yes ☐ No ☐

56. If the answer is yes to Q 56 what was the time interval between episodes? ----------

57. Presence ofconcomitant bacteraemia Yes ☐ No ☐

Number of Repeat Culture

Number of repeat cultures	Growth	Date
1.	Yes No	
2.	Yes No	
3.	Yes No	
4.	Yes No	

Empirical antifungal prophylaxis/treatment in the current admission

58. Empirical antifungal prophylaxis/treatment Yes ☐ No ☐
59. Name of antifungal----------
60. Date of start ----------
61. Duration----------
62. Route of administration----------

Antifungal sensitivity profile to *Candida Spp*

63. C.albicans

A. Fluconazole Sensitive ☐ Resistant ☐
B. Voriconazole Sensitive ☐ Resistant ☐
C. Amphotericin B Sensitive ☐ Resistant ☐
D. Echinocandins Sensitive ☐ Resistant ☐
E. 5-flourocytosine Sensitive ☐ Resistant ☐

64. *C. parapsilosis*

A. Fluconazole Sensitive ☐ Resistant ☐

B. Voriconazole Sensitive ☐ Resistant ☐

C. Amphotericin B Sensitive ☐ Resistant ☐

D. Echinocandins Sensitive ☐ Resistant ☐

E. 5-flourocytosine Sensitive ☐ Resistant ☐

65. *C. glabrata*

A. Fluconazole Sensitive ☐ Resistant ☐

B. Amphotericin B Sensitive ☐ Resistant ☐

C. Echinocandins Sensitive ☐ Resistant ☐

D. 5-flourocytosine Sensitive ☐ Resistant ☐

66. *C. tropicalis*

A. Fluconazole Sensitive ☐ Resistant ☐

B. Voriconazole Sensitive ☐ Resistant ☐

C. Amphotericin B Sensitive ☐ Resistant ☐

D. Echinocandins Sensitive ☐ Resistant ☐

E. 5-flourocytosine Sensitive ☐ Resistant ☐

67. *C. auris*

A. Fluconazole Sensitive ☐ Resistant ☐

B. Voriconazole Sensitive ☐ Resistant ☐

C. Amphotericin B Sensitive ☐ Resistant ☐

D. Echinocandins Sensitive ☐ Resistant ☐

E. 5-flourocytosine Sensitive ☐ Resistant ☐

68. Others----------(specify)

A. Fluconazole Sensitive ☐ Resistant ☐

B. Voriconazole Sensitive ☐ Resistant ☐

C. Amphotericin B Sensitive ☐ Resistant ☐

D. Echinocandins Sensitive ☐ Resistant ☐

E. 5-flourocytosine Sensitive ☐ Resistant ☐

Antifungal treatment in response to *Candida* BSI

69. Name of anti-fungal----------

70. Date of start ----------

71. Duration(days)----------

72. Route of administration----------

Outcome

73. Discharge Yes ☐ No ☐

74. If the answer is Yes to Q 74, Date of discharge----------

75. Transferred Yes ☐ No ☐

76. If the answer is Yes to Q 76, Date of transferred----------

77. Death Yes ☐ No ☐

78. If the answer is Yes to Q 78

A. Date of death----------

B. Cause of death----------

79. Unknown Yes ☐ No ☐

4. AUTHORS INSTRUCTIONS: Southern African Journal of Infectious Diseases

SUBMISSION GUIDELINES

1. Types of articles published

Overview

The author guidelines include information about the types of articles received for publication and preparing a manuscript for submission. Other relevant information about the journal's policies and the reviewing process can be found under the about section. The **compulsory cover letter** forms part of a submission and must be submitted together with all the required **forms**. All forms need to be completed in English.

Original Research Article

An original article provides an overview of innovative research in a particular field within or related to the focus and scope of the journal, presented according to a clear and well-structured format.

Word limit	3500 words (excluding the structured abstract and references)
Structured abstract	250 words to include a Background, Methods, Results and Conclusion
References	50 or less
Tables/Figures	no more than 7 Tables/Figure
Ethical statement	should be included in the manuscript
Compulsory supplementary file	ethical clearance letter/certificate

Original Research Article full structure

Title: The article's full title should contain a maximum of 95 characters (including spaces).

Abstract: The abstract, written in English, should be no longer than 250 words and must be written in the past tense. The abstract should give a succinct account of the objectives, methods, results and significance of the matter. The structured abstract for an Original Research article should consist of four paragraphs labelled Background, Methods, Results and Conclusion.

- Background: Summarise the social value (importance, relevance) and scientific value (knowledge gap) that your study addresses.

- Methods: Clearly express the basic design of the study, and name or briefly describe the methods used without going into excessive detail.
- Results: State the main findings.
- Conclusion: State your conclusion and any key implications or recommendations. Do not cite references and do not use abbreviations excessively in the abstract.

Introduction: The introduction must contain your argument for the social and scientific value of the study, as well as the aim and objectives:

- Social value: The first part of the introduction should make a clear and logical argument for the importance or relevance of the study. Your argument should be supported by use of evidence from the literature.
- Scientific value: The second part of the introduction should make a clear and logical argument for the originality of the study. This should include a summary of what is already known about the research question or specific topic, and should clarify the knowledge gap that this study will address. Your argument should be supported by use of evidence from the literature.
- Conceptual framework: In some research articles it will also be important to describe the underlying theoretical basis for the research and how these theories are linked together in a conceptual framework. The theoretical evidence used to construct the conceptual framework should be referenced from the literature.
- Aim and objectives: The introduction should conclude with a clear summary of the aim and objectives of this study.

Research methods and design: This must address the following:

- Study design: An outline of the type of study design.
- Setting: A description of the setting for the study; for example, the type of community from which the participants came or the nature of the health system and services in which the study is conducted.
- Study population and sampling strategy: Describe the study population and any inclusion or exclusion criteria. Describe the intended sample size and your sample size calculation or justification. Describe the sampling strategy used. Describe in practical terms how this was implemented.
- Intervention (if appropriate): If there were intervention and comparison groups, describe the intervention in detail and what happened to the comparison groups.
- Data collection: Define the data collection tools that were used and their validity. Describe in practical terms how data were collected and any key issues involved, e.g. language barriers.

- Data analysis: Describe how data were captured, checked and cleaned. Describe the analysis process, for example, the statistical tests used orsteps followed in qualitative data analysis.

- Ethical considerations: Approval must have been obtained for all studies from the author's institution or other relevant ethics committee and the institution's name and permit numbers should be stated here.

Results: Present the results of your study in a logical sequence that addresses the aim and objectives of your study. Use tables and figures as required to present your findings. Use quotations as required to establish your interpretation of qualitative data. All units should conform to the **SI convention** and be abbreviated accordingly. Metric units and their international symbols are used throughout, as is the decimal point (not the decimal comma).

Discussion: The discussion section should address the following four elements:

- Key findings: Summarise the key findings without reiterating details of the results.

- Discussion of key findings: Explain how the key findings relate to previous research or to existing knowledge, practice or policy.

- Strengths and limitations: Describe the strengths and limitations of your methods and what the reader should take into account when interpreting your results.

- Implications or recommendations: State the implications of your study or recommendations for future research (questions that remain unanswered), policy or practice. Make sure that the recommendations flow directly from your findings.

Conclusion: Provide a brief conclusion that summarises the results and their meaning or significance in relation to each objective of the study.

Acknowledgements: Those who contributed to the work but do not meet our authorship criteria should be listed in the Acknowledgments with a description of the contribution. Authors are responsible for ensuring that anyone named in the Acknowledgments agrees to be named. Refer to the acknowledgement structure guide on our *Formatting Requirements* page.

Also provide the following, each under their own heading:

- Competing interests: This section should list specific competing interests associated with any of the authors. If authors declare that no competing interests exist, the article will include a statement to this effect: *The authors declare that they have no financial or personal relationship(s) that may have inappropriately influenced them in writing this article.* Read our **policy on competing interests**.

- Author contributions: All authors must meet the criteria for authorship as outlined in the **authorship** policy and **author contribution** statement policies.

- Funding: Provide information on funding if relevant

- Data availability: All research articles are encouraged to have a data availability statement.
- Disclaimer: A statement that the views expressed in the submitted article are his or her own and not an official position of the institution or funder.

References: Authors should provide direct references to original research sources whenever possible. References should not be used by authors, editors, or peer reviewers to promote self-interests. Refer to the journal referencing style downloadable on our *Formatting Requirements* page.

2. Formatting requirements

Style and format

File format

- Manuscript files can be in the following formats: DOC, DOCX, or RTF. Microsoft Word documents should not be locked or protected.
- LaTeX documents (.tex) should be converted into Microsoft Word (.doc) before submission online.
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Length

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Acknowledgements structure

Acknowledgements

The acknowledgement section follows the conclusions section and addresses formal, required statements of gratitude and required disclosures. It includes listing those who contributed to the work but did not meet authorship criteria, with the corresponding description of the contribution. Acknowledge anyone who provided intellectual assistance, technical help (including with writing and editing), or special equipment and/or materials. Authors are responsible for ensuring that anyone named in the Acknowledgements agrees to be named.

Also provide the following, each under their own subheading:

- Competing interests
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- Funding information
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cenario	**Suggested competing interest statements**
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Example 3	A.B. developed the theoretical formalism, performed the analytic calculations and performed the numerical simulations. Both A.B and B.C. contributed to the final version of the manuscript. B.C. supervised the project.
Example 4	A.B., B.C., C.D., D.E., E.F., F.G., and G.H. conceived and planned the experiments. A.B., B.C., C.D. and D.E. carried out the experiments. A.B., F.G. and E.F. planned and carried out the simulations. J.K., K.L., A.B., B.C., D.E., C.D., F.J., and F.G. contributed to sample preparation. A.B., B.C., C.D., D.E., FJ, E.F., F.G. and G.H. contributed to the interpretation of the results. A.B. took the lead in writing the manuscript. All authors provided critical feedback and helped shape the research,

	analysis and manuscript.
Example 5	A.B. and B.C. designed the model and the computational framework and analysed the data. A.B. and C.D. carried out the implementation. A.B. performed the calculations. A.B. and B.C. wrote the manuscript with input from all authors. D.E. and E.F. conceived the study and were in charge of overall direction and planning.
Example 6	A.B. designed and performed the experiments, derived the models and analysed the data. B.C. assisted with XYZ measurements and C.D. helped carry out the XYZ simulations. A.B. and D.E. wrote the manuscript in consultation with C.D., B.C. and E.F..
Example 7	A.B. devised the project, the main conceptual ideas and proof outline. B.C. worked out almost all of the technical details, and performed the numerical calculations for the suggested experiment. C.D. worked out the bound for quantum mechanics, with help from D.E.. E.F. verified the numerical results of the XYZ by an independent implementation. F.G. and G.H. proposed the XYZ experiment in discussions with A.B.. B.C., C.D., G.H. and A.B. wrote the manuscript.
Example 8	A.B., B.C. and C.D. designed the study. A.B., D.E. and E.F. performed the XYZ experiments. F.G. and G.H. performed XYZ simulations. I.H. and M.C. expressed and purified all proteins. A.B., H.J., B.C. and C.D. analysed the data. A.B., B.C. and C.D. wrote the paper with input from all authors.
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Example 2	A.B. and B.C. carried out the experiment. A.B. wrote the manuscript with support from C.D.. D.E. and E.F. fabricated the XYZ sample. F.G. and G.H. helped supervise the project. G.H. and H.I. conceived the original idea. H.I. supervised the project.
Example 3	A.B. developed the theoretical formalism, performed the analytic calculations and performed the numerical simulations. Both A.B and B.C. authors contributed to the final version of the manuscript. B.C. supervised the project.
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Example 5	A.B. and B.C. designed the model and the computational framework and analysed the data. A.B. and C.D. carried out the implementation. A.B. performed the calculations. A.B. and B.C. wrote the manuscript with input from all authors. D.E. and E.F. conceived the study and were in charge of overall direction and planning.
Example 6	A.B. designed and performed the experiments, derived the models and analysed

	the data. B.C. assisted with XYZ measurements and C.D. helped carry out the XYZ simulations. A.B. and D.E. wrote the manuscript in consultation with C.D., B.C. and E.F..
Example 7	A.B. devised the project, the main conceptual ideas and proof outline. B.C. worked out almost all of the technical details, and performed the numerical calculations for the suggested experiment. C.D. worked out the bound for quantum mechanics, with help from D.E.. E.F. verified the numerical results of the xyz by an independent implementation. F.G. and G.H. proposed the xyz experiment in discussions w ith A.B.. B.C., C.D., G.H. and A.B. wrote the manuscript.
Example 8	A.B., B.C. and C.D. designed the study. A.B., D.E. and E.F. performed the xyz experiments. F.G. and G.H. performed XYZ simulations. I.H. and M.C. expressed and purified all proteins. A.B., H.J.., B.C. and C.D. analysed the data. A.B., B.C. and C.D. wrote the paper with input from all authors.
Example 9	A.B. and B.C. designed and directed the project; C.D., D.E., A.B. and B.C. performed the experiments; C.D. and B.C. analysed spectra; A.B. and E.F. made the simulations; B.C. developed the theoretical framework; C.D., A.B. and B.C. wrote the article.
Example 10	A.B., B.C. and C.D. performed the measurements, D.E. and E.F. were involved in planning and supervised the work, A.B. and B.C. processed the experimental data, performed the analysis, drafted the manuscript and designed the figures. F.G., and G.H. performed the xyz calculations. H.I., and I.J. manufactured the samples and characterized them with xyz spectroscopy, J.K. performed the xyz characterization.

	K.L. aided in interpreting the results and worked on the manuscript. All authors discussed the results and commented on the manuscript.
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Data openly available in a public repository that issues datasets with DOIs	The data that support the findings of this study are openly available in [repository name e.g 'figshare'] at http://doi.org/[doi], reference number [reference number].
Data openly available in a public repository that does not issue DOIs	The data that support the findings of this study are openly available in [repository name] at [URL], reference number [reference number].
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Instead of writing in the first person, as shown in examples below:

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- Typically masked self-citation that doesn't really hide identities: 'One major problem experienced is that learners who are meant to be accommodated in mainstream schools often find themselves as a "guest" in the classroom (Author 2013).'

The journal suggests using the third person to mask self-citations, as shown in the examples. Third-person reference to self-citation: 'In the evaluation of major problems experienced, Walton (2013) found that learners who are meant to be accommodated in mainstream schools often find themselves as a "guest" in the classroom.' OR 'In the evaluation of major problems experienced, the researcher found that learners who are meant to be accommodated in mainstream schools often find themselves as a "guest" in the classroom (Walton 2013).'

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5. 2022 ANNUAL PROGRESS REPORT / ETHICS RENEWAL

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FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS017: Annual Progress Report / Renewal

Record Reviews/Audits/Collection of Biological Specimens/Repositories/Databases/Registries

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☐ Approved	Annual progress report	Approved until/next renewal date	30.3.22
☐ Not approved	See attached comments		
Signature Chairperson of the HREC/ Designee		Date Signed	19/3/22

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HUMAN RESEARCH ETHICS COMMITTEE
16 MAR 2021
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

Please clarify your plan for research-related activities during COVID-19 lockdown

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	14 March 2021		
HREC REF Number	159/2020	Current Ethics Approval was granted until	30 March 2021
Protocol title	*Candida* bloodstream infection among children hospitalized in three public-sector hospitals in the Metro West region of Cape Town, South Africa		
Principal Investigator	Brian Eley		
Department / Office Internal Mail Address	Room 520, 5th floor ICH building, Red Cross War Memorial Children's Hospital, Klipfontein Road, Rondebosch, 7700		
1.1 Does this protocol receive US Federal funding?		☐ Yes	✓ No

2. Protocol status (tick ✓)

✓	Research-related activities are ongoing
☐	Data collection is complete, data analysis only

Please indicate (in the block below) the titles and HREC reference numbers of any projects currently making use of the Database/registry/repository.

3. Protocol summary

Total number of records or specimens collected, reviewed or stored since the original approval		84
Total number of records or specimens collected, reviewed or stored since last progress report		84
Have any research-related outputs (e.g. publications, abstracts, conference presentations) resulted from this research? If yes, please list and attach with this report.	☐ Yes	✓ No

4. Signature

Signature of PI	BIEly	Date	15 March 2021

6. 2023 ANNUAL PROGRESS REPORT / ETHICS RENEWAL

UNIVERSITY OF CAPE TOWN
FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS017: Annual Progress Report / Renewal

Record Reviews/Audits/Collection of Biological Specimens/Repositories/Databases/Registries

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☐ Approved	Annual progress report	Approved until/next renewal date	30.3.23
☐ Not approved	See attached comments		
Signature Chairperson of the HREC/ Designee		Date Signed	9/3/22

Note: Please note that incomplete submissions will not be reviewed.
Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za.

Please clarify your plan for research-related activities during COVID-19 lockdown

Principal Investigator to complete the following:

1. Protocol Information

Date (when submitting this form)	8 March 2022		
HREC REF Number	159/2020	Current Ethics Approval was granted until	30 March 2022
Protocol title	*Candida* bloodstream infection among children hospitalized in three public-sector hospitals in the Metro West region of Cape Town, South Africa		
Principal Investigator	Brian Eley		
Department / Office Internal Mail Address	Room 520, 5th floor ICH building, Red Cross War Memorial Children's Hospital, Klipfontein Road, Rondebosch, 7700		
1.1 Does this protocol receive US Federal funding?		☐ Yes	✓ No

2. Protocol status (tick ✓)

☐	Research-related activities are ongoing
✓	Data collection is complete, data analysis only
Please indicate (in the block below) the titles and HREC reference numbers of any projects currently making use of the Database/registry/repository.	

3. Protocol summary

Total number of records or specimens collected, reviewed or stored since the original approval		97
Total number of records or specimens collected, reviewed or stored since last progress report		13
Have any research-related outputs (e.g. publications, abstracts, conference presentations) resulted from this research? If yes, please list and attach with this report.	☐ Yes	✓No

4. Signature

Signature of PI	BEley	Date	8 March 2022