Direct treatment costs of invasive candidiasis in haematology patients at a South African private hospital

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DECLARATION

In fulfilment of the requirements of the coursework degree of Masters in Pharmacy in the Discipline of Pharmacoeconomics, University of KwaZulu-Natal, Durban, South Africa, I, Ms Rozlyn Cruickshank, declare as follows:

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ii. The research reported in this dissertation, except where referenced, is my original work.

iii. This dissertation does not contain other person's text, tables, data, graphs or other information, unless specifically acknowledged as being sourced from other persons.

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ABBREVIATIONS AND ACRONYMS

AML – Acute myeloid leukaemia

BSI – Blood stream infection

CANDIPOP - Prospective population study on candidemia in Spain

CDC – Centers for Disease Control and Prevention

CPI – Consumer price index

ECIL – European conference on infections in leukaemia

ECMM – European confederation of medical mycology

EPIC – Extended prevalence in intensive care

ESCMID – European society for clinical microbiology and infectious diseases

GVHD – Graft-versus-host disease

HSCT – Haematopoietic stem cell transplant

IC – Invasive candidiasis

ICER – Incremental cost effectiveness ratio

ICU – Intensive care unit

IDSA – Infectious disease society of America

IFD – Invasive fungal disease

IFI – Invasive fungal infection

IV – Intravenous

KZN – KwaZulu-Natal

LOS – Length of stay

MDHDDS – Maryland hospital discharge data survey

MIC – Minimum inhibitory concentration

NAC – Non-albicans Candida

NCCN – National comprehensive cancer network

NHDS – National hospital discharge survey

PCR – Polymerase chain reaction

RCT – Randomised clinical trial

SA – South Africa

SEP – Single exit price

USA – United States of America

UK – United Kingdom

ZAR – South African Rand

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ABSTRACT

Background: Haematology patients are at a high risk of developing invasive candidiasis (IC). Fluconazole has been the mainstay of prophylaxis and treatment but recently a newer class of therapeutic options, the echinocandins, has seen a considerable improvement in treatment success. However, these agents are associated with substantial acquisition costs when compared to fluconazole.

Objective: This study analysed the direct treatment costs of invasive candidiasis in haematology patients.

Methods: This is a retrospective, single-centre economic analysis of haematology patients with IC, at a private hospital in Durban, KwaZulu-Natal province, South Africa.. The direct medical costs related to managing IC were analysed. These included antifungal administration costs, hospital ward costs, haematologist consultation costs and laboratory costs for blood cultures. Adult patients (≥18 years old) diagnosed with a haematology disorder and a positive blood culture for Candida who were prescribed fluconazole and/or an echinocandin as treatment were included in the study, patients in the three groups were analysed separately and compared.

Results: There was a statistically significant difference for duration of antifungal treatment ($p = 0.013$) and antifungal administration costs ($p = 0.003$) between the three groups. Median overall direct treatment costs per patient were, ZAR110 365 for patients treated with fluconazole, ZAR219 915 for patients receiving an echinocandin and ZAR181 502 (for patients treated with both the antifungals. Overall hospital stay was the biggest cost contributor to the overall cost of treatment.

Conclusion: The results of this cost analysis found that treatment with fluconazole only is considerably less expensive, almost half of the mean daily treatment cost, when compared to an echinocandin only and treatment using both agents is still less expensive than an echinocandin as first line therapy.

Chapter One: Introduction

1.1 Introduction

As is the case in many countries invasive candidiasis (IC) is a problem in South Africa (SA), especially in terms of haematology patients, whose compromised health results in increased morbidity and mortality where initial treatment is delayed or fails. This chapter presents the background to the study, outlines the research problem and the study significance and states the aim and objectives.

1.2 Background

The past 20 years have seen an increase in the severity of illness in hospitalised patients with a substantial rise of invasive fungal infections caused by Candida spp. (Hachem et al., 2008). People are becoming more sensitive to invasive fungal infections, while moulds and yeasts are being more frequently reported as pathogens, increasing the prevalence of opportunistic infections (Yapar, 2014). Factors such as organ transplantation, treatment used to manage HIV/AIDS and malignant diseases, as well as medical advances in intensive care unit (ICU) are contributing factors (Yapar, 2014). Over the past decade, the incidence of candida infections due to non-albicans Candida (NAC) species that are resistant to fluconazole has increased, highlighting the need for an optimised antifungal regimen (Vazquez et al., 2014). Finding an appropriate treatment approach for invasive candidiasis (IC) is therefore important for healthcare settings (Cui et al., 2017). Culture-directed (defined as patients with a diagnostic confirmation of a fungal infection) antifungal therapy provides specific pathogen and susceptibility results for targeted therapy (Armaganidis et al., 2017). However, it has been increasingly recognised that this traditional paradigm is unsatisfactory (Playford, Lipman & Sorrell, 2010) due to the need to wait for a positive culture result, which is associated with high crude mortality rates (Armaganidis et al., 2017). The evidence shows that while a delay in treatment negatively affects the prognosis and impacts on mortality, the overuse of antifungals leads to resistance and wasted resources, thereby escalating healthcare costs (Cui et al., 2017). This has led to the development of early antifungal intervention strategies, such as prophylaxis, pre-emptive, and empiric therapy, which are required to improve patient outcomes (Playford, Lipman & Sorrell, 2010).

In the United States of America (USA) in 2011, candidaemia was the fourth most common hospital acquired bloodstream infection (Kontoyiannis, 2001), and in 2014, Badiee and

Hashemizadeh reported that Candida species remained the third or fourth most frequently isolated organisms in hospital acquired bloodstream infections. The incidence of candidaemia is said to be considerably higher in the USA than in Canada and Europe (Vazquez, 2014). According to the annual surveillance report and antibiotic guide by Lancet in 2017 for the KwaZulu-Natal (KZN) private healthcare sector in South Africa (SA), Candida species are the fourth most frequently isolated organism from blood cultures (Lancet Laboratories, 2017)

Although the incidence and prevalence of Candida species is not well documented in SA, it is well known that C. *albicans* is the most prevalent cause of invasive fungal disease (Glöckner et al., 2011). In the study performed by Mnge et al. (2017), a total of 209 Candida isolates (from 206 clinical samples) were collected during a cross-sectional study among patients at the Nelson Mandela Academic Complex in the town of Mthatha. C. *albicans* accounted for 45.5% (95/209) of the species isolated while 31.1% (65/209) were C. *glabrata*, 12.4% (26/209) C. *tropicalis*, and C. *dubliniensis* accounted for 11.0% (23/209).

The National Institute for Communicable Diseases' GERMS audit report for South Africa,reported that azole-resistant strains of *C. parapsilosis* and *C. auris* dominated in the SA private healthcare sector during 2016, particularly in Gauteng Province. According to the Lancet laboratories Annual Surveillance Report and Antibiotic Guide for KwaZulu-Natal (KZN) Province for 2014 to 2016, more than 50% of non-albicans Candida species are resistant to the azoles, fluconazole and voriconazole, which makes these agents inappropriate for empiric therapy where IC is suspected. The Lancet report stated that echinocandin resistance has not been detected to date, and that empiric therapy choices in the private sector for suspected IC remain an echinocandin or amphotericin B (Lancet Laboratories, 2017). Conventional amphotericin B remains the empiric antifungal agent of choice for candidaemia in the public sector in South Africa (GERMS – SA Annual Report, 2016).

Patients with underlying haematology diagnoses are immunocompromised as a result of malignancy or therapeutic interventions (Vasquez et al., 2014). Neutrophils and mononuclear cells are very important, as they are able to damage and kill yeast cells, hyphae and pseudohyphae, their absence in patients with haematological neoplasms resulting in invasive fungal infections (IFIs) being a major threat (Pasqualotto et al., 2006), in spite of the progress made in recent years with supportive care. The threats posed by bacterial and cytomegalovirus

infections have been reduced, and invasive fungal diseases (IFD) are now the main infective cause of mortality in this patient population (Rogers, Slavin & Donnelly, 2011).

Risk factors for IFI in haematology patients includes mismatched donors in haematopoietic stem cell transplants (HSCT), severe acute and extensive chronic graft-versus-host disease (GVHD), as well as associated therapies such as high dose steroids, antithymocyte globulins, and antitumor necrosis factor strategies (Cornely et al., 2011). Other risk factors for invasive candidiasis (IC) in these patients include neutropenia, mucositis and the presence of central venous catheters (Lamoth et al., 2018). Candidaemia is the most frequent bloodstream fungal infection affecting these individuals (Pasqualotto et al., 2006), while the proportion of non-albicans Candida species, in particular C. *krusei* and C. *glabrata*, and is higher in this population as a possible consequence of prolonged azole exposure (Lamoth et al., 2018).

The challenges posed by IFIs in managing these patients, and those undergoing HSCT, result in delayed treatment, can hamper the curative effect and result in high rates of morbidity and mortality, of up to 75% at year one post-transplant (Fleming et al., 2014). The prevalence of IFI is dependent on a variety of factors, and ranges between 2% to 40% (Hahn-Ast et al., 2010). While antifungal prophylaxis during the treatment for haematological malignancies has been studied for 50 years, its use has not been entirely effective (Rogers, Slavin & Donnelly, 2011), although it has become an increasingly common treatment after clinical trials demonstrated a reduction in the morbidity and mortality in high-risk patients (Heimann et al., 2014). Given the high mortality rate and the lack of reliable diagnostic tools, antifungals are often started in these high-risk patients, despite the absence of a proven disease (Bruyère et al., 2014), the evidence being questionable as to whether this empiric therapy approach, which is associated with considerable costs, actually results in a survival benefit (Barnes et al., 2009).

1.2.1 Pharmacoeconomics and the economic burden of healthcare

Healthcare resources available for medical procedures, including pharmaceuticals, are limited all over the world (Bodrogi & Kalo`, 2010). In this regard, economic evaluations help to alleviate the burden of scarce resources by improving the allocative efficiency of healthcare financing (Bodrogi & Kalo`, 2010).

The field of pharmacoeconomics identifies the costs and consequences of competing healthcare options in order to make the best possible decision, while ensuring the maximum benefit and efficiency of resources. The practice of pharmacoeconomics utilises evidence-based research to quantify the value of pharmaceutical care and services by comparing the relative efficacy and safety of each option (Drummond, 2006). This informs decision makers who must determine where to allocate limited healthcare resources, although it is only one of a number of criteria that should be applied to determine whether the product or service is made available (Phillips et al., 2009). Issues of equity, needs, and priorities should also be included in the decision-making process (Phillips et al., 2009).

Assessing the costs and consequences depends on the perspective of the study, which determines the costs that are included (Robertson, Lang & Hill, 2003). Costs can be direct medical, direct nonmedical and indirect nonmedical. Direct medical costs are those that are incurred for medical products and services used to prevent, detect, and/or treat a disease. Examples of these costs include medicines, medical consumables, and equipment, laboratory and diagnostic tests, hospitalisations, and physician visits. Direct nonmedical costs - are those that are as a result of the disease, costs that are paid to purchase services other than medical care, including resources spent by patients for transport to and from the medical centre, child or family care expenses, special diets, and other out-of-pocket expenses. Indirect nonmedical costs - are the costs of reduced productivity (e.g., morbidity and mortality costs) (Trask, 2011). The patient perspective includes the direct medical and nonmedical costs (Robertson, Lang & Hill, 2003). The societal perspective considers the benefits to society, and therefore measures both direct and indirect costs associated with the treatment (Robertson, Lang & Hill, 2003). In the payer perspective, the costs are represented by the costs of delivering the health services (Robertson, Lang & Hill, 2003). As a general rule, direct costs can be reimbursed with money (Phillips et al., 2009), while direct non-medical costs (transport and food), indirect medical costs (loss of income) and intangible costs (pain and suffering) are not considered in a payer perspective analysis (Phillips et al., 2009).

As seen in the Council for Medical Schemes 2017 Annual Report, healthcare costs in SA are rising, with total healthcare benefits paid (sum of benefits paid from risk pool and savings accounts of members) increasing by 8.87% between 2015 and 2016 (Council for medical schemes annual report, 2017), which is higher than the consumer price index (CPI) of 4.6% and 6.34% in 2015 and 2016 respectively (Stats SA, n.d.) According to Fourie (2017), the

average medical inflation between 2003 and 2017 was 6.2%, compared to an average headline inflation of 5%. This is similar to international trends, which suggest that healthcare inflation is two or three percentage points above headline inflation (Fourie, 2017). These increases place considerable stress on the healthcare system, specifically for contributing parties, such as the government, funders, institutions and healthcare professionals, who must carry the responsibility of making difficult decisions. For the 8.878 million beneficiaries on private medical schemes in SA in 2016, hospital expenditure accounted for 37.44% of total annual medical scheme expenditure, an increase of 9.8% from 2015. Medicines and consumables dispensed by pharmacists and other providers, excluding hospitals, was R23.95 billion (15.84% of total healthcare expenditure by medical schemes in 2015). Specialist payments (including anaesthetists, medical specialists, pathology, radiology, and surgeons) accounted for 24.02%, equating to R36.32 billion (Council for medical schemes annual report, 2017)

This study utilises the perspective of a South African private hospital, and included direct medical costs, specifically hospital ward fees, medication acquisition and administration, haematology consultation and laboratory blood culture costs. The assessment is important to understand the contributing cost drivers in an episode of IC, and to use the data to establish improved and more cost-effective treatment strategies in high risk haematology patients.

1.3 Research problem and study significance

Medical expenditure to treat and prevent fungal infections in haematology patients is high in SA, with private health facilities having to factor in these costs. Available hospital data at a private facility in Durban, KZN, shows that intravenous antifungal agents, which include the azoles and echinocandins, accounted for ZAR3 078 103.54 out of a total of ZAR35 478 786.70 over the study period from August 2015 to the end of August 2017. No formulary, guidelines or restrictions are enforced by the institution, with prescribers' having the freedom to choose between these agents. Furthermore, the haematologists have indicated that only originator intravenous (IV) fluconazole, Diflucan®, can be dispensed to haematology patients. However, no local studies have been done to determine the appropriate selection of medicine treatment for invasive candidiasis in haematology patients based on the best clinical outcomes and the most cost-effective approach. In the absence of such studies, it has not been possible to develop and implement local antifungal treatment guidelines that will result in cost-effective prescribing while maintaining good outcomes. This study therefore

focuses on intravenous fluconazole (the original only - Diflucan®) and the three echinocandins currently available in SA, micafungin, anidulafungin and caspofungin.

1.4 Aim and Objectives

To determine the appropriate selection of medicine treatment for invasive candidiasis in haematology patients with the most cost-effective approach.

The study had the following objectives:

1. To conduct a cost analysis of the direct treatment costs of invasive candidiasis in haematology patients.
2. To assess whether the choice of treatment had an impact on the length of hospital stay.
3. To determine which of the direct costs contributed the most to the overall cost of treating an episode of IC.

1.5 Document structure

This dissertation comprises of this introductory chapter and the forthcoming three chapters as follows:

Chapter 2. Literature review: this chapter details the local and international studies used to describe an overview of IC, the treatment options available and the costs involved in the management of an episode.

Chapter 3. Manuscript: this chapter details the methods used to achieve the three objectives, as presented in the Results and Discussion.

Chapter 4. Conclusions and recommendations: this chapter details the significance of the findings, the limitations and recommendations.

Chapter 2: Literature review

2.1 Introduction

This chapter reviews the local and international literature relating to the costs to treat an episode of invasive candidiasis, sourced from Cochrane Library, Wiley online library, PubMed and Google Scholar. The search terms employed included: haematology, invasive candidiasis, echinocandins, fluconazole, and costs. The following types of studies were included: systematic reviews, meta-analyses, pharmacoeconomic evaluations, clinical trials, review articles, guidelines and retrospective cohort studies. An overview of invasive candidiasis is provided, its diagnosis and risk factors, epidemiology and species distribution, antifungal agents used to manage it, direct costs associated with its treatment, selecting the most appropriate treatment approach, choosing between fluconazole and an echinocandin, and treating IC in haematology (high risk) patients are also outlined.

2.2 Overview of invasive candidiasis

Candida species are commensal fungi of the human gastrointestinal and lower genital tracts and the mouth cavity (Mnge et al., 2017), being ubiquitous, with more than 200 species having been described but only 10% being responsible for infections in people (Eggimann, Garbino & Pittet, 2003). The term ‘candidiasis’ covers a wide array of diseases, such as more superficial and milder clinical manifestations, such as oesophageal or oropharyngeal candidiasis (Yapar, 2014), which are usually self-limiting in immunocompetent hosts, and easy to treat with basic hygiene measures and local treatment (Mnge et al., 2017). At the other end of the spectrum is invasive candidiasis (IC), which is responsible for severe diseases, such as candidaemia, endocarditis, disseminated infections, central nervous system infections, endophthalmitis, and osteomyelitis (Yapar, 2014). Any organ, or combination of organs, can be affected acutely or chronically (Kontoyiannis, 2001). Mucocutaneous surface colonisation is rare under normal conditions, with colonisation being a prerequisite for the development of candidiasis (Eggimann, Garbino & Pittet, 2003), its incidence being more frequent in immunocompromised patients with impaired physiological and cellular barriers (Mnge et al., 2017). It is often difficult to distinguish colonisation with Candida species from invasive infection in critically ill patients (Eggimann, Garbino & Pittet, 2003). Isolation of these organisms from clinical samples may indicate colonisation, infection or disease (Badiee & Hashemizadeh, 2014).

2.3 Diagnosis and risk factors of invasive candidiasis

Diagnosing IC poses a challenge for clinicians, as it requires a high index of clinical suspicion (Webb & Mer, 2016), with the clinical features being nonspecific, mirroring quantitatively more common aetiologies, such as bacterial infection or non-infective processes (Playford, Lipman & Sorrell, 2010). Diagnosis is often delayed due to pathogen discovery relying on detecting fungi in blood culture (Glöckner & Karthaus, 2011), the gold standard for diagnosing IC (Chen et al., 2014). Due to their questionable sensitivity, repeated cultures are often required to increase the probability of detection (Badiee & Hashemizadeh, 2014), with time to detection sometimes taking several days, reports stating a median duration of 33 hours to positivity (Glöckner & Karthaus, 2011). Blood cultures are helpful to determine the sensitivity of the isolated fungi to antifungal medications and identify resistance patterns (Badiee & Hashemizadeh, 2014), but sensitivity is low, as these methods rely on phenotypic characteristics, resulting in closely related species (such as *C. albicans* and C. *dubliniensis*) being misidentified (Ahmad et al., 2012). A recent study found that only 17% of cases of deep seated candidiasis were detected by blood culture, while another found that this method only had a 45% sensitivity, suggesting that many cases could be undetected (Lamoth et al., 2018). Blood cultures are frequently negative, which does not exclude infection, with the concentrations of viable Candida not necessarily being adequate to be detected within a collected sample, or being an indication of the intermittent or transient release of viable cells into the bloodstream (Clancy & Nguyen, 2013). Post-mortem studies indicate that only approximately 25% of invasive fungal infections are diagnosed while the patient is still alive (Webb & Mer, 2016).

Non-culture-based diagnostics, such as polymerase chain reaction (PCR), are more sensitive and rapid than blood culture, but do not allow identification to species level. In addition, these tests are expensive, and in the case of Candida PCR assays, are not yet standardised. They do however add value as a complementary test, as they can increase diagnostic yields and direct diagnostic-driven antifungal therapy (Chen et al., 2014). In addition, radiological evidence from X-rays and high-resolution computed tomography can be useful (Badiee & Hashemizadeh, 2014). Improved diagnostic tests for invasive candidiasis are among the most pressing needs in infectious diseases (Clancy & Nguyen, 2013). A high degree of clinical suspicion, and more than one method of diagnosis, should be used to enable an early verdict and optimal management (Badiee & Hashemizadeh, 2014). There is therefore a need for attention to be focused on either a novel diagnostic tool to aid earlier detection of Candida in

the bloodstream, or ways to enhance the clinicians' ability to identify high risk patients (Glöckner & Karthaus, 2011).

The risk factors for IC can be divided into two categories: host-related and healthcare-associated factors. The leading host factors include: immunosuppressive diseases, neutropenia, age, a deteriorating clinical condition due to underlying diseases (Yapar, 2014); malignant haematological disorders, particularly acute myeloid leukaemia (AML); stem cell and solid organ transplantation; cytomegalovirus disease and intensive cytotoxic chemotherapy (Al-Anazi & Al-Jasser, 2006). Healthcare-associated factors include haemodialysis, mechanical ventilation, prolonged ICU stay (Lamoth et al., 2018), the use of intravascular catheters, steroid therapy, broad spectrum antibiotic treatment, and antifungal prophylaxis with fluconazole and surgical intervention (Al-Anazi & Al-Jasser, 2006). Other major predisposing conditions for candidaemia include neutropenia, abdominal surgery, diabetes mellitus, cancer, and renal failure (Kreusch & Karstaedt, 2013). The majority of risk factors identified for candidaemia is common for multidrug-resistant bacteria, and are not supportive in distinguishing patients with bacteraemia from those with candidaemia (Garey et al., 2006).

2.4 Epidemiology of invasive candidiasis

Candida species are the fourth most common cause of nosocomial blood stream infections (BSIs) worldwide (Garey et al., 2006), and the third most frequent cause of infection in ICUs, accounting for 17% of all infections in culture-positive infected patients, according to the extended prevalence in intensive care (EPIC) II point prevalence study (Lamoth et al., 2018). The Centers for Disease Control and Prevention (CDC) and the National Healthcare Safety Network data indicates that Candida species are ranked fifth among hospital-acquired pathogens and fourth among blood stream infections (Yapar, 2014). According to a large survey on bloodstream infections comprising a total of 24 000 cases in USA hospitals, Candida species rank fourth, with 4.6 sepsis cases per 10 000 admissions (Glöckner & Karthaus, 2011). A population-based surveillance study conducted in Australia between 2001 and 2004 reported a yearly candidaemia incidence of 1.81 cases per 100 000 population (Yapar, 2014), which rose between 2004 and 2015 to 2.4 per 100 000 (Lamoth et al., 2018). A study at six United Kingdom (UK) hospitals found the rate of candidaemia to be more than three cases per 100 000 bed days, while a recent prospective survey in Scotland reported an incidence rate of 4.8 cases per 100 000 population per year (Hassan et al., 2009). In a single

hospital in Soweto, South Africa, the rate was 0.28 per 1000 admissions in 2002, but increased to 0.36 per 1000 admissions in 2007 (Lamoth et al., 2018), with the incidence and prevalence of Candida species not being well documented (Mnge et al., 2017). Although good data exists for North America and Europe, there are no population-based data from Africa, Asia, and the Middle East or Latin America from which to establish an overall worldwide rate (Lamoth et al., 2018).

Invasive candidiasis is an important clinical entity, specifically among critically ill ICU patients, with crude mortality rates of 40–60% (Playford, Lipman & Sorrell, 2010). Kreusch and Karstaedt (2013) states that the crude mortality rate ranges from 20% to 61% while in the USA, Wang et al. (2015) reported mortality attributable to candidaemia in the range of 30–50 % from studies conducted in the USA and Spain. The survey of the European confederation of medical mycology (ECMM) found a mortality rate of 42% in intensive care patients (Glöckner & Karthaus, 2011). To establish excess mortality, which is difficult to determine, due to the underlying comorbidities and risk factors usually associated with these patients, Hassan et al. (2009) conducted a retrospective analysis of candidaemia cases and appropriate matched controls at a hospital in Manchester, England, from November 2003 to February 2007. Overall, 19 of 22 candidaemia patients died within 30 days of the development of candidaemia. When the analysis was limited to adult patients (defined as those ≥ 16 years old), the attributable mortality was 30.6% for all patients and 21.5% for ICU patients (Hassan et al., 2009).

2.5 Distribution of Candida species

Only 15 of the 150 known species of Candida have been isolated as infectious agents from patients (Yapar, 2014). The distribution of isolates in a given patient population is influenced by many factors, including geographic localisation, age, comorbidities, duration of hospital stay and local epidemiology (Glöckner & Karthaus, 2011). witNinety-five percent of infections are being caused by *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, and *C. krusei*. *C. glabrata* is a more common infectious agent among older and neoplastic patients, *C. tropicalis* among leukaemia and neutropenic patients, *C. krusei*, among haematopoietic stem cell recipients and neutropenic leukaemia patients receiving fluconazole prophylaxis and *C. parapsilosis* is the most common pathogen found in catheter-related infections due to colonization of the skin (Yapar, 2014). Outcomes of IC vary substantially according to the

causative Candida species, the highest mortality rates being observed with *C. krusei*, followed by *C. tropicalis* and *C. glabrata* (Mayr, Aigner & Lass-flörl, 2011).

The distribution of Candida species has been changing over the last decade, with a decrease in the proportion of *C. albicans* and an increase in *C. glabrata* and *C. parapsilosis* (Lamoth et al., 2018). There is considerable geographic variation, particularly in the relative proportion of episodes caused by C. *glabrata* (higher in the United States) or C. *parapsilosis* (higher in some European centres) (Playford, Lipman & Sorrell, 2010). In the USA, the proportion of *C. albicans* has dropped, and now accounts for 50% of Candida infections, with the largest proportional increase being *C. glabrata*, which now accounts for one-third or more of all candidaemia isolates, followed closely by *C. parapsilosis*. In a seven-country, 13-hospital study in the Asian Pacific, *C. albicans* was most common (36%) and *C. tropicalis* was second (31%). In India and Pakistan, *C. tropicalis* is the most prevalent species, followed by *C. albicans* (Lamoth et al., 2018). One of the factors proposed to explain this shift in the distribution of the Candida species is the widespread use of fluconazole as a prophylactic antifungal agent, particularly in patients with haematologic malignancies and recipients of bone marrow transplantation (Hachem et al., 2008).

Little has been published on candidaemia among adults in Southern Africa, with Africa being conspicuous by its absence in a review of worldwide publications from 1996 to 2009 detailing candidaemia isolates (Kreusch & Karstaedt, 2013). In the South African public sector hospitals during 2009 to 2010, *C. albicans* and *C. parapsilosis* accounted for 48% and 37% of Candida isolates respectively. In the private sector, *C. parapsilosis* was more common, accounting for 55% of isolates, in comparison to 28% for *C. albicans* and 11% for *C. glabrata* (Webb & Mer, 2016). The Lancet laboratories Annual Surveillance Report and Antibiotic Guide for 2014 to 2016 describe the results for the private sector in KwaZulu-Natal Province, with Candida species remaining the fourth most common organism isolated from blood cultures, with the predominant species being *C. parapsilosis* in addition to the recent emergence of *C. auris* (Lancet Laboratories, 2017).

According to the GERMS-SA Annual Report in 2016, there continue to be differences in the epidemiology of invasive candidiasis between the public and privatesector, with variation by province. In 2016, 1760 cases of candidaemia were detected, 64% of which were diagnosed in Gauteng Province. Overall, *C. parapsilosis* was the most common species, followed by *C.*

albicans, with 9% of cases being due to *C. auris*, which is a concern, as it is fluconazole resistant, with few exceptions. *C. auris* was the second commonest species in the privatesector and the fourth commonest in the publicsector, while azole-resistant strains of *C. parapsilosis* and *C. auris* now dominate in the private sector, particularly in Gauteng Province. It is well known that early recognition, coupled with knowledge of the local patterns of Candida resistance, assists with the clinician's selection of the most appropriate antifungal treatment, which should result in improved clinical outcomes (Zilberberg et al., 2010).

2.6 Antifungal agents used to manage invasive candidiasis

Invasive candidiasis is an illness of the severely ill (Glöckner & Karthaus, 2011), and results in patients often dying of complications attributed to the infection, despite antifungal therapy (Badiee & Hashemizadeh, 2014). There is a strong association between the inappropriate selection of an antifungal agent and worsened clinical outcomes, as well as a substantial increase in mortality (Glöckner & Karthaus, 2011). Prompt initiation, within 24 hours after confirmation of a positive blood culture, of the appropriate antifungal is associated with significantly improved clinical outcomes (Webb & Mer, 2016).

Effectively treating IC is difficult, as there are only a few antifungal agents available, and organisms are developing resistance (Badiee & Hashemizadeh, 2014). For many years, amphotericin B was the gold standard of treatment, but it has become associated with substantial renal toxicity (Hahn-Ast et al., 2010), with lipid formulations of amphotericin B being subsequently developed, which had an improved nephrotoxicity profile compared to the parent compound (Kontoyiannis, 2001). The next class of medications that were registered to treat fungal infections was the broad-spectrum oral and parenteral triazoles, such as fluconazole and itraconazole (Kontoyiannis, 2001). The newest class now available is the echinocandins (Hahn - Ast et al., 2010), which include caspofungin, micafungin and anidulafungin (Kontoyiannis, 2001).

Fluconazole is a member of the triazoles class of antifungal agents, which are potent and selective inhibitors of the synthesis of fungal ergosterol, leading to defects in the cell membrane, and having selective toxicity due to their greater affinity for fungal than human cytochrome P450 enzymes. As a group, the azoles are relatively nontoxic, the most common adverse reaction being relatively minor gastrointestinal upset. All azoles have been reported

to cause abnormalities in liver enzymes and, very rarely, clinical hepatitis. The azole agents are prone to drug interactions, as they affect the mammalian cytochrome P450 system of enzymes, with, fluconazole having the least effect of all the azoles on hepatic microsomal enzymes. Fluconazole has the widest therapeutic index of the azoles due to fewer hepatic enzyme interactions and better gastrointestinal tolerance, therefore permitting more aggressive dosing in a variety of fungal infections (Katzung et al., 2012).

Fluconazole was considered an option as first-line treatment of candidaemia in stable patients by the 2009 infectious disease society of America (IDSA) guidelines, based on the evidence that less critical patients with IC who were treated with fluconazole or anidulafungin had a similar mortality (Tagliaferri & Menichetti, 2015). As these guidelines were presented in 2009, there has been new data relating to the diagnosis, prevention, and treatment for proven or suspected invasive candidiasis, leading to substantial adjustments in the treatment recommendations (Pappas et al., 2015). Fluconazole was downgraded by The European society for clinical microbiology and infectious diseases (ESCMID) guidelines, due to a limited spectrum of activity and the lack of fungicidal activity (Tagliaferri & Menichetti, 2015). The 2016 IDSA guidelines recommends oral or intravenous fluconazole as an acceptable alternative for first line treatment in selected patients, including those who are not critically ill and considered unlikely to have a fluconazole-resistant Candida species. Additionally, it is recommended for the empiric treatment for suspected IC in non-neutropenic patients in the ICU who have had no recent azole exposure and are not colonized with azole-resistant Candida species. There is a weak recommendation based on moderate-quality evidence for the use of fluconazole as prophylaxis to prevent Candidiasis in high-risk patients in adult ICUs with a high rate (>5%) of invasive candidiasis (Pappas et al., 2015). With the availability of more effective medicines, the use of fluconazole in critical patients to treat candidaemia is no longer justified (Tagliaferri & Menichetti, 2015).

Echinocandins are a novel class of antifungal agents, and are semisynthetic, amphiphilic large cyclic peptides linked to a long-chain fatty acid. Caspofungin, micafungin, and anidulafungin are the only licensed agents in South Africa in this category of antifungals, these agents being active against Candida and Aspergillus (Katzung et al., 2012), with other medicines being under active investigation. Their mechanism of action is to noncompetitively inhibit the synthesis of the β-(1, 3) - D-glucan part of the cell wall of fungi (Wang et al., 2015), which leads to osmotic instability and eventual cell death (De La Torre & Reboli, 2014). The

prevalence of their target in certain fungi, coupled with its absence in mammals, helps make the echinocandins very attractive in terms of low toxicity and reduced side effects (James et al., 2017).

Echinocandins are available only in intravenous formulations, with caspofungin being administered as a single loading dose of 70 mg, followed by a daily dose of 50 mg, being water soluble and highly protein-bound, with a half-life of 9–11 hours. The metabolites are excreted by the kidneys and gastrointestinal tract, with dosage adjustments being required only in the presence of severe hepatic insufficiency. Micafungin displays similar properties, with a half-life of 11–15 hours, the recommended dosage being 100 mg/day to treat candidaemia, and 50 mg/day for the prophylaxis of fungal infections. Anidulafungin has a half-life of 24–48 hours, and to treat candidaemia, a loading dose of 200 mg is recommended, with 100 mg/day thereafter for at least 14 days after the last positive blood culture (Katzung et al., 2012).

The results of the study conducted by Pfaller et al. (2008) demonstrates the comparable spectrum and potency of all three available echinocandin antifungal agents against a large collection of clinically important Candida species. They demonstrated that the activities of all three agents remain consistent over time and broad geographic regions (Pfaller et al., 2008), with the echinocandins having presented unique activity against the biofilms associated with various Candida species (De La Torre & Reboli, 2014). Echinocandins have advantages over fluconazole as the treatment of choice for systemic candidiasis, being potent fungicidals, and having a broader spectrum of activity (including fluconazole resistant C. *glabrata* and C. *krusei)* and exhibiting lower minimum inhibitory concentrations (MICs) *in vitro* compared to fluconazole against *C. albicans* (Reboli et al., 2011). The three echinocandins currently available have proven to be highly effective against invasive Candida species isolated with reduced susceptibility to azoles (Ahmad et al., 2012). Among patients with proven or suspected infection due to *C. glabrata*, an echinocandin is the preferred choice as initial therapy, as well as in neutropenic patients if the Candida species is unknown (De La Torre & Reboli, 2014).

2.7 Direct costs associated with treating invasive candidiasis

The growing incidence of fungal infections, and therefore expenditure related to their treatment, has been increasing worldwide (Gedik et al., 2014). Evidence shows that patients

with IFD have a longer inpatient admission and higher associated hospital costs than those without, but having similar underlying diagnoses, suggesting that it contributes to longer length of stay (Ceesay et al., 2015). Attributing adverse outcomes specifically to a superimposed infection is methodologically difficult (Playford, Lipman & Sorrell, 2010), due to the challenges of separating these costs from those attributable to underlying or associated diseases (Wilson et al., 2002). However, there is agreement that invasive candidiasis is independently associated with adverse clinical outcomes and excess economic costs among ICU patients (Playford, Lipman & Sorrell, 2010). Cost driving factors that are responsible for the major financial load of candidaemia include those associated with diagnosis, treatment and treatment failure, as well as hospitalisation (Ashley et al., 2012), including healthcare personnel (Heimann et al., 2015). Inappropriate antifungal treatment, which can be categorised as either resistance to the antifungal agent, inadequate drug dosage or delayed therapy, is related to worse clinical outcomes with an increased length of stay (LOS), resulting in increased associated costs compared to appropriate treatment (Armaganidis et al., 2017).

The financial burden of fungal disease annually in the USA, based on data from 1998, was $2.6 billion, or 0.24% of total US health expenditure, which is high, considering that only 0.03% of the total population contracts fungal infections. The average annual health expenditure per person in the USA was $4,094, while the average added expenditures for patients with fungal infections was $31,200 per person, almost eight times greater (Wilson et al., 2002). The study conducted by Menzin et al. (2009) in the USA, based on estimates, reported that 64,480 patients were hospitalised each year for invasive fungal infections, with an estimated 735,000 additional hospital days annually contributing to approximately $1,89 billion in additional costs (Menzin et al., 2009). Ashley et al. (2012) reported the treatment of an IFI episode was estimated at a similar value of $32,000, based on results from an economic analysis at Duke University Medical Centre between 2004 and 2005 on 119 cases with proven invasive candidiasis. They reported adjusted costs were higher than previous studies reported in 2002, but comparable to reports in 2005. Contributing factors at the time were the introduction of generic fluconazole and price decreases of the echinocandins due to the approval of two additional agents in the class, but an increase in associated laboratory costs due to the introduction of new diagnostic tools (Ashley et al., 2012). It has been demonstrated that IC increases hospital length of stay (LOS) by 10 to 20 days per episode; hospitalisation

costs are therefore the highest contributor, and antifungal therapy being the next highest cost driver' at 10% of total costs of treating an episode of IC (Ha et al., 2012).

The Wilson and colleagues' (2002) study, which addressed the incidence and incremental costs of candidiasis for 1998, using a case-controlled method with data from the National Hospital sischarge survey (NHDS) and the Maryland hospital discharge data survey (MDHDDS), showed that across all diagnoses and types of fungal infections, the room rate contributed the most to total hospitalisation costs at 47%, medication for approximately 17%, laboratory costs at 11% and other factors between 3% and 6% (Wilson et al., 2002). The study by Armaganidis et al. (2017) concluded that the major cost section in an episode of invasive fungal infections in Greek hospitals was LOS, which contributed €17,787 of the total mean costs per patient of €22,013 (Armaganidis et al., 2017). In contrast to this data, the study performed by Ha et al. (2012) at four university-affiliated tertiary hospitals in South Korea, on patients who had candidaemia and received antifungal treatment from July 2008 to June 2009, showed that the cost of hospitalisation, antifungal medicines, and other medical treatments each comprised approximately 25% of the total costs (Ha et al., 2012).

Wilson et al. (2002) found a statistically significant difference in the average hospital costs between cases and controls, with candidiasis accounting for an incremental cost of $14,804, and patients with neoplasms infected with fungal disease an additional cost of $21,571 per person (Wilson et al., 2002). Menzin et al. (2009) performed a similar retrospective database study using data from the 2004 Healthcare Cost and Utilization ProjectNationwide Inpatient Sample (HCUP-NIS); their study showing that patients with invasive fungal infections accrued $29,281 more in medical costs, which was statistically significant (Menzin et al., 2009). The same pattern is seen in data from a study performed in Manchester, England, over the period November 2003 to February 2007, where there was a statistically significant difference in the mean additional costs for adult patients of £16,595 (Hassan et al., 2009).

Data from a study in the USA in 1998 showed that patients with candidiasis stayed an additional 14 days in hospital on average (Wilson et al., 2002), this was seen using data from 2004, where the patients with invasive fungal infections stayed an average of 11.4 days longer in hospital than the control group (Menzin et al., 2009). The study performed by Hassan et al. (2009) indicated a mean duration of ICU LOS for cases of 17.8 days, and 12.2 days for controls, indicating a mean attributable increase of 5.6 days due to candidaemia. This was

much lower than the study results from Armaganidis et al. (2017) from a Greek social insurance perspective, which showed a mean LOS in the ICU of 37.2, days and a mean duration of antifungal therapy of 12.2 days.

Recent data showed that initial inappropriate antifungal therapy was a major cause of increased LOS, costs and poor outcomes (Ha et al., 2012). To evaluate the impact of inappropriate therapy on hospital length of stay and costs, Arnold et al. (2010) performed a single centre retrospective cohort study at Barnes-Jewish Hospital in St. Louis, Missouri, USA, between January 2004 and May 2006. The most frequent finding, and the greatest impact on the measured outcome, was a delay in treatment, which caused a statistically significant increased length of stay in hospital and increased costs. The study shows that early treatment with the most appropriate agent is essential (Arnold et al., 2010). A similar study was performed at the same institution by Zilberberg and colleagues (2010) over a longer time period, between January 2004 and December 2007. Ninetyfive percent of inappropriate therapy received was due to ≥24-hour delay in therapy, and 26% was due to an inadequate fluconazole dose. The median hospital LOS was 13 days longer, and the median hospital costs were nearly double in the group receiving inappropriate compared to appropriate treatment (Zilberberg et al., 2010). The results of the study by Armaganidis et al. (2017) demonstrated that choosing an appropriate first-line antifungal agent is crucial for reducing LOS and lowering hospital cost of managing candidiasis, as patients who switched antifungal treatment during the study had a significantly longer LOS in the ICU (53.8 days vs 35.5 days; P=.0204) and duration of antifungal therapy (27.3 days vs 13.1 days; P≤.0001) (Armaganidis et al., 2017). There is an urgent need for physicians to maintain a high index of suspicion for candida blood stream infection due to the impact that delayed treatment has on a patient's clinical outcome and the financial impact (Zilberberg et al., 2010).

2.8 Selecting the most appropriate treatment approach

Early treatment strategies may lead to improved clinical outcomes (Playford, Lipman & Sorrell, 2010) and can reduce fungal infections and mortality (Clancy & Nguyen, 2012), but their use in patients at low risk of invasive candidiasis has the potential to increase costs, toxicity, and generate ecological selection pressure for antifungal resistance (Playford, Lipman & Sorrell, 2010). A prophylactic approach that sees all patients receiving antifungal therapy (Clancy & Nguyen, 2012), seems a very attractive management approach, as it may reduce candidaemia incidence rates, as well as mortality, in selected populations, although

the treatment value in non-neutropenic ICU patients' needs to be studied further (Mayr, Aigner & Lass-flörl, 2011). Due to the substantial differences in the epidemiology of invasive candidiasis, particularly in respect to species distribution, the choice of antifungal for prophylaxis must be informed by local epidemiological surveillance (Playford, Lipman & Sorrell, 2010). An ideal antifungal for prophylaxis should have potent extended-spectrum activity, be available both orally and parenterally, and be well tolerated (Cornely et al., 2011).

A randomised study of 304 allogeneic HSCT recipients demonstrated that micafungin was as efficacious as fluconazole as a prophylactic agent against candidiasis, with no difference in overall or fungal-free survival. Conversely, in a randomised, double-blind, comparative study in 882 HSCT recipients, micafungin was found to be superior to fluconazole in preventing invasive fungal disease (Cornely et al., 2011).

Pre-emptive therapy, defined as the initiation of antifungal treatment in patients suspected of a fungal infection, but without the diagnostic confirmation (Armaganidis et al., 2017), is possibly a more appropriate alternative to chemoprophylaxis, specifically when combined with infection control measures (Mayr, Aigner & Lass-flörl, 2011). Pre-emptive therapy incorporates an assortment of strategies aimed at selecting patients suitable for early treatment with a combination of risk factor evaluations, and assessing diagnostic markers (e.g. Candida colonisation, β-D-glucan, procalcitonin, fungal DNA, mannan/anti-mannan antibodies, and Candida germ-tube antibodies) (Mayr, Aigner & Lass-flörl, 2011). The pre-emptive approach is a logical alternative to empirical therapy, the aim being to better target antifungal therapy and avoid over-treatment (Pagano et al., 2011). A combination of many of the well-established risk factors for invasive candidiasis may help to promptly identify patients with a risk of invasive candidiasis higher than 10%, making these selected populations more likely to benefit from early pre-emptive antifungal treatment (Eggimann & Ostrosky-Zeichner, 2010).

Empiric therapy is generally defined as antifungal therapy administered to patients with clinical features of the inflammatory response that is consistent with a fungal aetiology, but without microbiological confirmation (Playford, Lipman & Sorrell, 2010). It is also defined as antifungal treatment given to patients with fever of unknown origin that was not responding to broad spectrum antibacterial therapy (Armaganidis et al., 2017). However, the appropriateness of using fever as the sole criterion for initiation of antifungal therapy has been debated (Cordonnier et al., 2009).

Increasing empirical antifungal prescribing would likely involve overprescribing for patients without candidaemia, which comes with increased toxicities and costs (Garey et al., 2006). The proportion of patients successfully treated with an empirical approach appears to have decreased over the last few years, raising doubts regarding its real benefits (Pagano et al., 2011). An urgent understanding is required to decide whether early empirical antifungal therapy with appropriate adjustments, according to clinical diagnosis versus waiting for the microbiological evidence to initiate treatment, is the best approach (Cui et al., 2017).

An alternative strategy to empirical antifungal therapy is diagnostic test-guided pre-emptive antifungal therapy. This approach entails reserving antifungal therapy for the subset of patients who have early evidence of invasive fungal disease by careful clinical assessments and serial fungal biomarker evaluations. This has the potential to reduce antifungal drug use and its attendant toxicity and costs, without increasing IFD-related morbidity or mortality (Fung et al., 2015).

Due to the conflicting data available, and the potential overuse of azoles and echinocandins, an antifungal de-escalation approach is becoming common practice (Bailly et al., 2015). An initial short course of an IV echinocandin, followed by the option to step-down to oral azole therapy, could be as effective to treat IC as conventional 10- to 14-day IV regimens, including for the rarer Candida species (Vazquez et al., 2014). Additionally, this step-down strategy could have added benefits, such as better tolerability, reduced use of IV catheters, earlier patient discharge, and substantial cost savings (Vazquez et al., 2014). In an attempt to reduce the emergence of echinocandin resistance and avoid the high cost of echinocandin therapy (Antinori et al., 2016), the ESCMID and IDSA guidelines recommend a de-escalation strategy (3 days in stabilised patients, as per IDSA, and 10 days overall, as per ESCMID) (Bailly et al., 2015). However, neither of these specific strategies has been prospectively studied, and the appropriate timing of step-down therapy remains unclear (Vazquez et al., 2014).

The transition from an echinocandin to fluconazole (usually within 5–7 days) is recommended for patients who are clinically stable, have isolates that are susceptible to fluconazole (e.g., *C. albicans*), and have negative repeat blood cultures following the initiation of antifungal therapy. Follow-up blood cultures should be performed every day or every other day to establish the time point at which candidaemia has been cleared (Pappas et al., 2015).

There are important and competing clinical and economic concerns about the different strategies that must be considered in order to enhance their benefits and minimise their problems (Playford, Lipman & Sorrell, 2010). Current guidelines do endorse the use of prophylaxis, empirical and pre-emptive treatment in the absence of solid evidence (Cui et al., 2017). The surveillance of candidaemia is essential, as it is important to recognise its epidemiological trends (Ulu Kilic et al., 2017), and the availability of new non-invasive diagnostic techniques (i.e. galactomannan, β-D-glucan). This will allow clinicians to anticipate the diagnosis (Pagano et al., 2011) or identify unique risk factors (Garey et al., 2006) to guide antifungal treatment options (Ulu Kilic et al., 2017).

2.9 Choosing between fluconazole and an echinocandin

Decisions need to be made about what treatment options to provide for patients with IC, and should take account of clinical and cost factors, which are detailed further.

2.9.1 Clinical factors

Treatment outcomes are heavily dependent on the appropriate use of available therapy options (Mayr, Aigner & Lass-flörl, 2011). Inadequate antimicrobial treatment is an independent determinant of hospital mortality, with fungal blood stream infections being among those with the highest rates of inappropriate initial treatment (Garey et al., 2006). Inappropriate first line treatment is mainly seen in the form of delayed or complete omission of antifungal therapy (Mayr, Aigner & Lass-flörl, 2011). Subsequent corrected regimens and post-microbiological identification of the pathogen, have not been associated with improved patient survival, therefore highlighting the importance of correct initial antimicrobial management (Parkins et al., 2007). Delayed treatment is associated with a dramatic increase in the mortality rate, with the mortality rate, being approximately 15% when treatment is started in the first 24 hours after confirmation of a positive blood sample, which increased to 50% when treatment was administered only 72-96 hours post a positive culture result (Webb & Mer, 2016). Early identification of patients at risk, knowledge of local epidemiology and prompt efforts to define etiologic diagnosis play an important role in the appropriateness of therapy (Tagliaferri & Menichetti, 2015).

The clinical practice guideline for managing candidiasis (2016) was updated by the Infectious Diseases Society of America, and recommends an echinocandin as initial therapy in non-neutropenic patients, with intravenous or oral fluconazole as an acceptable alternative in

certain patients, including those not critically ill and considered unlikely to have a fluconazole-resistant Candida species (Pappas et al., 2015). Table 2.1 below describes the treatment doses according to IDSA.

Table 2.1 Treatment doses to manage invasive candidiasis, as per the infectious disease society of America (IDSA) guidelines (Pappas et al., 2015).

Medication	Loading dose	Daily dose
Fluconazole	800mg (12mg/kg)	400mg (6mg/kg)
Anidulafungin	200mg	100mg
Caspofungin	70mg	50mg
Micafungin	N/A	100mg

Reboli et al. (2007) performed a phase III, randomised, double-blind study comparing anidulafungin with fluconazole as the primary treatment of systemic candidiasis in adult patients infected with any Candida species, except C. *krusei*. The global response rates at the end of the intravenous study treatment in the modified intention to treat patients were significantly higher with anidulafungin (76%) than fluconazole (60%). *C. albicans* was the major cause of most of the infections (62%), 81% of these patients were treated with anidulafungin and 62% with fluconazole, the difference in the global responses in this sub group was statistically significant (p=0.02). The positive blood cultures cleared significantly more rapidly in patients treated with anidulafungin, where the median time to negative blood culture was two days, compared to five days with those treated with fluconazole. The Kaplan-Meier estimates of survival at six weeks were not significantly different between the treatment groups. The study concluded that anidulafungin was at least non-inferior to fluconazole in treating invasive candidiasis (Reboli et al., 2007). Mills et al (2009) supported this conclusion in their mixed treatment comparison meta-analysis, which concluded that azoles and echinocandins are equally effective interventions for treating invasive candidiasis when considering global response rates (the objective response of therapy on the disease), mortality and safety (Mills et al., 2009). Wang et al. (2015) performed a meta-analysis to compare the safety and efficacy of echinocandins with triazoles to treat proven or probable fungal infections. The pooled analysis of ten randomised clinical trials (RCT), with 1 469 patients in the echinocandins group and 1 368 in the triazoles group, reported that there was no significant difference between the two groups in the treatment success rate (Wang et al., 2015).

Conversely, findings from a randomized clinical trial performed by López-Cortés et al. (2016), using data from the Prospective Population Study on Candidemia in Spain (CANDIPOP) project (ClinicalTrials.gov registry NCT01236261), a prospective, population-based surveillance cohort study on blood stream infections due to Candida, conducted from May 2010 to April 2011 in 29 Spanish hospitals, did not support the use of echinocandins over fluconazole for more severely ill patients. Their results found the 30-day mortality rate in both the empirical and targeted therapy group were significantly higher in patients who were administered an echinocandin compared to fluconazole. In addition, the empirical use of fluconazole was not associated with higher rates of persistent candidaemia or clinical failure (López-Cortés et al., 2016).

Kett et al. (2011) concluded that treatment with anidulafungin for candidaemia in severely ill patients was associated with an improved global response, and was therefore more effective than fluconazole in their post hoc analysis on a previously published study comparing anidulafungin with fluconazole in adult patients with culture confirmed candidaemia. Anidulafungin was administered in 54.6% of the patients and 45.4% were treated with IV fluconazole. There were no significant differences in the baseline characteristics between the groups. The global response rate was 70.8% for anidulafungin and 54.1% for fluconazole (p=0.03; 95% CI, 2.0 to 31.5), with the all-cause mortality being half in the former group. Reboli et al (2011) performed a post-hoc multivariate analysis of a previous randomised clinical trial conducted by Reboli et al. (2007), and directly compared the efficacy of a fungicidal with a fungistatic in *C. albicans* infections without potential confounding by differences in susceptibility. In these patients, anidulafungin was more effective than fluconazole in terms of better global response, faster clearance of Candida from the bloodstream, and fewer persistent infections, although it did not translate into a difference in long-term survival (Reboli et al., 2011).

2.9.2 Cost factors

The echinocandins are a newer class of medicines, the acquisition price in South Africa being higher than fluconazole, with no generics in the market of any of the three echinocandin molecules. Assessing and comparing the associated costs between these two classes is complicated, as more than only the acquisition costs must be accounted for (Grau et al., 2015).

There is a strong negative impact on budgets when only considering the acquisition costs of echinocandins (Grau et al., 2015). Ulu Kilic et al. (2017) performed a 6-year retrospective analysis of the data belonging to patients with candidaemia who were hospitalised between 2010 and 2016 in a tertiary care centre in Central Turkey. A total of $20,308 was paid for fluconazole during the whole study period compared to the cost of caspofungin used in 2015 which was more than 10-fold. Despite a higher acquisition cost, echinocandins have demonstrated a reduced mortality and decrease in overall in-hospital costs compared to fluconazole in the setting of both empirical and definite treatment of IC (Tagliaferri & Menichetti, 2015). This is supported by model simulation studies, which reported that the empirical use of echinocandins was more cost-effective than fluconazole and amphotericin (Ha et al., 2012).

A non-interventional observation study was performed during 2005 to 2010 at the tertiary care University Hospital of Cologne (UHC), from the perspective of the German healthcare system. It showed the mean direct overall costs per patient treated with an echinocandin to be significantly higher than the fluconazole (€37,995 vs €22,305, p=0.012), with the mean daily costs for the antifungal treatment being €165 for an echinocandin vs €86 for fluconazole (p=<0.001). It was evident that although daily treatment costs were higher in patients receiving echinocandins, this was largely due to the underlying disease, as patients in the echinocandin group were considered sicker and required longer ICU stays. The mean antifungal treatment costs were relatively low, comprising <10 % of the overall treatment costs (Heimann et al., 2015). In opposition to this finding, the review performed by Reboli et al. (2011) on the charts from the original trial which was a randomised, double-blind, multicentre, and non-inferiority phase III study between March 2003 and October 2004, found no statistically significant difference in the length of stay in ICU or total hospital days between the anidulafungin and fluconazole treatment groups using the unadjusted data. Post APACHE II score and absolute neutrophil count adjustment, the ICU patients treated with anidulafungin tended to need fewer overall hospital and ICU days. The study concluded that for ICU patients, treatment with anidulafungin compared with fluconazole resulted in a reduction in total IC related costs, although this was not statistically significant (Reboli et al., 2011).

A decision tree model from the Australian hospital perspective was performed based on the results from Reboli et al's. (2007) double blind RCT, which reported that anidulafungin is at

least noninferior to fluconazole. Anidulafungin was associated with an incremental cost-effectiveness ratio (ICER) of AUD 88,584 per additional patient successfully treated, or AUD22,003 per life-year gained. The probabilistic sensitivity analysis showed that anidulafungin was cost-effective (below the accepted threshold for Australia of AUD76,000 per life-year gained) in treating invasive candidiasis in almost 100% of simulations (Neoh et al., 2011). This finding was reinforced by Zilberberg, Kothari and Shorr (2009), in which a decision model demonstrated that the empiric use of 100 mg daily of micafungin was cost-effective in ICU patients with septicaemia and at risk of IC when compared with both watchful waiting and delaying antifungal therapy until the return of cultures (Zilberberg, Kothari & Shorr, 2009).

2.10 Treatment of IC in haematology (high risk) patients

Invasive fungal infection poses a serious risk to critically ill and immunocompromised patients, particularly HSCT recipients and those who have received intensive chemotherapy for acute leukaemia (Cornely et al., 2011). These patients experience febrile neutropenia, which complicates the differential diagnosis between a fungal infection and colonisation (Gedik et al., 2014). Fungal infections are an area of concern clinically (Schonfeld et al., 2008), as they are associated with a high rate of treatment-related morbidity and mortality (Bertz, Drognitz & Finke, 2016), and economically, as their inpatient costs are already high and further increased by the complication of systemic fungal infections (Schonfeld et al., 2008).

There are three controversial features in the treatment of IFD in this patient group, these being: which antifungal prophylaxis and which diagnostic techniques are most effective, as well as whether the empirical or pre-emptive therapy approach is superior (Bertz, Drognitz & Finke, 2016). The literature review by Schonfeld et al. (2008), concluded that successful prophylaxis for fungal infections in transplant recipients has been demonstrated to reduce the incidence of infection and the potential to lower the overall costs of care, with different regimens having various efficacies, and therefore not being equally cost-effective (Schonfeld et al., 2008). Conversely, Ananda-Rajah and colleagues (2011) determined that using antifungal therapy as prophylaxis in this high-risk patient group has its downfalls, due to the number of eligible candidates and the length of treatment required, resulting in over-treatment, increased resistance and high costs. Treating physicians often choose to treat

empirically at the first sign of a fever, despite being aware of the increased costs, followed by microbiological and radiological investigations (Gedik et al., 2014).

Evidence-based guidelines for using antifungal prophylaxis have been developed by the European conference on infections in leukaemia (ECIL) and the national comprehensive cancer network (NCCN), and give the highest rating to fluconazole or micafungin for patients undergoing allogeneic HSCT in the neutropenic phase, and autologous HSCT recipients with mucositis (Cornely et al., 2011). The 2009 IDSA guidelines recommend an echinocandin as first line therapy in neutropenic patients with moderate to severe illness, but this is not commonly implemented in countries where resources are limited, due to their high acquisition costs (Ha et al., 2012).

Bertz and colleagues (2016) performed a one-year prospective study between January and December 2010 on 106 adult patients treated with myeloblative and reduced intensity conditioning in a German hospital. Their results showed that, with the use of fluconazole as antifungal prophylaxis in low risk patients, no deaths occurred during and after the allogenic HSCT, and only a 20% proven/probable IFD breakthrough was seen, which they deemed successful, and maintained the use of this guideline. Mould active agents, such as liposomal amphotericin B, voriconazole and posaconazole prophylaxis, were used in high risk patients, but were not effective enough, as empiric or pre-emptive therapy was started in 65% of patients.

Randomised multi-centre studies conducted by Van Burik et al. (2004) and Hiramatsu et al. (2008), which compared micafungin and fluconazole as antifungal prophylaxis in neutropenic patients undergoing HSCT, both concluded that micafungin is at least as effective and an appropriate alternative. The overall treatment success rate in the micafungin arm was 94% versus 88% in the fluconazole arm (Hiramatsu et al., 2008), with similar statistically significant results of 80% in the former compared to 73.5% in the latter (Van Burik et al., 2004). Micafungin was more effective in reducing the need for empirical antifungal therapy, and time to treatment success was significantly shorter (Van Burik et al., 2004). Wang et al. (2015) supported the results that echinocandins were associated with significantly higher treatment success rates for prophylaxis in this patient subgroup. Schonfeld et al. (2008) performed an economic evaluation to determine if prophylaxis using micafungin is more cost effective than using fluconazole. Based on 2006 costs, the daily prophylactic medicine costs

corresponded to $112 with micafungin and $48 with fluconazole. The base–case analysis found that mean hospital costs were $3859 lower for patients in the micafungin prophylaxis group compared with those who received fluconazole prophylaxis, with mean (SD) total hospital costs of $121,098 and $124,957, respectively. The study concluded that due to a reduced need for empiric antifungal therapy and fewer breakthrough infections when using micafungin as prophylaxis, although it has a higher acquisition cost, it is still a more cost-effective approach compared to fluconazole (Schonfeld et al., 2008).

Empirical antifungal therapy in neutropenic febrile patients was introduced in the early 1980s due to the high incidence of invasive fungal diseases, high mortality rate, low sensitivity of cultures, late diagnosis of fungal infections, and consequent low success rates of delayed treatment (Playford, Lipman & Sorrell, 2010). It is a cornerstone of supportive care for patients diagnosed with haematologic malignancies (Ruggero & Topal, 2014), and the standard of care used to decrease the number of deaths due to invasive fungal infection among neutropenic patients who have persistent or recurrent fever, despite broad-spectrum antibacterial treatment (Cordonnier et al., 2009).

Cordonnier et al. (2009) performed a prospective, randomised, open-label non-inferiority trial from April 2003 through February 2006 in 13 French teaching hospitals, and compared the survival with empirical treatment versus pre-emptive antifungal treatment in high-risk neutropenic patients with persistent or recurrent fever, despite antibacterial therapy. The total number of days of antifungal treatment and the mean costs of antifungal drugs were significantly lower for the pre-emptive treatment group (Cordonnier et al., 2009). On the contrary, the prospective observational study performed by Pagano et al. (2011) in 23 Italian haematology units from March 2007 to March 2009 found that the mean duration of antifungal treatment was significantly shorter in patients treated empirically than in those treated with a pre-emptive approach (Pagano et al., 2011). Both studies found the incidence of invasive fungal infection to be significantly higher in the pre-emptive than in the empirical treatment arm.

The Pagano et al. (2011) study showed that the overall mortality rates were significantly lower in patients treated with empirical therapy (6.3%) than in those with pre-emptive antifungal therapy (15.9%) (Pagano et al., 2011). However, the results from the Cordonnier et al. (2009) study showed that overall survival was not lower with pre-emptive treatment

(95.1%) compared to empirical treatment (97.3%), the results being consistent with no inferiority with regard to mortality two weeks after recovery from neutropenia (Cordonnier et al., 2009). A systematic analysis of available evidence performed by Fung et al. (2015) compared empirical and pre-emptive antifungal therapy strategies among haematologic malignancy or HSCT patients with high-risk febrile neutropenia. The study supported that a diagnostic test-guided pre-emptive approach to antifungal management in this category of patients is a clinically and economically reasonable alternative to fever-based empirical therapy (Fung et al., 2015).

Ananda-Rajah et al. (2011) undertook a retrospective case-control study of patients with acute leukaemia, or HSCT, from 2002 to 2007 at a quaternary university-affiliated hospital network in Australia, and identified pharmacy costs as the main cost driver (Ananda-Rajah et al., 2011). In contrast, Ceesay et al. (2015) reported that 74% of the costs were determined by the length of stay, proven/probable IFD length of stay being 119 days compared to 57 days where no evidence of IFD existed, from their prospectively collected data for 203 haematology patients at Kings College Hospital in London between December 2008 and May 2010. Diagnostic tools and antifungal regimen policies are additional important factors contributing towards the costs (Ceesay et al., 2015).

2.11 Conclusion

Decreasing the economic burden of IFD and maximising the return of limited healthcare resources is possible with the improved diagnostics, antifungal stewardship and individualised prophylaxis (Ananda-Rajah et al., 2011). ICU stay is one of the dominant cost drivers in a hospital admission to treat IC, and any increase in the days spent there adds to the economic burden, with efforts needing to be focused on innovative ways to reduce the length of stay in order to make a substantial reduction in the cost of treating candidaemia (Heimann et al., 2015). There is a need for ongoing investigations into the efficacy and cost of existing fungal diagnostic tests, and the development of efficient, accurate, and cost-effective diagnostic strategies to shift economic momentum towards more rational pre-emptive therapeutic approaches (Fung et al., 2015). With 33% of costs spent on patients without invasive fungal disease being on antifungal medicines, the important role of antifungal stewardship and hospital protocols is highlighted, this being necessary to ensure that the minimum requirements are met before these expensive medicines are prescribed (Ceesay et al., 2015).

Chapter 3. Paper 1

This article has been submitted to Global Journal of Health Science. See the submission acknowledgment email as proof (submission ID 3298) (Appendix A).

Authors: Rozlyn Cruickshank, Fatima Suleman

This chapter presents the submitted paper as per the journal stipulated format and limitations in terms of graphs, tables and word count. Written permission to conduct the study was sought from and granted by the Research Ethics Committee of the University of KwaZulu-Natal, (BE403/17 and Appendix B). See also the Hospital permission letter (Appendix C). See too the data collection sheet (Appendix D).

R Cruickshank was responsible for proposal development, data collection and analyses (with the assistance of a statistician) and the write up. Prof F Suleman served as supervisor.

Title:

Direct treatment costs of invasive candidiasis in haematology patients at a South African private hospital

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Abstract

Background: Haematology patients are at a high risk of developing invasive candidiasis (IC). Fluconazole has been the mainstay of prophylaxis and treatment but recently a newer class of therapeutic options, the echinocandins, has seen a considerable improvement in treatment success. However, these agents are associated with substantial acquisition costs when compared to fluconazole.

Objective: This study analysed the direct treatment costs of invasive candidiasis in haematology patients.

Methods: This is a retrospective, single-centre economic analysis of haematology patients with IC, at a private hospital in Durban, KwaZulu-Natal province, South Africa. The direct medical costs related to managing IC were analysed. Adult patients (≥18 years old) diagnosed with a haematology disorder and a positive blood culture for Candida who were prescribed fluconazole and/or an echinocandin as treatment were included in the study. Patients treated with echinocandins, fluconazole or both classes of antifungals were analysed separately and compared.

Results: There was a statistically significant difference for duration of antifungal treatment ($p = 0.013$) and antifungal administration costs ($p = 0.003$) between the three groups. Median overall direct treatment costs per patient were, ZAR110 365 for patients treated with fluconazole, ZAR219 915 for patients receiving an echinocandin and ZAR181 502 (for patients treated with both the antifungals. Overall hospital stay was the biggest cost contributor to the overall cost of treatment.

Conclusion: The results of this cost analysis found that treatment with fluconazole only is considerably less expensive, almost half of the mean daily treatment cost, when compared to an echinocandin only and treatment using both agents is still less expensive than an echinocandin as first line therapy.

Introduction

Candidaemia is the fourth most common hospital acquired bloodstream infection in the United States and the most frequently occurring worldwide, and its frequency is rising rapidly [1]. Candida species are also the fourth most frequently organism isolated from blood cultures in the private sector in the KwaZulu-Natal Province, South Africa [2]. Invasive candidiasis (IC) is an important clinical entity, specifically among critically ill Intensive Care Unit (ICU) patients, with crude mortality rates of 40–60% [3]. Invasive fungal infection poses a serious risk to critically ill and immunocompromised patients, particularly haematopoietic stem cell transplant (HSCT) recipients and those who have received intensive chemotherapy for acute leukaemia [4]. These patients experience febrile neutropenia, which complicates the differential diagnosis between a fungal infection and colonisation [5]. The outcome of IC is dependent on early initiation of effective antifungal therapy as inadequate first line treatment results in a significant increase in mortality [6]. The main therapeutic agents that are currently used in the treatment of IC include broad-spectrum oral and parenteral triazoles such as fluconazole and itraconazole, lipid formulations of amphotericin B and the newest class of antifungals, echinocandins, including caspofungin, micafungin and anidulafungin [1]. The growing incidence of fungal infections, and therefore expenditure related to their treatment, has been increasing worldwide [5]. IC along with life-threatening complications are associated with increased hospital length of stay, costly treatment in the ICU and the necessity of expensive antifungal agents, resulting in a significant rise in healthcare costs [7]. This study utilises the perspective of a South African private hospital, and includes direct medical costs, specifically hospital ward fees, medication acquisition and administration, haematology consultation and laboratory blood culture costs. The literature review identified hospitalisation costs and treatment costs as being the main cost contributors to the total costs of treating an episode of IC. The medical aid tariffs for the different levels are varied between a general ward compared to high care and ICU and thus the length of stay for each patient was broken down into the number of days in each level and the associated costs calculated. The treatment costs for the antifungals differed depending on the agents that were used based on their SEP as well as the consumables used for their administration. The haematologist consultation fees and the blood culture costs were included as they are charged to the medical aid independently from the hospitalisation costs.

This assessment is important to understand the contributing cost drivers in an episode of IC, and to use the data to establish improved and more cost-effective treatment strategies in high risk haematology patients.

Materials and methods

Study Design

This was a descriptive, retrospective, non-interventional, cost analysis study using quantitative data from the electronic and paper medical records for all included patients to compare the direct treatment cost of treating IC in high-risk haematology patients. The patients were divided into three groups according to the antifungal medicine they were prescribed during their admission: fluconazole, echinocandin or both medicines.

Study setting and population

The study took place in a private urban hospital in Durban, South Africa, which consists of 36 beds, of which 12 are used exclusively for haematology patients with underlying diagnoses. Data were collected from the 1st August 2015 to 31st August 2017, with all patients admitted during this period, and meeting the inclusion criteria, being included in the study. The perspective of the economic evaluation was from a private hospital sector perspective.

The following inclusion criteria applied:

- Adult patients (aged 18 years and older).
- Patients with an underlying haematology diagnosis, such as lymphoma, leukaemia, myeloma and haemolytic anaemia, as well as those undergoing HSCT.
- Patients with a positive blood culture for Candida spp.

The following exclusion criteria applied:

- Patients who died before being treated with an antifungal agent.
- Patients who were treated with an antifungal other than an echinocandin and/or fluconazole.

Data collection

Data was extracted from the electronic and paper medical records for all patients meeting the inclusion criteria that were maintained on the private institution's information system, specifically those from 1st August 2015 to 31st August 2017. A data collection sheet was

created as the data extraction instrument (Appendix D), with the following variables being extracted:

- Demographic data: age, gender and underlying haematology diagnosis, name of medical aid.
- Hospital data: admission and discharge date, total length of stay, length of stay in each level of care (i.e. general, high care, isolation and ICU), number of blood cultures during hospital admission, and number of doses of fluconazole and an echinocandin.

The data was extracted by the principal investigator who then captured the data onto an excel spreadsheet which was then verified for correctness by a study assistant.

The independent and dependent variables are presented below.

Independent

- The number of echinocandin and/or fluconazole doses administered
- Haematologist consultation costs

Dependent

- Single Exit Price of the antifungal medication
- Cost of consumables used in administering the antifungal medicines
- Length of hospital stay (LOS)

Confounding Variables

- Haematology diagnosis
- Prescriber's first line choice of therapy

Costing Variables

Only direct medical costs were considered for this study, and included antifungal medications and consumables used for their administration, blood cultures, haematology consultations and hospitalisation costs. Direct non-medical costs and indirect medical costs as well as intangible costs were not included in the study. The antifungal administration costs were based on the single exit price (SEP) of the antifungal medication, obtained from the Government gazetted SEP database for the years 2015, 2016 and 2017. The SEP is adjusted annually based on a calculation that incorporates the South African CPI (consumer price index), the Euro Rand exchange rate and the Dollar Rand exchange rate. The cost of a medication administration

pack, specific for each antifungal, which included the costs of the syringe, needle, alcohol swabs, diluent, infusion fluid and infusion set was also included (Table 1). For the purpose of the study the total direct costs were calculated by summing the median and mean, where appropriate, costs per unit and the daily direct cost was calculated as the total direct cost per mean number of days for each of the three groups.

Table 1 – Antifungal medication and consumable costs (ZAR)

		Antifungal costs								
		2015			2016			2017		
		SEP (Single Exit Price)	Daily administration consumable costs	Total daily cost	SEP (Single Exit Price)	Daily administration consumable costs	Total daily cost	SEP (Single Exit Price)	Daily administration consumable costs	Total daily cost
Fluconazole	**(Dilfucan®)**	197.29	368.52	1131.61	206.74	737.03	1150.51	212.72	737.03	1162.47
Echinocandin	**Caspofungin (Cancidas®)**	2888.60	396.12	3284.72						
	Anidulafungin (Eraxis®) – loading dose (day 1)	4838.96	390.80	5229.76						
	Anidulafungin (Eraxis®) – maintenance dose	2419.48	387.58	2807.06						
	Micafungin (Mycamine®)	1824.00	435.94	2259.94	1824	436.72	2260.72	1960.80	438.34	2399.14

The hospital ward charges were based on the National Health Network agreed tariffs with the individual medical aids for that specific year, and the laboratory costs for a blood culture for each year of the study (Table 2) and Table 3 denotes the haematologist consultation rates that were based on the agreed fees by the hospital with the medical funders for each year.

Table 2 - Cost of hospital stay and laboratory costs (ZAR)

Hospital rates*					
Date	**General**	**Isolation**	**High Care (HC)**	**ICU**	**Laboratory rates**
2015	1932.40	2545.85	5129.80	8614.65	212.25
2016	2224.40	2887.14	5903.92	9785.70	220.85
2017	2329.95	3002.45	6066.65	10362.48	229.75

**Average costs were calculated for each level of care for a particular year based on the individual medical aid tariffs applicable to each patient included in the study.*

Table 3 – Haematologist inpatient consultation costs (ZAR)

Haematologist inpatient consultation rates*								
	Initial				**Follow up**			
	General	**Isolation**	**HC**	**ICU**	**General**	**Isolation**	**HC**	**ICU**
2015	619.05	619.05	391.58	1305.75	263.89	263.89	391.58	652.87
2016	564.13	564.13	401.29	1343.02	285.44	285.44	401.29	671.50
2017	656.15	656.15	458.09	1527.17	340.21	340.21	458.09	761.85

**Average costs were calculated based on the individual medical aid tariffs applicable to each patient included in the study.*

Data analysis

The data analysis consisted of two components, the first entailing a statistical analyses of the data to establish any statistically significant relationships between the variables. The second was a sensitivity analysis that increased and decreased each cost parameter to identify the factor that had the greatest impact on the total cost of treating an IC episode.

The data were analysed using IBM SPSS Statistics software, for Windows version 25. The normality of distribution of the continuous variables was tested by Kolmogorov-Smirnov test. Continuous variables with normal distribution were presented as mean (standard deviation [SD]); non-normal variables were reported as median (interquartile range [IQR]).One-way ANOVA was applied to test the statistical significance of the normally distributed continuous variables between the three groups and Kruskal-Wallis was used for the variables that were not normally distributed. Due to the small sample size the relationship between the categorical variables were tested using Fisher's exact test, with a *p*-value of <0.05 being considered significant. For descriptive purposes, patient and cost data are presented as the median and the interquartile range (IQR) or the mean and standard deviation (SD) as appropriate.

One-way sensitivity analysis was performed using Microsoft® Excel 2010, by increasing and decreasing each direct cost parameter over a range between 5% and 20%, while keeping the other costs constant, observing the effect of the results and identifying which variable had the greatest impact on the total cost of treating an episode of IC. The following factors were analysed with the one-way sensitivity analysis:

1. Mean ICU ward costs
2. Mean high care ward costs
3. Mean isolation ward costs
4. Mean general ward costs
5. Mean antifungal medication administration costs for the treatment duration
6. Mean laboratory culture costs
7. Mean haematologist consultation costs

Ethical considerations

The protocol received approval from the Biomedical Research Ethics Committee at the University of KwaZulu-Natal in South Africa (reference number BE403/17) (Appendix B). As this was a retrospective chart review study, the patient's permission was not required.

However, permission was obtained to access the data from the hospital manager (Appendix C). To prevent any bias, no randomisation or blinding in the sample selection was introduced.

Results

The final dataset included any patient over the age of 18 years old with an underlying haematology diagnosis and a positive blood culture for Candida. A total of 321 patient admissions were identified that included treatment with fluconazole and/or an echinocandin during the study period from 1 August 2015 to 31 August 2017. Of these, 96 episodes were excluded based on the inclusion and exclusion criteria regarding age and underlying haematology diagnosis. Of the remaining 225 episodes, only 24 had a positive blood culture for Candida and therefore were eligible to be included in the cost analysis (Figure 1).

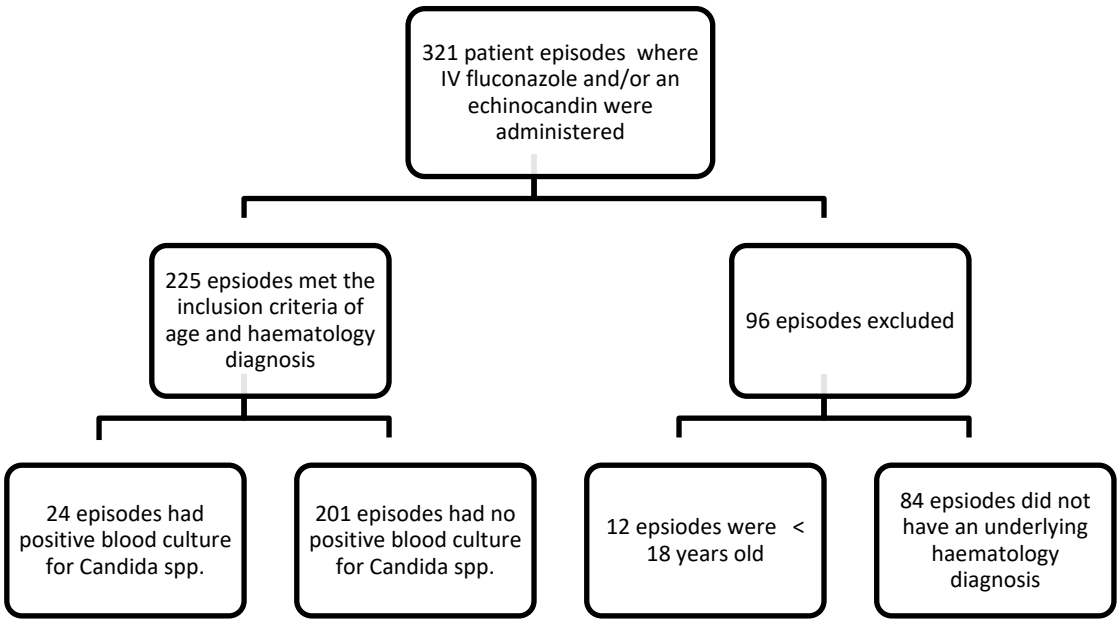

Figure 1 - Selection of study population

Demographic data

According to Kolmogorov-Smirnov test the variable age was normally distributed, since it is normal, the means and standard deviation are depicted. The mean age of the patients was 55.20 years (*SD,* 20.24), 41.91 years (*SD,* 17.73) and 46.25 years (*SD,* 22.37) in the fluconazole, echinocandin and both groups respectively. Gender and underlying haematology diagnosis was not normally distributed. Of the 24 patients, 33.3% (n=8) were female, and the most common underlying haematology diagnoses were acute myeloid leukaemia (n=6), acute

lymphoblastic leukaemia (n=4) and multiple myeloma (n=4) (Table 4). The one-way ANOVA showed no statistically significant difference in baseline characteristics in terms of mean age between the three groups. The Fisher's exact test showed no statistically significant difference between the groups with regards to gender and haematology diagnosis.

Table 4 - Patient characteristics and underlying haematology diagnosis

	Fluconazole, N = 5 n (%)	**Echinocandins, N = 11 n (%)**	**Both, N = 8 n (%)**	***p* value***
Age (years), mean (*SD*)	55.20 (20.24)	41.91 (17.73)	46.25 (22.37)	0.476#
Female	3 (60)	3 (27.3)	2 (25)	0.457¥
Haematology diagnosis				0.165¥
Acute promyelocytic leukaemia	-	-	1 (12.5)	
ALL	1 (20)	3 (27.3)	-	
AML	1 (20)	3 (27.3)	2 (25)	
Burkitt Lymphoma	1 (20)	-	1 (12.5)	
Diffuse large B cell lymphoma	-	-	2 (25)	
Haemolytic anaemia	-	1 (9.1)	-	
Hepatosplenic T cell lymphoma	-	1 (9.1)	-	
Hodgkin lymphoma	-	-	2 (25)	
Multiple myeloma	1 (20)	3 (27.3)	-	
Non Hodgkin lymphoma	1 (20)	-	-	
#One way ANOVA ; ¥Fischer's exact test				

Statistical analysis

According to Kolmogorov-Smirnov test the variable overall hospital stay was normally distributed, since it normal, the means and standard deviation were depicted. The duration of antifungal treatment variable was not normally distributed and was thus depicted as the median and IQR. Patients receiving both fluconazole and an echinocandin had a much longer duration of antifungal treatment as well as overall hospital stay (Table 5). The patients who were treated with fluconazole only had much shorter antifungal treatment duration and an overall hospital stay. The patients receiving an echinocandin had the shortest general ward

stay but the longest ICU stay. There was no statistically significant difference in length of stay at any of the levels of care or overall hospital stay. The Kruskal-Wallis test showed a statistically significant difference for the duration of antifungal treatment between the three groups (p = 0.013).

Table 5 - Duration of antifungal treatment and length of hospital stay

	Fluconazole, N = 5	**Echinocandins, N = 11**	**Both, N = 8**	***p* value***
Duration of antifungal treatment (days)median (IQR)	6.5 (5.00 – 12.75)	15 (11 – 23)	20.5 (15.5 – 27.5)	*0.013+
Overall hospital stay (days), mean (SD)	23.3 (11.68)	28.5 (11.05)	38.7 (21.57)	0.197#
Length of stay – General ward (days)median (IQR)	4.00 (1.75 – 22.00)	2.5 (0.00 – 8.50)	11.75 (1.13 – 18.50)	0.222+
Length of stay – Isolation ward (days)median (IQR)	1.0 (0.00 – 12.00)	0.00 (0.00 – 7.50)	4.25 (0.25 – 14.13)	0.729+
Length of stay – High Care (days)median (IQR)	0.00 (0.00 – 6.75)	0.5 (0.00 – 10.00)	9.25 (4.63 – 12.25)	0.079+
Length of stay – ICU (days)median (IQR)	0.00 (0.00 – 13.25)	10.00 (0.00 – 24.00)	1.0 (0.00 – 28.88)	0.57+
#One way ANOVA; +Kruskal-Wallis test				

The overall direct costs, calculated by summing the medians and means of the four cost study variables, per patient were, ZAR110 365 for patients treated with fluconazole, ZAR219 915 for those receiving an echinocandin and ZAR181 502 for patients treated with both medications (Table 6). There is an excess cost of ZAR109 550 per patient in the echinocandin group and of ZAR71 137 in the group treated with both medications compared to the fluconazole group. The direct costs per day, calculated by dividing the total direct cost by the mean overall hospital days, were ZAR4 736 in the fluconazole group vs ZAR7 716 in the echinocandin group and ZAR4 689 in the group with both medications. The Kruskal-Wallis test showed a statistically significant difference (p = 0.003) for the antifungal administration treatment costs between the three groups. This cost variable contributed 6.9% in the

fluconazole group, 19.0% in the echinocandin group and 21.4% in the group treated with both, to the overall direct costs. The median number of antifungal treatment days in the fluconazole group was 6.5 with a mean daily cost of ZAR1162, 15 days in the echinocandin group with a mean daily cost of ZAR2 784 and 20.5 days with a mean daily cost of ZAR1 895 in the combined treatment group.

Table 6 - Overview of the direct cost distribution among groups

Direct cost parameter (ZAR)				
	Fluconazole, N = 5	**Echinocandins, N = 11**	**Both, N = 8**	**p value***
Length of stay, median (IQR)				
General	9 319 (4 077 – 50 414)	5 561 (0 – 18 907)	24 580 (2 173 – 36 712)	0.232+
Isolation	3 002 (0 – 34 846)	0 (0 – 21 631)	12 435 (721 – 35 960)	0.781+
High care	0 (0 – 40 949)	3 033(0 – 59 039))	50 963(24 983 – 66 951)	0.088+
ICU	0(0 – 137 302)	97 857(0 – 234 856)	10 362 (0 – 282 562)	0.618+
Total length of stay, median (IQR)	93 273 (38 197 – 188 917)	161 444 (78 324 – 275 484)	128 783 (68 432 – 341 272))	0.392+
Haematologist consultation, median (IQR)	8 713(4 771 – 16 521)	14 805 (8 194 – 21 901)	11 831 (7 524 – 22 476)	0.477+
Antifungal treatment, median (IQR)	7 556(5 812 – 14 764)	41 774 (30 634 – 51 996)	38 849 (31 715 – 67 021)	***0.003+**
Blood cultures, mean (SD)	823 (340 – 1 306)	1 892 (1 098 – 2 686)	2039 (1 043 – 3 035)	0.134#
Total direct costs	110 365	219 915	181 502	0.135+
Daily direct costs	4 736	7 716	4 689	0.145+

#One way ANOVA; +Kruskal-Wallis test

Sensitivity analysis

One-way sensitivity analysis was performed in Microsoft ®Excel by varying the mean or median cost of each parameter of the three groups over a range between 5% and 20%. Changes in the total direct costs base value (fluconazole = ZAR110 365, echinocandin = ZAR219 915 and both = ZAR181 502) were noted. The one-way sensitivity analysis showed that the median ICU ward costs was a considerable cost driver in the echinocandin group due to the high number of ICU days in this treatment group, and high care ward costs in the group treated with both antifungals over the 7.5%, 10%, 15% and 20% change. This is in line with the data that showed that ward costs contributed the most towards the overall cost of treating an episode of IC. Medicine administration costs for the duration of therapy was an important cost driver in the echinocandin only group and the combined treatment group but not in the fluconazole group, although there was a minor impact at the 10% and 15% change (Table 7). This is due to the much higher acquisition costs of the echinocandins compared to fluconazole.

Table 7 – One-way sensitivity results

	% CHANGE IN TOTAL DIRECT COSTS														
MEAN OR MEDIAN COSTS	20 %	15 %	10 %	7.5%	5 %	20 %	15 %	10 %	7.5 %	5%	20 %	15 %	10 %	7.5 %	5%
	FLUCONAZOLE					ECHINOCANDIN					BOTH				
ICU	0.0	0.0	0.0	0.0	0.0	8.9	7.4	4.9	3.7	2.5	1.1	0.9	0.6	0.4	0.3
High Care	0.0	0.0	0.0	0.0	0.0	0.3	0.2	0.2	0.1	0.1	5.6	4.2	2.8	2.1	1.4
Isolation	0.5	1.3	0.9	0.6	0.4	0.0	0.0	0.0	0.0	0.0	1.4	1.0	0.7	0.5	0.3
General	1.7	4.0	2.6	2.0	1.3	0.5	0.4	0.3	0.2	0.1	2.7	2.0	1.4	1.0	0.7
Antifungal medication administration	1.4	3.2	2.1	1.6	1.1	3.8	3.2	2.1	1.6	1.1	4.3	3.2	2.1	1.6	1.1
Laboratory culture	0.1	0.3	0.2	0.2	0.1	0.2	0.1	0.1	0.1	0.0	0.2	0.2	0.1	0.1	0.1
Haematologist consultation	1.6	3.7	2.5	1.9	1.2	1.3	1.1	0.7	0.6	0.4	1.3	1.0	0.7	0.5	0.3

Discussion

The results of the study showed that the overall direct cost of treating an episode of IC was much higher in the group that was treated with an echinocandin even when compared to the group treated with both fluconazole and an echinocandin, either due to treatment failure or a step-down approach. The total direct costs were almost 50% more in the echinocandin group when compared to the fluconazole only group. The study by Heimann et al. (2015) supported this finding; their study showed that the mean overall direct treatment costs per patient treated with an echinocandin to be significantly higher than fluconazole, the main contributor being that the echinocandin treated patients were more ill and had longer ICU stays. This is contrary to the findings from Tagliaferri and Menichetti (2015) who found that echinocandins reduce overall in-hospital costs compared to fluconazole and Reboli et al. (2011) who concluded that anidulafungin versus fluconazole in ICU patients resulted in a reduction in total IC related costs due to the decreased length of stay. The patient's age, gender and haematology diagnosis had no statistically significant impact on the results of the study, and there was no difference between the three groups.

Hospital ward costs contributed 70.9% in the group treated with fluconazole and an echinocandin, 84.5% in the fluconazole group and 73.4% in the echinocandin group towards the overall direct cost. This outcome is consistent with the findings from the literature review that length of hospital stay has a substantial impact on the cost of treating an episode of IC. Studies using data spanning over many years and in various countries conducted by Wilson et al. (2002), Ha et al. (2012), Ceesay et al. (2015) and Armaganidis et al. (2017) all agreed with the findings of this study. From the study results, it can be seen that the ICU length of stay was much longer in the echinocandin group, possibly indicating that this class of antifungal was used in more clinically unwell patients, particularly when compared to the patients treated with fluconazole. This significantly contributed to the overall direct cost where median ICU ward fees were ZAR97 857, (IQR, 0 – 234 856) in the echinocandin group compared to almost ZAR0 (IQR, 0 – 137 302) in the fluconazole group.

In addition, this study showed that patients in the group treated with both fluconazole and an echinocandin had a much longer mean hospital stay (38.7 days) compared to the fluconazole group (23.3 days) and the echinocandin group (28.5 days). Armaganidis et al. (2017) had a

similar result; patients who switched antifungal treatment had a longer length of stay in ICU with a mean of 53.8 days.

The second biggest cost contributor, although much less substantial, after the hospital ward costs were the antifungal treatment costs. There was a statistically significant difference in the duration of antifungal therapy treatment days between the three groups. The duration of antifungal treatment was the highest in the group treated with both medicines with a median of 20.5 days, contributing 21.4% to the overall direct cost. A similar result was seen in the study by Armaganidis et al. (2017) where patients who switched antifungal therapy had a much longer duration of treatment with a mean of 27.3 days. In this study the echinocandin group was the second longest with a mean of 15 days and contributing 19%. The fluconazole treatment group was the shortest with a mean of only 6.5 days and a modest 6.9% toward the overall direct cost. This is reasonably similar to the results of studies discussed in the literature review, where Ha et al. (2012) concluded that antifungal treatment costs contributed 10% of the total direct cost, Heimann et al. (2015) found the treatment costs to be less than 10% and Wilson et al. (2002) results showed antifungal treatment costs to contribute approximately 17%. Conversely the study conducted by Ananda-Rajah et al. (2011) at an Australian quaternary university-affiliated hospital network, was the only study included in the review that found pharmacy costs responsible as the main cost contributor, this was attributed to the high acquisition costs of the antifungals that were used as anti-mould prophylaxis and treatment. There was a statistically significant difference in the antifungal treatment costs between the groups which was supported by the results of the study by Heimann et al. (2015).

The other two costs factors considered in this study contributed small amounts to the overall treatment cost. The haematologist consultation costs were dependent on the length of hospital stay and the level of care of the patient as the ICU charge was higher than the general and high care ward consultation costs. The blood culture costs contributed a minor portion towards the overall costs and were independent from the choice of antifungal treatment.

Conclusion

The main cost driver in the overall cost of treating IC is due to the ward costs which contributed 76.3% on average between the three groups. This was dependent on the level of care of the patients stay, where it can be seen that patients spending longer in the ICU have much higher costs. The antifungal administration costs also contribute a substantial amount to the overall treatment costs, this varies dependent on the choice of first line therapy as well as its success, as a change in the treatment resulted in increased treatment costs as well as extended length of stay. Further studies with larger sample sizes are required to establish whether fluconazole should be used as first line therapy and only changed to an echinocandin where resistance is identified on blood culture.

Conflict of interest: None

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Chapter 4: Conclusion and recommendations

This study analysed the direct costs associated with the treatment of invasive candidiasis with fluconazole or an echinocandin in haematology patients in a private hospital in South Africa. The aim of the study was to analyse the costs and then subsequently use the findings to facilitate the implementation of treatment guidelines for invasive candidiasis at the institution.

The outcomes of this retrospective cost analysis of 24 episodes of invasive candidiasis found that there was a statistically significant difference in the duration of antifungal treatment days and the antifungal treatment cost between the three groups of patients either treated with fluconazole, fluconazole and an echinocandin or only an echinocandin. Treatment with fluconazole is considerably less expensive, almost half of the mean daily treatment cost, compared to an echinocandin, while treatment using both agents, fluconazole and an echinocandin, is less expensive than an echinocandin only as first line therapy. This study does not support the initial hypothesis that the first line use of fluconazole followed by an echinocandin only after a positive culture result is received appeared to be a costlier approach than using an echinocandin as first line therapy in these high-risk patients. The study showed that although the cost of antifungals is high, they only contribute approximately 15.8% towards the direct treatment cost of an episode of IC. Although antifungal costs are not a big cost contributor, treatment failure does result in increased length of stay, which increases the overall costs. Optimising the treatment choice and therapeutic approach is still an important factor to consider, as it has other important implications, such as clinical outcomes and resistance patterns.

The study results showed that the greatest contributing factor to the direct treatment cost of IC was length of hospital stay, which contributed 76.3% on average between the groups. Future focus needs to be on mechanisms to reduce the length of hospital stay for these patients to ensure cost containment.

A limitation is that the study was only done in one private hospital, and the results may therefore not reflect those of other such facilities in terms of medicines used and treatment approach. However, the costs are likely to be very similar, with those results having implications for other private facilities across the country. The study did not include any

public sector facilities. However, the study has implications for these facilities, which carry a considerable burden of patients who are immunocompromised and highly susceptible to acquiring secondary infections due to their HIV status. Public sector facilities need to be aware of the implications of not treating infections appropriately the first time, and the potential for an extended stay, with considerable associated costs.

It is recommended that further research incorporating a larger sample size in private health facilities across South Africa be undertaken to obtain a more in depth understanding of the direct treatment costs of IC in these haematology patients.

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Appendix A – Acknowledgment of receipt of submission

From: Global Journal of Health Science <gjhs@ccsenet.org>
Date: 08 January 2019 at 15:30:56 GMT+1
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Subject: [GJHS] Submission Acknowledgement 3298

Dear Fatima Suleman:

Thank you for submitting the manuscript, "Direct treatment costs of invasive candidiasis in haematology patients at a South African private hospital" to Global Journal of Health Science.

Submission ID: 3298

Your manuscript will be processed for the similarity check and peer review. We use the double-blind system for peer reviews. The manuscript will be peer-reviewed by at least two experts. The review process may take two to three weeks. We will inform you of our decision and the reviewers' comments as soon as possible.

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Appendix B – BREC approval

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

13 November 2017

Ms R Cruickshank (216015075)
Discipline of Pharmaceutical Sciences
rozycruickshank@gmail.com

Dear Ms Cruickshank

PROTOCOL: Comparing the costs and clinical outcomes of using a de-escalation approach with an echinocandin versus an escalation approach with fluconazole in the prophylaxis and treatment of invasive candidiasis in haematology patients at a South African private hospital
Degree: MPharm
BREC Ref No: BE403/17

EXPEDITED APPLICATION

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application received on 22 June 2017.

The study was provisionally approved pending appropriate responses to queries raised. Your response received on 29 September 2017 to BREC correspondence dated 15 August 2017 have been noted by a sub-committee of the Biomedical Research Ethics Committee. The conditions have now been met and the study is given **full ethics approval** and may begin as from 13 November 2017.

This approval is valid for one year from **13 November 2017.** To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2015), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be **RATIFIED** by a full Committee at its next meeting taking place on **12 December 2017.**

We wish you well with this study. We would appreciate receiving copies of all publications arising out of this study.

Yours sincerely
[redacted]
Professor J Tsoka-Gwegweni
Chair: Biomedical Research Ethics Committee

cc supervisor: sulemanf@ukzn.ac.za
cc postgraduate administrator: nenep1@ukzn.ac.za

Biomedical Research Ethics Committee
Professor J Tsoka-Gwegweni (Chair)
Westville Campus, Govan Mbeki Building
Postal Address: Private Bag X54001, Durban 4000
Telephone: +27 (0) 31 260 2486 **Facsimile:** +27 (0) 31 260 4609 **Email:** brec@ukzn.ac.za
Website: http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx

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Appendix C – Hospital permission letter

capital haematology HOSPITAL

Capital Oncology (Pty) Ltd 2009/023804/07
Practice no 0570000511560

Tel: +27 31 832 9700
Email: info@capitalsurgical.co.za
Website: www.capitalhospital.co.za
95 King Cetshwayo Highway, Westridge, 4091
PO Box 30590, Mayville, 4058

11th September 2017

TO WHOM IT MAY CONCERN

RE: Access to the hospital electronic information system for data collection for Masters in Pharmacy (online) Research Project

Primary investigator: R. Cruickshank (216015075)

Title of research project: Comparing the costs and clinical outcomes of using a de-escalation approach with an echinocandin versus an escalation approach with IV fluconazole in the prophylaxis and treatment of invasive candidiasis in haematology patients at a South African private hospital

This is to confirm that the management at Capital Hospital, give R. Cruickshank access to the hospital electronic information system for data collection of the relevant data required for her research project.

Kindly be advised that if it does not have any negative implications for Capital Hospital or any of its related entities, access is approved but the information is NOT for publication.

Yours sincerely

[redacted]

Devika Pillay

Hospital Management

capital hospital Capital Haematology Hospital is part of the Capital Hospital Group.

Appendix D – Data collection tool

<table>
<tr><td>Name:</td><td></td><td>Hospital no:</td><td></td></tr>
<tr><td>DOB:</td><td></td><td>Age:</td><td></td></tr>
<tr><td>Gender:</td><td></td><td>Date of admission:</td><td></td></tr>
<tr><td>Haematology diagnosis:</td><td></td><td>Date of discharge:</td><td></td></tr>
<tr><td rowspan="4">Total hospital length of stay:</td><td rowspan="4"></td><td>General ward days:</td><td></td></tr>
<tr><td>Isolation days:</td><td></td></tr>
<tr><td>High care days:</td><td></td></tr>
<tr><td>ICU days:</td><td></td></tr>
<tr><td rowspan="2">Total antifungal treatment days:</td><td rowspan="2"></td><td>Fluconazole days:</td><td></td></tr>
<tr><td>Echinocandin days:</td><td></td></tr>
<tr><td colspan="4">Total number of blood cultures performed during admission:</td></tr>
<tr><td colspan="4">Comments:</td></tr>
</table>