

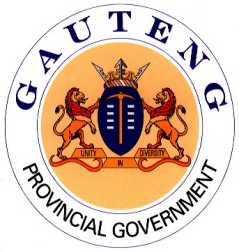
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Factors associated with nosocomial fungal sepsis among patients in the paediatric intensive care unit at the Chris Hani Baragwanath academic hospital

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2017
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FACTORS ASSOCIATED WITH NOSOCOMIAL FUNGAL SEPSIS AMONG PATIENTS IN THE PAEDIATRIC INTENSIVE CARE UNIT AT THE CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

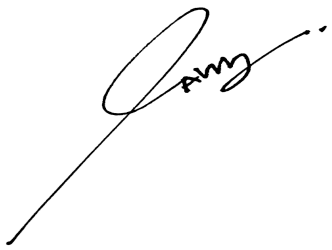
Seung-Hye Ahn

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

29 May 2017

DECLARATION

I, Seung-Hye Ahn, declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in the branch of Paediatrics and Child Health, to the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.



Seung-Hye Ahn

On the 29th day of May 2017

DEDICATION

First and above all, I praise God my Father for granting me the capability and wisdom to proceed and complete this project. I dedicate this work to my husband, Jin-Gu Kim who has been my constant source of support and encouragement, and to my family and Reverend Bong-Suk Oh's family for their unconditional love and prayers.

ABSTRACT

Introduction

Sepsis, and in particular, severe sepsis, remains a major cause of death in children worldwide. One of the areas where the burden of sepsis is keenly felt is in the paediatric intensive care unit (PICU) setting, contributing significantly to childhood mortality. Fungal organisms have emerged as a major organism contributing to nosocomial sepsis in PICU. No local data regarding nosocomial fungal sepsis in the non-neonatal, PICU population exists regarding this matter. This study describes the characteristics of patients with nosocomial fungal sepsis in the PICU at South Africa's largest hospital Chris Hani Baragwanath Academic Hospital (CHBAH).

Methods

This study was a retrospective review of patient records. All patients aged 0-16 years admitted to the PICU at Chris Hani Baragwanath Academic Hospital (CHBAH) from January 2008 through December 2011 were assessed. A total of seventeen patients who developed nosocomial fungal sepsis were included in this study.

Results

The incidence of candidaemia was reported to be 3.2 per 100 cases. The major age group affected by nosocomial fungal sepsis was the under one age group. The most common diagnoses on admission were lower respiratory tract infection (LRTI) followed by haematology-oncology and acute gastroenteritis cases. ICU factors found to commonly co-exist with proven nosocomial fungal sepsis were presence of a central venous

catheter (100%), mechanical ventilation (82%), arterial line (70%), and systemic corticosteroid use (47%). The penicillin class was the most common antimicrobial that patients were found to be on at the time of nosocomial sepsis. The most common fungal organism as a cause for nosocomial sepsis was *C. parapsilosis* rather than *C. albicans*. Furthermore, the majority of this study's isolates were susceptible to voriconazole rather the current empiric antifungal of choice, namely fluconazole.

Conclusion

The presence of central venous catheters, arterial lines, mechanical ventilation and systemic corticosteroid use is common in paediatric patients with nosocomial fungal sepsis. However, this study was unable to determine statistically significant factors associated with fungal sepsis in a tertiary PICU due to the surprisingly small number of cases (n=35) detected over a four-year period. This perhaps represents the most striking finding of the study together with a concerning pattern of fluconazole resistance (14%) among isolated organisms.

ACKNOWLEDGEMENTS

I would like to express my deepest appreciation to my supervisor Dr Kuban Dhasaradha Naidoo, for his full support, expert guidance, encouragement and most importantly his patience throughout the entire process of this research work.

I would also like to thank the Main ICU staff at CHBAH, namely Ms. Mpho Nkobe and Ms. Mapule Mathonzi for sacrificing their time and assisting me in retrieving all necessary patient records.

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ABBREVIATIONS

ALL	Acute Lymphoblastic Leukaemia
AML	Acute Myeloid Leukaemia
BDG	(1,3)- β−D-glucan
BSI	Blood Stream Infections
CA	Candida albicans
CHBAH	Chris Hani Baragwanath Academic Hospital
CVC	Central Venous Catheter
ELISA	Enzyme-linked Immunosorbent Assay
EPA	Epithelial Adhesin
FDA	Food and Drug Administration
HIV	Human Immunodeficiency Virus
LRTI	Lower Respiratory Tract Infection
NAC	Non-albicans Candida
NHLS	National Health Laboratory Services
PCR	Polymerase Chain Reaction
PICU	Paediatric Intensive Care Unit
SD	Standard Deviation
SDB	Sabouraud Dextrose Broth
SIRS	Systemic Inflammatory Response Syndrome
TPN	Total Parenteral Nutrition
US	United States
WHO	World Health Organization

CHAPTER ONE

1. INTRODUCTION

1.1 Background

Sepsis, and in particular, severe sepsis, remains a major cause of death in children worldwide. (1-3) Sepsis is defined as a systemic inflammatory response syndrome (SIRS) in the presence of or as a result of a suspected or proven infection. (4) This definition, including the definitions for the continuum of sepsis was defined for the paediatric population by the International Pediatric Sepsis Consensus Conference in 2002. These include definitions for infection, SIRS, sepsis, severe sepsis and septic shock, which are summarized in appendix A.

The World Health Organization (WHO) reported infectious diseases as the number one killer of children under the age of five years, causing 68% of deaths in this age group in 2008. (5) One of the areas where the burden of sepsis is keenly felt is in the paediatric intensive care unit (PICU) setting, contributing significantly to childhood mortality. (6,7) A Japanese study reported PICU mortality of 28% in patients diagnosed with septic shock between 2007 and 2009. An Italian study reported a staggering 51% mortality rate among children with septic shock in the PICU. (8) Likewise, high mortality rates due to septic shock were also reported in Pakistan, affecting approximately a third (32,8%) of the population admitted to the PICU from 2007 through 2008. (9)

With such a significant burden to childhood mortality, extensive research is aimed at improving the diagnosis and management of sepsis. (1,4,10,11) However despite these efforts, studies continue to demonstrate a rise in the incidence of severe sepsis. A 1995

population-based study investigating severe sepsis reported an incidence in excess of 42,000 new cases among American children. (3) Further epidemiological data from the United States (US) reported a staggering increase in the incidence of sepsis from 82.7 per 100,000 population to nearly 240.4 per 100,000 population over a 21-year period between 1979 and 2000. (6)

Not only does severe sepsis impact dramatically on childhood morbidity and mortality, it also poses a significant healthcare problem due to the extensive usage of healthcare resources. The attributable annual cost to the US health-care system in 1995 was 1.97 billion US dollars, which more than doubled to 4.8 billion US dollars per annum over the subsequent ten year period. (12) With sepsis attributing heavily to childhood mortality both in developed and developing countries, as well as heavily burdening health-care costs, extensive research is required in determining the cause, pathophysiology and management of sepsis in PICU. (10)

1.2 Microbial aetiology of sepsis in the PICU

The three most common microbial groups causing sepsis in the PICU are Gram-positive bacteria, Gram-negative bacteria and fungi. (13-15) In the mid 1990's the most common infecting organisms were *Staphylococcus* species, however by 2005 it had become apparent that Gram-negative organisms were responsible for a large proportion of severe sepsis cases in the PICU. (3,14,15) The most common Gram-negative pathogens were *Pseudamonas aeruginosa* and *Enterococcus faecalis* in a Japanese and Brazilian study, respectively. (14,15) This evolving face of microbial epidemiology was also noted in North America where a significant increase in organisms other than bacteria, such as

fungal infections was noted over a 22-year period. *Candida* species (responsible for the vast majority of fungal infections) has been reported as the fourth most common pathogen responsible for nosocomial (hospital-acquired) sepsis. (6,16)

1.3 Nosocomial fungal sepsis

A few decades ago, fungi were uncommon nosocomial pathogens. (17) However, since 1979 fungi have emerged as important pathogenic organisms among patients with nosocomial sepsis. (18,19) The last two decades of the twentieth century saw a staggering 207% increase in new cases of fungal sepsis. (6) Italian researchers found that the incidence of candidaemia had more than doubled among critically ill patients around the turn of the century. (20)

Among fungal organisms, *Candida* species are the most common organisms responsible for fungal bloodstream infections (BSI). (16,21) Overall, they are the fourth most common isolate in nosocomial BSI and the third most common cause of nosocomial BSI in critically ill patients. (16,22,23) Consistent with the overall increase in fungal infections, the incidence of nosocomial candidaemia has also risen rapidly over the past two decades. (6,24-26) A five-fold increase of candidaemia from 0.06 to 0.3 per 1,000 inpatients was observed between 2000 and 2009 in the US. (25) Of note, the rate of nosocomial candidaemia among the non-neonatal paediatric population doubled during a 9 year period between 1997 and 2005. (24)

Candida species can be broadly classified into two groups namely *Candida albicans*

(CA) and the non-*albicans Candida* (NAC). Over recent years, despite the emergence of NAC species causing disease, CA remains the most common fungus to cause bloodstream infections in the paediatric population, accounting for 40-60% of cases. (24,27-32)

2.0 BASIC MYCOLOGY OF CANDIDA

The genus Candida is classified as follows:

- Kingdom: Fungus
- Phylum: Ascomycota
- Subphylum: Saccharomycotina
- Class: Saccharomycetes
- Order: Saccaromycetales and
- Family: Saccharomycetaceaea. (33)

Candida colonies appear cream to yellow macroscopically and are typically grown on Sabouraud dextrose agar. Colony texture may differ according to the species and may be smooth, dry or wrinkled. Growth occurs as blastoconidia, which are spherical to oval shaped budding cells. (34) Certain morphological features help in distinguishing between *Candida* species such as branch-like extensions from the budding cell, otherwise known as true hyphae or pseudohyphae. (35) True hyphae and/or pseudohyphae are diagnostic features of *C. albicans*. In contrast, *C. glabrata* lack the ability to grow hyphae and exist as ovoid blastoconidia. (34,35) Other distinguishing features include the size of blastoconidia of which *C. glabrata* measures the smallest (1-4 μm) and the largest species

C. albicans (4–6 μm) and *C. tropicalis* (4–8 μm). (36)

The *Candida* genus contains over 150 species of which a minority (13 species) have been implicated in the pathogenesis of disease in humans. The most common of these are *C. albicans* and among the NAC species, *C. glabrata, C. krusei, C. parapsilosis*, and *C. tropicalis.* (21,24,28) Furthermore, approximately two thirds of *Candida* species are unable to grow at temperatures around 37°C rendering them unable to successfully dwell and colonize human hosts. (35)

Candida species usually exist as human commensals as part of the normal flora found on the skin, oropharyngeal cavity, gastrointestinal tract and vaginal tract. (37) *Candida* can also be found on other mammals, birds, arthropods, fish, plants, as well as soil, water and airborne particles. (38) Pathogenicity of *Candida* is initiated once the immune defenses of the host have been compromised and/or following events resulting in a disruption or imbalance of the host's normal commensal flora. (37)

2.1 PATHOGENESIS OF CANDIDA SPECIES

Broadly speaking, the pathogenicity of *Candida* species can be attributed to two primary virulence factors:

1. adherence and biofilm formation on host tissue and medical devices
2. host tissue-damage by the production of hydrolytic enzymes such as phospholipases, proteases and haemolysins. (34,39)

2.1.1 Adherence and biofilm formation

Adherence to host tissue is the initial step for *Candida* species to ensure persistence of the organism within the host, which ultimately leads to the establishment of disease. Specific cell wall proteins (adhesins), allow *Candida* to adhere to human tissue as well as to other surfaces such as medical devices. (34) These adhesin proteins are encoded by different gene families, depending on the specific Candida species. (34)

C. glabrata's adhesins are encoded by the gene family EPA (epithelial adhesin) and have the ability to adapt to a wide variety of environmental conditions. (40) The advantage conferred to the organisms by this adaptability results in an improved ability to adhere to, and subsequently colonise host tissue.

Once adherence to the host tissue has been established, *Candida* species undergo the processes of cell division and proliferation, in order to produce a population of microorganisms incorporated within an extracellular matrix (biofilm). (41) The biofilm, by virtue of its solid matrix, is able to resist the host immune responses and minimize the penetration of antifungal substances. (42) Thus the biofilm contributes significantly to the outcome of patients who have established fungal disease. The attributable mortality rate in patients with bloodstream infections caused by biofilm-positive organisms compared to those without biofilm formation was reported to be as high as 30%. (43)

The formation of a biofilm is influenced both by the *Candida* species, as well as the environment to which the organism is exposed. (41) In particular, *C. albicans* isolates

produce quantitatively and qualitatively superior biofilm matrices in substrate similar to indwelling devices, when compared to NAC species such as *C. parapsilosis*, *C. glabrata* and *C. tropicalis*. (44) In contrast, C. albicans produced the least amount of biofilm on Sabouraud dextrose broth (SDB) containing 8% glucose (similar to milieu of patients receiving total parenteral nutrition via a central venous catheter) compared to *C.tropicalis* followed by *C. parapsilosis*. (43,45) Furthermore, *C. glabrata* was reported as the most frequent organism forming biofilms on indwelling catheters in the presence of urine. (46)

2.1.2 Host Tissue Damage By Hydrolytic Enzyme Production

Host tissue destruction may be expedited by the release of hydrolytic enzymes produced by *Candida* species. The most frequently encountered enzymes are secreted aspartyl proteinases, phospholipases, lipases and haemolysins. (34)

Secreted aspartyl proteinases contribute to pathogenicity by digesting mucosal membranes and molecules of the host immune system. (34) Phospholipases and lipases are involved in the hydrolysis of fatty acids and triacylglycerol components of host cells. (34) *C. albicans* strains, in particular, show significant extracellular phospholipase activity which contributes to the enhanced virulence of this species. (47)

2.2 RISK FACTORS FOR NOSOCOMIAL CANDIDA BLOODSTREAM INFECTION

Knowledge of the population at risk for nosocomial *Candida* BSI is imperative for further preventative measures and empiric treatment of the disease. Risk factors can be broadly grouped into defects of host's immunity and effects from the external

environment increasing the probability of acquiring a *Candida* BSI.

2.2.1 Host factors

Once host immune defences have been compromised, *Candida* species, which formerly existed as human commensals, are able to invade, populate and exert its detrimental effects on the host. Paediatric immunocompromised states described in the literature include immunodeficiency disease, malignancy, neutropaenia, bone marrow transplantation, undergoing surgery, critical illness, prematurity, very-low-birth-weight and congenital anomalies. (28)

In particular, South Africa still carries the highest burden of people living with HIV (6,1 million of the global 35,3 million global estimates) at the end of 2012. (48) Of the 6,1 million affected individuals in South Africa, children from zero to fourteen years of age account for 6,7% (410,000) of South Africa's total. (49) Data from the Chris Hani Baragwanath Hospital paediatric medical wards showed an approximate 10-fold increase in the prevalence of HIV infected individuals from 1992 to 1997. (50) Furthermore, in the same period the study reported a longer length of stay, higher readmission rate and a staggering 42% increase in the in-hospital mortality of patients infected with HIV compared to the non-HIV population. (50)

With regards to PICU and HIV, a first-world study in the late 1980's showed case fatality rates of up to 84% in HIV-infected children requiring intensive care. (51) Offering intensive care to this population in a resource poor country such as South Africa remains a difficult decision. (52) However, South African studies that were conducted in 2003 and 2009 have seen a decline in mortality rate of 30% and an increased survival rate up to

64% in the HIV-infected admissions to PICU. (52,53) A possible reason for the improved survival rate could be attributed to the rollout of Highly Active Antiretroviral Treatment to HIV-infected children. (54) With prolonged survival of this HIV-infected population, fungal infections have begun to emerge as a key organism in causing morbidity and mortality in the immunocompromised host. (28,55)

Candida species remain one of the most common opportunistic infections in children infected with HIV. (55,56)In the late 90's, a European study among HIV infected individuals reported *C. albicans* as the most frequently isolated pathogen, followed by *C. tropicalis* and *C. glabrata*. (57) It is the response of the host's immune system, which determines the extent of *Candida* pathogenicity. Manifestations of *Candida* infection have been described as benign oral mucosal overgrowth to widespread haematogenous dissemination causing organ compromise in the host. (55)

Invasive fungal infections are also an important cause of morbidity and mortality among neutropenic patients. (58) A 2015 retrospective analysis in Turkey showed a 3.1 fold increase in mortality among patients with neutropenia and Candidaemia. (59) Radiation, chemotherapy, bone marrow failure, or the replacement of hematopoietic cells in the bone marrow by malignant cells, are the main causes of neutropenia. (60) Neutropenia in itself is a significant risk factor for the development of systemic Candida disease. (60) The main portal of entry is via the alimentary tract and when disrupted, invasion to the main bloodstream ensues. (60) Candida infection manifestations range from oropharyngeal candidiasis, oesophageal candidiasis, candidaemia, acute disseminated candidiasis or chronic disseminated candidiasis. (60)

2.2.2 Environmental factors

Environmental risk factors described are as follows:

- endotracheal intubation with mechanical ventilation
- central venous lines
- arterial lines
- urinary catheter
- hypoalbuminaemia
- male gender
- neutropaenia
- total parenteral nutrition (TPN)
- prolonged ICU stay
- broad-spectrum antibiotics
- bacterial infections
- corticosteroids
- blood transfusions and
- peritoneal or haemodialysis. (24,26-28,59)

Specifically, two factors were independently associated with the development of candidaemia in the PICU, namely the presence of a central venous catheter (CVC) and the receipt of a glycopeptide antibiotic (Vancomycin) or antimicrobial activity against anaerobic organisms for more than three days. (27) A study in 2015 showed a 20.5 fold increase in mortality due to failure of removal of a CVC in patients with candidaemia. (59)

The first line of defense in the human body against infections is the presence of physical barriers, such as the skin and other epithelial surfaces, to prevent the entry of foreign micro-organisms. CVC's penetrate these natural barriers of the body and allow for the invasion of *Candida* species into otherwise sterile sites. (28,31) CVC placement for three days or longer, has been associated with a three-fold risk for developing disseminated candidiasis in children with candidaemia. (61)

The glycopeptide antibiotic Vancomycin has activity against anaerobic bacteria in the gastrointestinal tract. (27) Under normal circumstances anaerobic gut flora contribute to the host's defense mechanisms by minimizing the growth of potentially pathogenic organisms such as *Candida* species. By eliminating this protective mechanism by the usage of antimicrobials, the probability for Candida species to colonize the gastrointestinal tract, and then subsequently invade the host, rises. (27)

Host and environmental factors frequently co-exist, especially in the PICU setting where critically ill patients with varying degrees of immunosuppression are exposed to multiple invasive procedures.

2.3 DIAGNOSIS OF CANDIDA BLOODSTREAM INFECTION

The definitive diagnosis of *Candida* BSI has represented a daunting challenge to both the clinician and the microbiologist. (62) Traditionally, the gold standard for the diagnosis of fungaemia has been isolation of the organism by blood culture from a normally sterile site. (62,63) Identification of yeasts is by carbohydrate assimilation and/or fermentation together with their macroscopic and microscopic morphologic features after growth on specialized culture media. (63) Disappointingly, the sensitivity of blood culture has

remained at a paltry 50%. This sensitivity is further compromised by technical errors such as use of non-sterile sites, insufficient blood sample volume and inadequate incubation time. Samples drawn from a non-sterile site make it virtually impossible to distinguish between colonization and invasive disease. Furthermore, due to the sluggish growth of yeast, the timeous initiation of antifungal therapy may be delayed, so much so, that the decision to start antifungal therapy is often an empiric one. (62,63)

Due to the poor yield of blood culture for the diagnosis of fungaemia, other tests using non-culture based tools have been developed and are currently used in conjunction with conventional blood culture methods. These tests include the (1,3)- β-D-glucan assay (BDG), fungal DNA using polymerase chain reactions and antibody assays.

Detection of a fungal cell wall component namely (1,3)- β-D-glucan (BDG) has been approved by the Food and Drug Administration of the US (FDA) as a diagnostic adjunct for invasive fungal disease including *Candida* species. (62) Being a fungal cell wall constituent, BDG can be used to detect the presence of most fungal species except for zygomycetes and *Cryptococcus* (63) The benefits of BDG as a biomarker when excluding invasive Candida infection was demonstrated by its negative predictive value of almost 99%. (64) However, false-positives are also common and measurement of BDG may be affected by exposure to glucan-containing gauze, intravenous administration of albumin, haemodialysis or Gram-positive bacteraemia such as *Streptococcus*. (62,65) It has been reported that certain Gram-positive bacteria such as *Streptococcus* and *Alcaligenes* also produce glucan-like polymers, which may falsely elevate the BDG levels. (66)

A rapid and more sensitive test using the polymerase chain reaction (PCR) method for the identification of Candida is being utilized more frequently in the PICU setting. (67) Isolates can be identified within 7 hours when compared to conventional phenotypic methods taking up to 48 to 72 hours long. (67)

Detection of antibodies against *Candida albicans* germ tubes has also been described. (63) However most critically ill patients may be unable to mount an adequate immune response, thus rendering tests utilizing the detection of antibodies as potentially ineffective. More specific markers of fungal components such as the cell wall and cytoplasmic antigens have provided an alternative means of providing a diagnosis. (63)

Attention has also been drawn to other potential biomarkers associated with the presence of fungal disease. The presence of thrombocytopaenia has been used as a marker for sepsis in critically ill patients. (68) Studies in the neonatal population have shown an association between thrombocytopaenia and fungal sepsis. (69-71) However scarce data exists for the non-neonatal paediatric population and further investigation into this phenomenon may be helpful in identifying patients at high risk of having a *Candida* BSI.

2.4 TREATMENT OF CANDIDA BLOODSTREAM INFECTION

Treatment of Candida BSI relies on timeous administration of antifungal therapy based on the polyene, azole or echinocandin families. (32,72) Choice of antifungal therapy must be based on knowledge of local epidemiology, organism susceptibility, exposure to previous antifungal agents and the patient's clinical status.

The polyene antifungal (Amphotericin B) has been the most commonly used agent in the treatment of candidaemia, owing to its broad-spectrum activity. (73-75) However, the conventional Amphotericin B deoxycholate is known for its dose-limited toxicity, of which nephrotoxicity has been most frequently described. (74,76) Amphotericin B is a fungicidal agent disrupting the cell membrane by binding to ergosterol. Subsequently pores are formed in the membrane causing it to become leaky and depolarize. (77) In an attempt to improve the therapeutic index and provide a safer alternative, three forms of the agent were developed. These lipid-containing forms are amphotericin B lipid complex, liposomal amphotericin B, and amphotericin B colloidal dispersion. (74) Currently, the high cost of these lipid-containing forms does not make them widely accessible in a resource-limited setting such as the Chris Hani Baragwanath Academic Hospital (CHBAH). However as the cost declines the newer forms of Amphotericin B will most likely play a significant role in the treatment of Candida BSI. (74) Despite its broad-spectrum activity and minimal intrinsic and acquired resistance, owing to its dose-limited toxicity, the polyene class is still limited in treatment when compared to the azoles and echinocandins. (77)

The azoles (fluconazole, voriconazole) are also a widely used antifungal drug with no nephrotoxic effects as compared to Amphotericin B. (77) This class inhibits cytochrome P-450 dependent enzyme C-14α−demethylase. This enzyme is essential in the conversion of lanosterol to ergosterol, which forms part of the fungal cell membrane. (77) Despite its' low cytotoxicity, this class also displays significant limitations, namely: the development of resistance with prolonged use and drug-drug interactions, specifically drugs metabolized by the cytochrome P-450 isoenzyme. (78,79)

The echinocandins (caspofungin) are an emerging class of antifungal agents. FDA approval for Caspofungin was granted in 2001. Echinocandins inhibit cell wall synthesis by inhibiting the enzyme BDG-synthase, an essential component for wall synthesis. (78) Caspofungin was found to be as effective as amphotericin B, while exhibiting fewer drug-related side effects and a 72% favourable response over the standard amphotericin B group in the treatment of invasive candidiasis. (79,80)

Caspofungin, fluconazole, an amphotericin B formulation or combination therapy have been suggested by recent guidelines for the treatment of invasive candidiasis. (72) Other studies have suggested caspofungin and amphotericin B as first line therapies in neutropenic and critically ill patients where fluconazole-resistant *Candida* isolates may predominate. (79) However, patient therapy needs to be targeted and individualized to provide the most cost effective, therapeutic and least toxic treatment to the critically ill paediatric patient. (72,79)

2.5 MORTALITY ASSOCIATED WITH CANDIDA BSI

Mortality due to candidaemia in hospitalised patients remains high. (81-83) Mortality rates of approximately 60% were reported in observational studies, owing to nosocomial *C. albicans* sepsis. (24,75,82,83) This could be due to *C. albican's* enhanced virulence by destroying host tissue through phospholipases. (47) However, non- *albicans* species are seen to be on the rise as significant causes of mortality, especially in the premature and immunosuppressed populations. (25,84)

This mortality is found to be increased due to other environmental factors shown in recent studies investigating risk factors for mortality in candidaemic pediatric patients. (59,85) A 2016 Brazilian study found increase in mortality in patients with sepsis, septic shock, acute renal insufficiency, mechanical ventilation and dialysis. (85) In 2015, a Turkish study showed a significant result of a 23-fold increase in mortality of patients with candidaemia, (more than 3 months of age) where failure to remove CVC's were noted. (59)

Furthermore, mortality rates were affected by the timing of initiation of antifungal therapy. An American study carried out from 2002 to 2005 showed a ten percent increase in mortality rate for every day that antifungal therapy was delayed. (29) Consequences of failure to treat with antifungal therapy resulted in more than 25% of deaths over a four year period. (83)

2.6 WHAT THIS STUDY ADDS

This study aims to describe the characteristics of patients with nosocomial fungal sepsis in the PICU at South Africa's largest hospital CHBAH. There is overwhelming literature regarding fungal sepsis and the neonatal population however, a paucity of studies exists among the older pediatric population requiring intensive care. With the emergence of fungal sepsis as one of the leading causes of mortality in the PICU, an understanding of the risk factors may aid in the development of future guidelines for the empiric treatment of fungal nosocomial sepsis in the South African setting. This study is the first to be undertaken among a predominantly black non-neonatal paediatric population at a hospital serving a community with a high burden of HIV disease.

CHAPTER TWO

2.1 OBJECTIVES

The objective for this study was to describe the characteristics of patients who had developed a nosocomial fungal bloodstream infection in the PICU at the Chris Hani Baragwanath Academic Hospital.

The specific objectives were to:

1. Determine the incidence of fungal infections in the PICU
2. Describe the demographics of patients with nosocomial fungal bloodstream infections in the paediatric intensive care unit
3. Describe the PICU factors associated with nosocomial fungal bloodstream infections.

2.2 METHODS

2.2.1 Study design

This study was a retrospective descriptive study.

2.2.2 Study population

All patients aged 0-16 years, admitted to the PICU at Chris Hani Baragwanath Academic Hospital (CHBAH) from January 2008 through December 2011. CHBAH is an academic tertiary hospital situated in Gauteng province with 3200 beds of which 408 are paediatric beds. It currently serves Soweto and surrounding communities. The PICU consists of an

8-bed critical care unit that has an estimate of 360 annual admissions. All patients admitted to the PICU were identified using the PICU admissions database.

2.2.3 Definition of Case Patients

Case patients were patients who had developed a nosocomial fungal BSI. Nosocomial fungal BSI was defined by proven fungal species yielded on blood culture that was taken at least 48 hours after admission to PICU, in addition to the presence of SIRS. Case patients were identified from the microbiology database at the National Health Laboratory Services (NHLS). Once patients were identified, databases were retrieved from the PICU records department situated at the CHBAH.

Patients with incomplete records and infected simultaneously with fungal and non-fungal organisms on blood culture were excluded.

2.2.4 Data Collection

All blood cultures, which deemed a positive fungal growth between 2008 and 2011 were identified through an extensive search performed by an NHLS accredited data analyst. Names of patients were identified and files were retrieved from the CHBAH ICU records department.

A data collection tool, RedCap was used to collect patient data. (Appendix B). This data sheet included four sections namely: patient demographics, background, laboratory results and PICU-related factors.

Demographics dealt with patient sex and age at time of diagnosis. Background factors included primary condition, pre-ICU major operation (any surgery requiring general anaesthesia) and HIV status. Laboratory data collected included organism yielded on blood culture and drug susceptibility at the time of SIRS. ICU-related factors included devices (CVC, urinary catheter, arterial-line, intercostal chest drain, endotracheal tube and tracheostomy devices), dialysis (haemo-dialysis and peritoneal dialysis), class of antimicrobial therapy used for more than 24 hours, receipt of TPN, immunosuppressant usage and three or more blood product transfusions. ICU-related factors were selected by review of previous studies with similar objectives.

2.2.5 Statistical Analysis

For descriptive purposes, means, medians, ranges (min-max) and proportions (percentages) were reported for categorical variables.

2.2.6 Ethical considerations

Ethics approval was obtained from the Committee for Research in Human Subjects at the University of the Witwatersrand (Medical) and the Medical Advisory Committee of the Chris Hani Baragwanath Academic Hospital. Permission to conduct research was obtained from the director of the PICU at CHBAH. The National Health Laboratory Service granted permission to access patient data from the central database.

CHAPTER THREE

3. RESULTS

3.1 Incidence

There were a total of 1085 admissions to the CHBAH PICU from January 2008 to December 2011. Thirty-five patients (3%) with positive fungal blood cultures were identified during the four year period. Fourteen of the 35 files were missing from the data department and four patients did not fit the inclusion criteria. Thus, 17 cases were included in the study.

3.2 Characteristics

The demographics of the 17 eligible patients are summarized in table 3.1. The gender distribution was similar with 53% female (9/17) and 47% males (8/17). Patient age ranged from day 1 of life to 11 years 5 months with a median age of 10 months. Age distribution was compared among male and female groups. Males presenting at PICU had a higher median age (1 year 6 months) while females presented at a younger age (4 months). Among the patients with HIV results available (n=12, 70%), the vast majority was HIV negative (92%) with only one patient with confirmed fungal sepsis testing HIV positive. The remaining 5 patients (30%) did not have an HIV result available at the time of their PICU admissions.. The time from admission up to the time where fungal sepsis occurred, ranged broadly from two to 122 days (median =9).

Table 3.1 Characteristics of PICU patients who developed nosocomial fungal sepsis

Gender	
Male	8 (47%)
Female	9 (53%)
Age distribution (All patients)*	10m (1d-11y5m)
Male age distribution*	1y6m (1m-11y5m)
Female age distribution*	4m (1d-9y)
HIV status	
Negative	11 (65%)
Positive	1 (6%)
Unknown	5 (29%)
Pre-ICU operation	
Yes	5 (29%)
No	12 (71%)
Onset of sepsis from admission* (days)	9 (2-122)

* Median (range: min-max)

3.3 Admission Diagnoses

The most common group of admission diagnoses was lower respiratory tract infections with nearly a third (29%) of patients admitted for either bronchopneumonia or a lobar pneumonia. A summary of the admission diagnoses is presented in table 3.2.

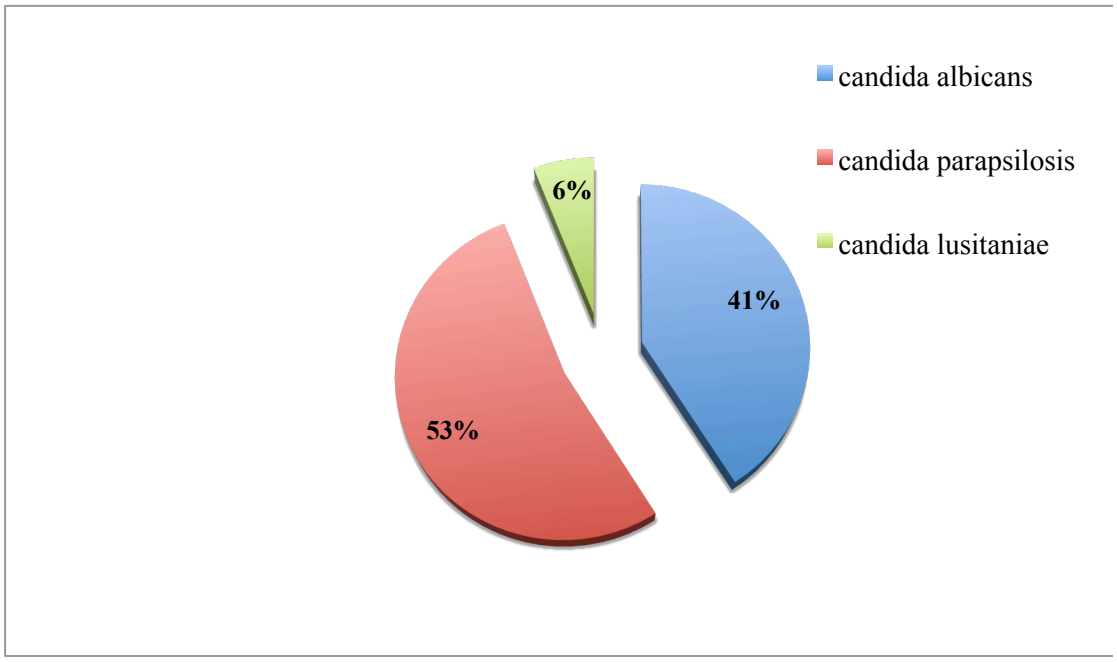
Table 3.2 Diagnoses of patients who developed nosocomial fungal sepsis

	n (%)
Respiratory	
Bronchopneumonia	3 (18%)
Lobar pneumonia	2 (12%)
Gastrointestinal	
Acute gastroenteritis (traditional medicine ingestion)	3 (18%)
Haematology-Oncology	
Acute lymphoblastic leukaemia (ALL)	1 (6%)
Acute myeloid leukaemia (AML)	1 (6%)
Osteogenic sarcoma	1 (6%)
Trauma	
Pedestrian vehicle accident	2 (12%)
Cardiovascular	
Congenital cardiac defect	1 (6%)
Urogenital	
Urinary tract infection	1 (6%)
Surgical	
Subphrenic abscess	1 (6%)
Intussusception	1 (6%)

3.3 Fungal isolates

The most common isolates from the paediatric intensive care unit were *Candida parapsilosis* (n=9), followed by *Candida albicans* (n=7).

Figure 3.1 Fungal isolates from blood culture in PICU



3.4 Susceptibilities

Susceptibilities were reported for 15 of the 17 (88%) fungal isolates. No susceptibilities were specified for *C. lusitaniae* and one of the *C. albicans* isolates. The remaining fifteen organisms' susceptibility patterns are summarized in Table 3.3. Seventy five percent (3/6) of the *C. albicans* group was susceptible to fluconazole ,an additional 16% (1/6) to voriconazole and all reported isolates remained sensitive to Amphotericin B (6/7). One of the six (17%) *C. albicans* isolates was resistant to both fluconazole and voriconazole. In the *C. parapsilosis* group, 22% were susceptible to fluconazole, 67% to voriconazole and all isolates

remained sensitive to Amphotericin B. One of the nine (11%) *C. parapsilosiss* isolates was resistant to both fluconazole and voriconazole..

Table 3.3 Reported Susceptibility to Antifungals

Organism (n)	Fluconazole Sensitive	Voriconazole Sensitive	Amphotericin Sensitive
C. parapsilosis (9)	2 (22%)	6 (67%)	9 (100%)
C. albicans (6)	4 (67%)	5 (83%)	6(100%)

3.5 ICU related factors

All of the patients with nosocomial fungal sepsis were found to have central venous catheters in situ (100%). Fourteen of the 17 patients received mechanical ventilation (82%). The most common antimicrobial received during the time of onset of sepsis was penicillin (71%). The other ICU related factors and subsequent findings on steroid use, TPN and other associated factors are summarized in table 3.4, which was found to be present in less than 50% of the patients.

Table 3.4 ICU related factors in patients who developed nosocomial fungal sepsis

ICU related factors	n (%)
Central venous catheter	17 (100%)
Mechanical ventilation	14 (82%)
Arterial line	12 (70%)
Steroids	8 (47%)
Total parenteral nutrition	6 (35%)
Multiple blood product transfusions (>3)	5 (29%)
Intercostal chest drain	2 (12%)
Antimicrobial therapy:	
Penicillin	12 (71%)
Antifungal	9 (53%)
Carbapenem	7 (41%)
Glycopeptide	5 (29%)
Cephalosporin	4 (24%)
Aminoglycoside	3 (17%)

CHAPTER FOUR

4. 0 Discussion

Local studies regarding epidemiology and factors associated with nosocomial fungal sepsis in the PICU is scarce. Nosocomial fungal sepsis is becoming an increasingly important subject of research owing to its high contribution to morbidity and mortality.

The aim of this study was to determine the incidence of nosocomial fungal sepsis, and to describe the demographics and PICU related factors of these affected patients. Knowledge regarding the trends of fungal organism growth and its associated factors are beneficial to the clinician when initiating treatment. Results from the analysis are discussed in this chapter, in light of other published studies.

4.1 Incidence

The incidence of candidaemia in the CHBAH PICU is 3.2 cases per 100 admissions. Thirty-five candidaemias were diagnosed in 1,085 patients (32.3 episodes per 1,000 ICU patients). These results are comparable to developed countries where the incidence lies between 1,7 to 10 episodes per 100,000 patients. (86) Although South Africa is considered to be an economically growing country, it is still considered a developing country where healthcare resources remain a scarce commodity especially in the intensive care setting.

4.2 Patient Demographics

The median age of fungal bloodstream infections was 10 months, which is similar to the findings of PICU studies conducted in Taiwan and Egypt, which both reported a majority of cases of fungal infection among the under-one age group (31,86).This could possibly be due to the vulnerability of this younger age group to serious diseases. These findings are in contrast to two other studies, which found most subjects with candidaemia to be over one-year of age. (87,88) The first study, performed in India (2011) found most patients in the 1 to 15 year old age group. (88) The second study, a case-control study in Turkey (2010) investigating the risk factors for candida in PICU reported a median age of 7.5 yrs. (87)

Gender distribution was fairly similar with an insignificantly higher percentage of females (53%). These findings are different to other studies from developing and developed countries. Male predominance was found in the Egyptian PICU study where 56.7% were male and 43.3% female. (86) An American study also showed a slightly higher male predominance (55.4%) in candidaemia infections (25).

Despite the high HIV burden in South Africa, 65% of cases were HIV negative and only one child (six percent) was confirmed to be HIV positive, thus the association between HIV and fungal sepsis could not be explored further. Kumar et al found 3.3% (7/210) association of HIV positive children and fungal sepsis. (88)

Of concern however, is the high proportion of subjects with unknown HIV status (29%). Three of the five patients had a medical diagnosis and the remaining two were admitted from the trauma unit, having both been involved in pedestrian vehicle accidents. At Chris Hani Baragwanath Academic Hospital, paediatric medical cases are referred from the general medical intake ward (ward 36). Here, patients are stabilized and relevant serological and radiological tests ordered prior to PICU referral. According to the hospital's paediatric policy, ward 36 is a crucial area where the patients' HIV status is either confirmed or investigated if unknown status. If the mother reveals that she is HIV positive during history-taking, an HIV-PCR is done on the patient provided the patient is under 18 months of age. If the patient is 18 months or older a confirmatory ELISA is taken and results followed up by the attending unit on call. However, if the mother reveals that she has been tested HIV negative, a confirmatory ELISA is done on the mother only and not on the patient. The three medical cases who had an "unknown" HIV status could possibly have had a mother who was HIV negative and a subsequent ELISA done on the mother, hence the actual HIV test not reflecting under the child's details. Or, the attending unit on call did not include an HIV test in their initial workup due to human error. The two trauma cases that were also of HIV "unknown" statuses are probably due to the trauma unit not requiring a mandatory HIV test on admission.

4.3 Admission Diagnoses

Admission diagnoses ranged across medical, surgical and trauma cases. Lower respiratory tract infections (LRTI) were shown to be the most common diagnosis among children with fungal nosocomial sepsis. A possible reason for patients with a LRTI

developing nosocomial fungal sepsis could be the prolonged stay in PICU due to their dependence on mechanical ventilation. The combination of prolonged exposure to nosocomial pathogens and contact with endotracheal tubing could form favourable conditions for the colonization and subsequent infection of nosocomial fungal pathogens (34).

Following LRTI's, haematology-oncology (18%) and acute gastroenteritis cases (18%) accounted for the second most common conditions with candidaemia. Similarly, an epidemiological study in Turkey also showed haematological malignancy as the second-most common underlying diagnosis. (24)

4.4 Organisms

C.albicans have accounted for the majority of Candida isolates among children during the 1990's and early 2000. (25-27,31) However from the mid 2000's an emergence of non-*Candida albicans* species, particularly *C. parapsilosis* was observed (89,90). These findings are similar to a Mexican study conducted in 2003 where *C. parapsilosis* attributed 52% in the pediatric population (90). This trend was also noted in a Spanish study showing a higher percentage of nosocomial infections due to *C. parapsilosis* (47%) and 37% due to *C. albicans* (62).Similarly, our study found *C.parapsilosis* as the predominant organism (53%) causing nosocomial fungal sepsis, followed by *C. albicans* (41%).

This rise in *C.parapsilosis* isolates can be attributed to three possible reasons. Firstly, poor infection control remains a major factor contributing to the spread of *C. parapsilosis*

despite the institution of ICU infection control programmes (24,91). An American study showed poor hand hygiene as an emerging cause of *C.parapsilosis* outbreaks in the neonatal ICU (91). Secondly, the organisms' ability to form biofilms in glucose containing media (eg. Parenteral nutrition) as well as its high propensity to adhere to medical devices may enhance its proliferation and survival in the human host in the PICU setting, where parenteral nutrition and intravascular catheters and other exogenous devices are common place. (34). Lastly, with the advent of newer techniques aiding in Candida species differentiation, the isolation of *C. parapsilosis* using CHROMagar ® has become more feasible (26, 36, 82)

4.5 Organism Susceptibility

Antifungal susceptibility and resistance patterns were documented in this study. This is the first study to provide this information in a local setting, thus allowing for improved empiric prescription in the PICU. Six of the 15 (40%) organisms showed susceptibility to fluconazole. This is strikingly different from an Iranian study, which showed 96.6% susceptibility to fluconazole (76). Additionally, this Iranian study showed both *C. albicans* and *C. parapsilosis* equally susceptible to fluconazole (76). However, our results showed the majority of isolates susceptible to fluconazole were *C. albicans* (67%).

In the *C. parapsilosis* group, a higher proportion was sensitive to voriconazole (67%) as opposed to fluconazole (22%). This is interesting of note as the unit's policy is to initiate fluconazole for suspected or proven fungal sepsis. Fluconazole is regarded as a favourable option as it is effective against most Candida species, has a low side-effect

profile and is also a cost-effective therapy (92). With the risk of fluconazole resistance among non-*Candida albicans* species, together with the higher incidence of *C. parapsilosis* in the CHBAH PICU, future policy recommendations could possibly be open for discussion within the unit (93). In view of these local findings, the initiation of voriconazole, instead of fluconazole could be a future recommendation in the empiric treatment of suspected nosocomial fungal sepsis at CHBAH PICU. However, in lieu of the small number of subjects, more research is needed in this field and prospective studies with a larger sample size are needed to confirm these findings.

4.6 ICU factors

Central venous catheters (CVC) were found in all the patients included in the study and arterial lines in 70% of patients with candidaemias. The CVC findings support the study done by Zaoutis et al, presenting CVC to be an independent risk factor for the development of candidaemia in PICU (27). A Turkish study in 2011 also found patients with candidaemia had higher rates of CVC. (87) A retrospective analysis in 2012 showed an alarming 23-fold increase in mortality due to failure of CVC removal. (59) Given that the placement of invasive vascular catheters is usually necessary in ICU patients, these findings emphasize the need for timely removal of such devices as a means to minimize the potential risk of nosocomial infections.

Furthermore, an American study showed a strong statistical significance between CVC's and *C. parapsilosis* (84). Central venous catheters introduce a portal of entry into the main vascular system and thus aiding the colonization and growth of opportunistic

infections (27). The placement of invasive catheters (CVC specifically) is routine in all patients admitted to PICU at CHBAH. It should be emphasized that their placement be performed under strictly sterile conditions, as their placement in critically ill patients poses a great risk in developing candidaemia. (27)

Among the ICU procedure category, mechanical ventilation also featured significantly in the study. Eighty-two percent of patients with nosocomial fungal sepsis were on mechanical ventilation. These findings are much higher than an American study showing 37% mechanically ventilated children (411 of 1118 hospitalized paediatric patients) who developed a nosocomial fungal infection. (27) A possible reason could be due to the limited resources and availability of ICU beds in South Africa, compared to first-world countries. This shortage means that patients who should be admitted earlier to PICU are kept in high care areas where treatment and ventilation may be sub-optimal, while awaiting an ICU bed. This delay could compromise the patient, resulting in a more severe phenotype of the presenting condition and possibly the development of a greater number of complications, which would thus necessitate a longer PICU stay.

Mechanical ventilation has been shown to be associated with candidaemia. (59,94) A case-control study showed a higher rate of mechanical ventilation in the candidaemia group. (94) Furthermore, Karadag-Oncel et al reported a 7.4-fold increased risk of mortality with candidaemia in mechanically ventilated patients. (59)

Lack of resources could also contribute to poor hygiene of equipment, re-usage of ventilation tubing and poor hand-washing contributing to prolonged ventilation. This study did not investigate how long it took for ventilated patients to develop nosocomial fungal sepsis so correlations between exposure and illness could not be drawn.

Corticosteroid usage has been described as a risk factor for nosocomial fungal sepsis (27,31,95). This has been hypothesized to the modulation of the immune system by corticosteroid therapy, crippling the patient's ability to prevent dissemination of candida infections (95). Almost half of the subjects in this study (47%) were documented to be on corticosteroid therapy at the time of nosocomial sepsis. However, the duration was not documented therefore no correlation between duration of treatment and development of nosocomial infections could be made.

Hyperalimentation has also been shown to be a suitable environment for the growth of Candida owing to its high glucose content (34). This study showed 35% of patients with a nosocomial fungal infection to have been on TPN. These findings are similar to Zaoutis et al's study mentioned above showing 33% of their patients having received hyperalimentation. (27) An American study showed exposure of parenteral nutrition for 12 days to be a risk factor for potential candidaemia in hospitalized patients . (26) Once again, the duration of exposure was not captured in this study so results from the aforementioned study could not be compared.

Broad-spectrum antibiotic use has been described as a risk factor for the development of nosocomial fungal sepsis (24,27,95). Antibiotic use has been shown to eliminate normal flora and thus encourage the colonization and growth of nosocomial organisms (96). This current study documented those patients who had received more than 24 hours of antibiotics and what class they had been on. Unfortunately the total duration of antibiotic exposure was not investigated so no comment regarding prolonged antibiotic use could be made.

In this study, the most frequently used antibiotic in the CHBAH PICU was of the penicillin group (71%). This high percentage of penicillin use could account for CHBAH's practice of prescribing either: ampicillin as the first-line antimicrobial for new admissions; or piperacillin-tazobactam used as a second-line option for a suspected nosocomial sepsis in the general paediatric ward. An American study found that patients receiving 3 or more days of vancomycin or an antimicrobial with anaerobic cover (piperacillin-tazobactam, Carbapenem, ceftriaxone, metronidazole, clindamycin etc), were independently associated with the development of nosocomial candidaemia in the PICU (61). Based on these findings, patients who are receiving piperacillin-tazobactam in CHBAH PICU should not be prescribed more than 3 days unless a specific indication exists, in the hopes of possibly decreasing the risk of developing a nosocomial fungal infection.

4.7 Potential limitations of the study

This study has potential limitations. As this study was a retrospective review of records, recruitment of patients relied solely on the adequacy of records. Many potential candidates were excluded from the study due to inadequate or absent records.

The lack of a control group was a great limitation in this study. Having a control group would have been beneficial as a comparison to substantiate and investigate further the associated risk factors in this study.

The small sample size made it difficult to find significant relationships within the data. This small sample size could also give a false representation of patient distribution.

The data collection tool did not include duration of treatment such as corticosteroids, antimicrobials, ventilation etc. These factors could have assisted in exploring the relationships between treatment and development of nosocomial fungal sepsis.

5.0 CONCLUSION

This study is the first in South Africa investigating factors associated with nosocomial fungal sepsis at CHBAH PICU. The incidence is higher than what has been reported in some other studies. The majority of patients were less than a year of age and all the patients had CVC's. However this might have been due to the fact that it is a general practice for the unit to routinely insert CVC's. Although there was a predominance of C. parapsilosis that is susceptible to voriconazole, the study sample size was small and this needs to be further investigated to revise the empiric antifungal choice at the PICU at CHBAH.

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APPENDIX A – REFERENCE VALUES

Age Group	Heart Rate (beats/min)	Respiratory rate (breaths/min)	Leukocyte count (leukocytes x 10^3/mm)
0 days to 1 wk	> 180	> 50	> 34
1 wk to 1 mo	> 180	> 40	> 19.5 or < 5
1 mo to 1 yr	> 180	> 34	> 17.5 or < 5
2-5 yrs	> 140	> 22	>15.5 or < 6
6-12 yrs	> 130	> 18	> 13.5 or < 4.5
13 to <18 yrs	> 110	> 14	> 11 or <4.5

APPENDIX B- DATA COLLECTION TOOL

STUDY NO:

Demographics:

Age __yr __mo

Gender: M□ F□

HIV status: Pos □ Neg□

Background:

DOA: __/__/__

Date of Sepsis: __/__/__

Pre-ICU major op: Y□ N□

Primary Condition: _____

Blood culture: _____

Sensitivity: _____

ICU-related factors:

CVC: Y□ N□

A-line: Y□ N□

Chest Drain: Y□ N□

Tracheostomy: Y□ N□

Antibiotic classes (given ≥24 hrs):

- Penicillin Y□ N□
- Cephalosporin Y□ N□
- Aminoglyc Y□ N□
- Carbapenem Y□ N□
- Glycopepep Y□ N□
- Antifungal Y□ N□
- TMX Y□ N□
- Rifampicin Y□ N□
- Metronidazole Y□ N□

Haemodialysis Y□ N□

Peritoneal dialysis Y□ N□

Mechanical vent Y□ N□

Immunosuppres Y□ N□

Multip Transfu Y□ N□

APPENDX C – ETHICS CLEARANCE CERTIFICATE

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr Seung-Hye Ahn

CLEARANCE CERTIFICATE	**M121003**
PROJECT	Factors Associated with Nosocomial Fungal Sepsis among Patients in the Paediatric Intensive Care Unit at th CH Baragwanath Academic Hospital
INVESTIGATORS	Dr Seung-Hye Ahn.
DEPARTMENT	Department of Paediatrics
DATE CONSIDERED	26/10/2012
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 26/10/2012 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Dr KD Naidoo

DECLARATION OF INVESTIGATOR(S)
To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

APPENDIX D – HOSPITAL PERMISSION LETTER

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

MEDICAL ADVISORY COMMITTEE
CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

PERMISSION TO CONDUCT RESEARCH

Date: 08 November 2012

TITLE OF PROJECT: Factors associated with nosocomial fungal sepsis among patients in the paediatric intensive care unit at the Chris Hani Baragwanath Academic Hospital

UNIVERSITY: Witwatersrand

Principal Investigator: Dr S-H Ahn

Department: Paediatrics

Supervisor (If relevant): Dr K Naidoo

Permission Head Department (where research conducted): Yes

Date of start of proposed study: December 2012
Date of completion of data collection: January 2013

The Medical Advisory Committee recommends that the said research be conducted at Chris Hani Baragwanath Hospital. The CEO /management of Chris Hani Baragwanath Hospital is accordingly informed and the study is subject to:-

- Permission having been granted by the Committee for Research on Human Subjects of the University of the Witwatersrand.
- the Hospital will not incur extra costs as a result of the research being conducted on its patients within the hospital
- the MAC will be informed of any serious adverse events as soon as they occur
- permission is granted for the duration of the Ethics Committee approval.

.....
Recommended
(On behalf of the MAC)
Date: 08 November 2012

.....
Approved/Not Approved
Hospital Management
Date: 12/11/12

APPENDIX E – TURNITIN REPORT

FINAL20161103.docx by Null Null

From FACTORS ASSOCIATED WITH NOSOCOMIAL FUNGAL SEPSIS AMONG PATIENTS IN THE PAEDIATRIC INTENSIVE CARE UNI (kb09a520am2XHSyOQw8z1xzb9G793h05L407HP8FiB005DQK5ly0ft96DuBfS2tdp9D0owMMBzcwLXf52hMbPKI09afHeMTuPHx)

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