The prescribing practices of echinocandins in adult patients in a private hospital

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Mini-dissertation submitted in *partial* fulfilment of the requirements for the degree *Magister Pharmaciae* in Advanced Clinical Pharmacy at the Potchefstroom Campus of the North-West University

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It all starts here ™

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This mini-dissertation is submitted in fulfilment of the requirements for the degree *Magister Pharmaciae* in Advanced Clinical Pharmacy at the Potchefstroom Campus of the North-West University.

The requirements entail to publish at least one article.

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ABSTRACT

The prescribing patterns of echinocandins in adult patients in a private hospital

Background: Antifungal stewardship, an entity that has been largely deserted, needs to be included in the initiative to fight antimicrobial resistance. Fundamentals that need to be addressed are such as the appropriate use and dose of antifungal agents, simple indicators to the most relevant risk factors associated with these infections and the effective and appropriate timing of the antifungal agent administration, as well as to monitor the appropriate use of these agents. For the last decade conventional amphotericin B and azole antifungals has been the mainstay of antifungal therapy in the South African setting. However, high frequency of infusion-related toxicity and nephrotoxicity associated with amphotericin B and the occurrence of fluconazole-resistant strains of the *C. glabrata* species (spp.) urged a search for alternatives. Alarmingly, resistance to amphotericin B (the antifungal with the broadest spectrum of activity) has been reported in all *Candida* spp., whilst resistance to the azole group of antifungals, such as fluconazole, has been reported to be as high as 50% in *Candida* spp., warranting antifungal stewardship implementation. Fortunately, echinocandins, a newer generation antifungal class has broad spectrum activity against a variety of *Candida* spp. and is indicated for the treatment of invasive candidiasis

Objective: The purpose of this study was to review the available literature regarding the appropriate prescribing of echinocandins and to compare the literature to the prescribing patterns of echinocandins in a private hospital in South Africa (SA).

Method: A retrospective quantitative research design was applied to collect data from patient files using a pre-developed data collection form. The inclusion criteria was adult patients (>18 years) who were on echinocandin treatment from 1 January 2015 – 1 January 2016. Patients were excluded if antifungal therapy formed part of their chronic medication, pregnant patients and patients who received more than one intravenous echinocandin. The data collection was conducted from 1 August 2016 – 31 October 2016. The data collection tool was used to collect the data and required the following information: demographic information, including age (inclusion criteria states only patients >18 years), and ward admitted in hospital (to comply with inclusion and exclusion criteria); the IV echinocandin that the patient was started with; Loading dose (LD); prescribed daily dose (PDD); start date and end date of echinocandin treatment; de-escalation of therapy; if yes, active ingredient of oral agent; presence of blood cultures; result of blood cultures; cost of antifungal treatment (i.e. the total amount that the hospital pharmacy charged the patient for the medication alone); and cost of blood tests and blood cultures performed.

Results: One hundred and forty six patients complied with the study criteria after a random selection. Among them 102 (69.863%) received caspofungin and 99 (97.058%) also received the correct LD while 3 (2.941%) did not receive a LD. 44 (20.127%) patients received anidulafungin, only 30 (68.18%) received the correct LD and 14 (31.819%) did not receive a LD. For the maintenance dose of caspofungin 98 (98.078%) patients received 50mg intravenous daily (IV) and 4 (3.922%) patients received 70mg IV per day. For anidulafungin 1 (2.273%) patient received 400mg IV per day, 23 (52.273%) patients received 200mg IV per day, 19 (43.182%) patients received 100mg IV per day and 1 (2.273%) patient received only 50mg IV per day. To determine whether there is an association between de-escalation of therapy and the presence of blood cultures the p-value (0.83) is bigger than 0.05, indicating that there were no association between the two variables. Cramér's *V* (0.018) is less than 0.5 indicating a small effect with no practical significance, meaning that there is no association between de-escalation of treatment and the availability of blood cultures. The p-value of 0.888 is greater than the p-value of significance (0.05) meaning that there are no statistical significant difference between the average duration of treatment between patients with blood cultures and patients without blood cultures. Cohen's *d* value = 0.031 indicating that there is a small effect with no practical significance, which indicates that the duration of echinocandin therapy is not dependant on the presence of a positive blood culture. The average cost between patients with positive blood cultures those patients without blood cultures do not differ statistically significantly from one another. Cohen's *d* value is less than 0.8 indicating that there is a small effect with no practical significance. The p-value (0.801), is greater than the significant level of p = 0.05 (5%), indicating that the presence of blood cultures do not differ statistically significantly from one another.

Conclusions and recommendations: The researcher has attempted to investigate and compare the prescribing patterns of echinocandins in a private hospital. After studying the literature it was observed that the prescribing doctors at this study setting are mostly compliant to the available guidelines regarding the appropriate use of echinocandins. In SA the cost of blood cultures are being weighed up against the cost of treatment and it is within this aspect that the doctors might feel that this requirement of the guidelines is not reachable. It is debatable if the literature is very practical in an environment where cost plays such a big role.

It is recommended that future research projects on this topic should include clinical data such as removal of catheters or indwelling devices as this aspect plays a big role in the duration of therapy and the source of the infection. A cost campaign regarding blood cultures versus treatment should be introduced to doctors and laboratories. More research is needed to establish if there is an effect such as a shorter duration of stay when blood cultures are performed more often.

Keywords: invasive candidiasis, echinocandins, caspofungin, anidulafungin, micafungin, antifungal stewardship, de-escalation, blood cultures, cost

UITTREKSEL

Die voorskryf patrone van eginokandien in volwasse pasiënte in ‘n privaat hospitaal.

Agtergrond: Die verantwoordelike gebruik van anti-fungale geneesmiddels is ‘n entiteit wat nagelaat is in die stryd om antibiotika weerstandigheid te beveg. Fundamentele aspekte is van belang wanneer ‘n mens fokus op die verantwoordelike gebruik van die groep anti-fungale geneesmiddels byvoorbeeld: toepaslike gebruik en doserings van anti-fungale geneesmiddels, toepaslike aanwysers vir die risiko faktore wat gepaard gaan met fungale infeksies, effektiewe en toepaslike tydsberekening in terme van die toediening van die middel, sowel as om die gebruik van die anti-fungale middels streng te monitor. Vir die laaste dekade was konvensionele amfoterisien B en die asool anti-fungale middels die standaard behandeling vir fungale infeksies in die Suid Afrikaanse omgewing. Ongelukkig het die hoë insidensie van infusie gedrewe toksititeit sowel as as nier toksisiteit wat gepaardgaan met amfoterisien B, en die flukonasool-weerstandige organismes soos *C. glabrata*, veroorsaak dat alternatiewe geneesmiddels gebruik moet word**.** ‘n Ontrustende feit is dat daar weerstandigheid aangeteken is vir amfoterisien B (die voorheen bekende middel met die breedste spektrum van aktiwiteit) vir alle *Candida* spesies. Daarmee saam is weerstandigheid van 50% vir *Candida* spesies aangeteken vir die azool groep antifungale middels soos flukonasool, en dus word dit genoodsaak om rentmeesterskap van die anti-fungale middels te implementeer. Maar danksy die eginokandiene is ‘n groep anti-fungale middels beskikbaar wat aktiwiteit het teen ‘n verskeidenheid *Candida* spesies en ook aangedui is vir ernstige sistemiese fungale infeksies.

Doelwit: Die doelwit van die studie was om die literatuur rakende die verantwoordelike gebruik van eginokandiene te bestudeer en die literatuur te vergelyk met die voorskryf patrone van eginokandiene in ‘n privaat hospitaal in Suid Afrika (SA).

Metode: ‘n Terugskouende, kwantitatiewe navorsingsontwerp is gevolg om die data uit pasiënte se mediese leers te verkry deur gebruik te maak van ‘n vooraf opgestelde data versamelingstemplaat. Die insluitingskriteria was volwasse pasiënte (>18 jaar), wat op eginokandien behandeling was in die tydperk 1 Januarie 2015 – 1 Januarie 2016. Pasiënte is uitgesluit van die studie populasie as antifunale geneesmiddels deel was van hul kroniese medikasie, swanger vrouens asook pasiënte wat op meer as een intraveneuse (IV) eginokandien was. Die data versameling het plaasgevind vanaf 1 Augustus 2016 – 31 Oktober 2016. Die data versamelingstemplaat was gebruik om die nodige data te versamel bv: demografiese inligting, insluitend ouderdom (insluitingskriteria slegs vir pasiënte > 18 jaar), saal waarin die pasiënt opgeneem was (om te voldoen aan insluitingskriteria); die IV eginokandien waarmee die pasiënt begin was; die ladings doserings (LD), die daaglikse dosering; begin en

eind datum van die eginokandien behandeling; de-eskelasie van terapie; indien ja, aktiewe bestanddeel van die orale geneesmiddel; teenwoordigheid van bloed kulture; resultaat van bloed kulture; koste van die antufungale behandeling; en die koste van bloed toetse en bloed kulture teenwoordig.

Resultate: Een-honderd-ses-en-veertig pasiënte het voldoen aan die insluitingskriteria na ‘n ewekansige seleksie. 102 (69.863%) van die pasiënte het kaspofungien ontvang en 99 (97.058%) het die korrekte LD ontvang terwyl 3 (2.941%) nie ‘n LD ontvang het nie. 44 (20.127%) pasiënte het anidulafungien ontvang waarvan 30 (68.18&) die korrekte LD ontvang het en 14 (31.81%) nie ‘n LD ontvang het nie. Vir die daaglikse dosering van kaspofungien het 98 (98.078%) pasiënte 50mg IV daagliks ontvang en 4 (3.922%) het 70mg IV daagliks ontvang. 1 (2.273%) pasiënt het met anidulafungien ‘n daaglikse dosering van 400mg IV ontvang, 23 (52.273%) pasiënte het 200mg IV per dag ontvang, 19 (43.182%) pasiënte het 100mg IV per dag ontvang en 1 (2.273%) het slegs 50mg IV per dag ontvang. Om die verwantskap te bepaal tussen die de-eskalasie van terapie en die teenwoordigheid van bloed kulture was die p-waarde van 0.83 groter as 0.05, wat daarop dui dat daar geen statistiese betekenisvolle verwantskap nie. Cramérs se *V* waarde was 0.018, en dus minder as 0.5, wat aandui dat daar ‘n klein verwantskap is met geen praktiese betekenis, en daar dus geen verwantskap is tussen die de-eskalasie van terapie en die teenwoordigheid van bloed kulture is nie. Die p- waarde 0.888 is groter as 0.05 wat daarop aandui dat daar ook geen statitsiese betekenisvolle verskil is tussen die gemiddelde behandelingsduur met eginokandiene van pasiënte met of sonder bloed kulture. Cohen se *d* waarde = 0.031 beteken dat daar ‘n klein effek is met geen praktiese betekenis, wat daarop aandui dat die behandelingsduur van eginokandien terapie nie afhanklik is van die teenwoordigheid van ‘n positiewe bloed kultuur nie. Die gemiddelde koste tussen pasiënte met positiewe bloed kulture teenoor die sonder bloed kulture het geen statistiese betekenisvolle verskil nie. Cohen se *d* waarde is minder as 0.8 en dui aan dat dit ‘n klein effek het met geen prakties betekenisvolle verskil nie. Die p-waarde (0.801), is groter as 0.05, wat beteken dat die teenwoordigheid van bloed kulture of al dan nie, nie statisties met mekaar verskil nie.

Gevolgtrekking en aanbevelings: Hierdie studie het gepoog om die voorskryf patrone van eginokandiene te bestudeer en vergelyk met voorskryf patrone in ‘n privaat hospitaal in SA. Na intensiewe literatuur bestudering was dit waargeneem dat die voorskrywende dokters by die studie instelling meestal voldoen aan die beskikbare riglyne in terme van die verantwoordelike voorskryf van eginokandiene. In SA word die koste van bloed kulture opgeweeg teen die koste van eginokandien behandeling, en dit mag moontlik die rede wees hoekom voorskywers kan voel dat die aspek van die riglyne ontuitvoerbaar is. Dit is debatteerbaar of die literatuur prakties geimplementeer kan word in ‘n omgewing waar koste ‘n groot rol speel.

Dit word aanbeveel dat navorsingsprojekte in die toekoms ook moet fokus op kliniese inligting soos verwydering van kateters en inwonende toestelle omrede dit ‘n rol speel in die duur van behandeling en ook kan dien as ‘n bron van infeksie. ‘n Koste veldtog rakende die koste van behandeling teen die koste van meer gereelde bloed kulture moet aan dokters en laboratoriums voorgestel word. Meer navorsing is nodig om te bepaal of die pasiënt ‘n korter hospitaal verblyf kan hê wanneer bloed kulture meer gereeld geneem kan word.

Trefwoorde: anti-fungale geneesmiddels, eginokandiene, kaspofungien, anidulafungien, mikafungien, de-eskalasie, bloed kulture, koste

PREFACE

This dissertation was presented up in article format. The findings of the study will be discussed in Chapter 3 in manuscript format as required by the regulations of the North-West University. One manuscript will be submitted for publishing in the following journal:

- South African Medical Journal

The manuscript will contain a reference list cited according to the instructions for authors required by the respective journal. The complete reference list is included at the end of the dissertation according to the reference style of the North-West University.

The chapters in this dissertation are stipulated as follows:

- Chapter 1 provides a brief introduction, followed by the methodology used to conduct this study.
- Chapter 2 entails a literature review of echinocandins and the international guidelines on invasive candidiasis.
- Chapter 3 consists of the results and discussions in article format.
- Chapter 4 is the conclusion, recommendations and limitations drawn from the study.
- The annexures and references will follow at the end.

The co-authors named in the manuscript were the supervisor and co-supervisors during the study. They gave approval that the manuscript may be used as part of the dissertation. The contributions of each author are subsequently outlined in the next pages.

AUTHOR'S CONTRIBUTIONS (STUDY AND MANUSCRIPT)

The contribution of each author to the study and Manuscript, entitled "The general prescribing patterns of echinocandins in adult patients in a private hospital in the Gauteng Province, South Africa." is stipulated in the following table.

Author	Role in studies
Mrs. A. Grey	Wrote the literature review Developing and design of the manuscript Statistical analyses of data Explanation of results Writing of dissertation and manuscript
Dr. M. Julyan (Supervisor)	Administration and supervision of concept of study and manuscript Advisor in the writing of the dissertation and manuscript Assistance in interpreting the data and statistical analysis Reviewing the manuscript critically for final approval
Dr. R. Joubert (Co-supervisor)	Co-supervision of concept of study and manuscript Co-supervision in the writing of the dissertation and manuscript Revising the manuscript critically for final approval of the version to be published
Mr. S.F. Steyn (Co-supervisor)	Co-supervision in the writing of the manuscript Revising the manuscript critically for intellectual content and final approval
Mrs. M. Cockeran (Statistician)	Verified all results from statistical analysis

The following statement provided by the co-authors confirms their individual roles in the study and their permission that the manuscript may form part of this dissertation:

I declare that I have approved the above-mentioned manuscript and that my role in this study, as indicated above, is a representation of my actual contributions and I hereby give my consent that it may be published as part of the MPharm (Advanced Clinical Pharmacy) study of Mrs A Grey.

.....	.....
Dr. M. Julyan	Dr. R. Joubert
.....	.....
Mr. S.F. Steyn	Mrs. M. Cockeran

LIST OF DEFINITIONS

Appropriate is defined as “suitable or **proper** in the circumstances” (Oxford Dictionary 2015).

Blood test is defined as “an analysis of a sample of blood, especially for diagnostic or therapeutic purposes” (Farlex Partner Medical Dictionary 2016).

Blood culture is defined as “a specific test to identify the type of fungal or bacterial infection present in the patient’s blood” (Lab Tests Online 2015).

Candida is defined as “a genus of yeast like fungi, formerly called *Monilia,* commonly found in nature; a few species are isolated from the skin, faeces, and vaginal and pharyngeal tissue, but the gastrointestinal tract is the source of the single most important species, *Candida albicans* spp*.”* (Farlex Partner Medical Dictionary 2012).

Echinocandin is defined as “a class of antifungal compounds targeting the fungal cell wall. Action is by specific and non-competitive inhibition of the (1, 3)-β-d-glucan synthase enzyme complex that forms glucan polymers; a major component of the fungal cell wall in several pathogenic fungi” (MediLexicon Dictionary 2006).

Empiric treatment is explained as “a treatment based on experience, usually without adequate data to support its use” (MediLexicon Dictionary 2006).

Endopthalmitis is “an inflammatory condition of the intraocular cavities usually caused by an infection” (Egan, 2015).

Evidence-based medicine requires the “integration of the best research evidence with clinical expertise and our patient’s unique values and circumstances” (Glasziou *et al.,* 2011:1).

Funduscopic examination is “an ophtalmoscopic examination of the fundus of the eye” (Merriam Webster Dictionary 2015).

Minimum inhibitory concentration is defined as “the lowest concentration of an antimicrobial that will inhibit the visible growth of a microorganism after overnight incubation” (Andrews, 2001:5).

Neutropenia is defined as “an abnormally low level of neutrophils in the blood; neutrophils are white blood cells produced in the bone marrow that ingest bacteria. Neutropenia is serious disorder because it makes the body vulnerable to bacterial and fungal infections” (Farlex 2016).

Loading dose (LD) is defined as “a comparatively large dose given at the beginning of treatment to start getting the effect of a drug, especially one with slow clearance, thus requiring a long period to achieve stable blood levels without a high initial dose” (Farlex Partner Medical Dictionary 2012).

Patterns are “the regular and repeated way in which something happen or is done” (Merriam Webster Dictionary 2015).

Practice is defined as “the exercise of the profession of medicine or one of the allied health professions” (MediLexicon Dictionary 2006).

Prescribe is defined as “to give directions, either orally or in writing, for the preparation and administration of a remedy to be used in the treatment of any disease” (MediLexicon Dictionary 2006).

Stewardship is defined as “the conducting, supervising, or managing of something; especially: the careful and responsible management of something entrusted to one's care” (Merriam Webster Dictionary 2015).

LIST OF ACRONYMS AND ABBREVIATIONS

AUC	Area under the curve
ADE	Adverse drug event
ERP	Enterprise Resource Planning
C.	*Candida*
CDCP	Centers for Disease Control and Prevention
CSF	Cerebrospinal fluid
CVC	Central venous catheter
DDD	Defined daily doses
HREC	Health Research Ethics Committee
ESCMID	European Society for Clinical Microbiology and Infectious Diseases
EFISG	European Fungal Infection Study Group
FDA	United States Food and Drug Administration
GRADE	Grading of Recommendations Assessment, Development and Education
ICU	Intensive Care Unit
IDSA	Infectious Diseases Society of America
IV	Intravenous
LD	Loading dose
LOS	Length of stay
MIC	Minimum inhibitory concentration
MUSA	Medicine Usage in South Africa
NWU	North-West University
SA	South Africa

SAP®	Systems, Applications and Products in data processing
SAMF	South African Medicines Formulary
SITA	Societá Itialiana di Terapia Antimicrobica
spp.	Plural of species
PCR	Polymerase chain reaction
PDD	Prescribed daily dose
PI	Package Insert
UK	United Kingdom
USA	United States of America

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CHAPTER 1: INTRODUCTION

1.1 Introduction

Echinocandins, a group of antifungals, are being used more and more in hospital patients with candidemia or invasive candidiasis. In this study, the researcher will investigate the prescribing patterns of echinocandins, an antifungal group of medicine, in a private hospital. The patient records of hospital patients who used echinocandins will be used retrospectively and data will be collected in the form of a data collection tool. For the purpose of this study, prescribing patterns will include duration of treatment, dosage, cost, blood tests and cultures, and de-escalation of therapy. De-escalation of therapy will include switching from the intravenous (IV) echinocandin to an oral antifungal agent.

In this research proposal, the background and problem statement, research aim and objectives, research methodology and ethical considerations will be discussed.

1.2 Background of the study

One of the greatest threats to public health is antimicrobial resistance (Brink *et al.,* 2016:1). The main driver for antimicrobial resistance is the excessive use of available antibiotics. Incorrect use of antibiotics for treatment of viruses that cause upper respiratory tract infections and acute bronchitis in the public, and misuse of antibiotics in hospitals have resulted in selection of so-called superbugs - multidrug resistant bacteria that are either sensitive to only last resort antibiotics or those that are pan resistant; therefor Brink *et al.,* stated that antibiotic stewardship programmes can reduce antibiotic consumption while maintaining or improving antibiotic resistance. Antifungal stewardship, an entity that has been largely neglected, needs to be included in the initiative to fight antimicrobial resistance. Important basic aspects that need to be addressed are such as the appropriate use and dose of antifungal agents, simple indicators to the most relevant risk factors associated with these infections and the effective and appropriate timing of the antifungal agent administration (Mer, 2014:96), as well as to monitor the appropriate use of these agents (Kett *et al.,* 2011:665).

Brink (2015:12) discovered that antimicrobial stewardship does not only entail the limitation of inappropriate use, but also optimisation of the antimicrobial choice, dosing, route and duration of therapy to maximize effectiveness (clinical cure or prevention of infection). With that being said it is then also very important to limit unintentional consequences such as the emergence of antimicrobial resistance and adverse drug events (ADEs). Antimicrobial stewardship may also reduce unnecessary costs that can result from suboptimal antimicrobial use (Society for healthcare epidemiology of America *et al.,* 2012:323).

Antimicrobial stewardship has been defined by Davidson and Doron (2011:1113) as “the optimal selection, dosage, and duration of antimicrobial treatment that results in the best clinical outcome for the treatment or prevention of infection, with minimal toxicity to the patient and minimal impact on subsequent resistance”. It also focuses on inappropriate or unnecessary antibiotic use. In fact, it has been estimated that more than 50% of antibacterial use in the inpatients setting in the United States of America (USA) is inappropriate. Similarly, recent investigations into antifungal drug use have revealed an alarming 57% of overall antifungal prescriptions were not on standard, based on the use of antifungal adequacy score, evidently establishing a need for stewardship of antifungal agents. Andruszko and Ashley (2016:111) identified numerous reasons for improvement in the antifungal prescribing practices which included:

- failure to streamline prescribing practices and appropriate antifungal agents (35%)
- incorrect treatment duration (27%)
- inappropriate agent selection (31%)
- inappropriate route of administration (20%)
- unnecessary antifungal treatment (16%) and
- inappropriate antifungal dose (16%)

Fungal species (spp.) develop resistance over time as a result of inappropriate antifungal use, for example dosages that are too low or treatment courses that are not long enough to reach clinical outcome (Desnos-Ollivier *et al.,* 2011:532; Lasco *et al.,* 2012:3239). The appropriate use of antifungal agents is one of the most important factors in combatting drug resistance. The Centres for Disease Control and Prevention (CDCP) (2014) have strategies in place to help reduce antifungal resistance, which include the appropriate prescribing of antifungals, assessing antifungals as part of antimicrobial stewardship and documenting the dose, duration and indication for antifungal agents.

It is now evident that the inappropriate use of antifungals has resulted in the global increase in antifungal resistance, increases in morbidity and mortality and has played a role in the shift in the aetiology of invasive fungal infections (Bouza *et al.,* 2015:14).

Therefore, antimicrobial stewardship requires harmonised interventions intended to increase and monitor the appropriate use of antimicrobial agents by encouraging the selection of the best antimicrobial drug regimen, including dosing, duration of therapy and route of administration. The key goal of antimicrobial stewardship is to reach best clinical outcome related to antimicrobial use, while reducing side effects and other adverse events, thereby preventing the selective pressure on bacterial populations that drive the emergence of antimicrobial-resistant strains.

The fungus *Candida* is the most common organism that causes healthcare-associated fungal bloodstream infections in the United States of America (USA) and each case of *Candida* infection is estimated to result in an additional three to 13 days of hospitalisation and a dramatic increase in cost (Hajjeh *et al.,* 2005:540). The development of *Candida* related infections has now urged for antifungal stewardship programmes to be implemented to reduce resistance, decrease mortality and morbidity and save cost (Bouza *et al.,* 2015:15).

Globally, fungal infections have a bad outcome and result in around 150 deaths per hour (Mer, 2014:96). Over the past several years, the quantity of patients with systemic infections has significantly increased, which has led to a substantial rise in morbidity and mortality.

According to the authors of the South African Medicine Formulary (SAMF) (Rossiter *et al.,* 2014:314-319), the following agents for fungal infections are available:

1. Polyene antibiotics that include amphotericin B
2. Imidazole derivatives that include ketoconazole
3. Triazole derivatives that include fluconazole, itraconazole, posaconazole and voriconazole
4. Flucytosine
5. Echinocandins that include anidulafungin, caspofungin and micafungin.

For the last decade conventional amphotericin B and azole antifungals has been the gold standard of antifungal therapy in the South African (SA) setting. However, high frequency of infusion-related toxicity and nephrotoxicity associated with amphotericin B and the rise of fluconazole-resistant strains of the *C. glabrata* spp. urged a search for substitutes (Wilke, 2011:180). Alarmingly, resistance to amphotericin B (the antifungal with the broadest spectrum of activity) has been reported in all *Candida* spp. (Abrantes *et al.,* 2014:225), whilst resistance to the azole group of antifungals, such as fluconazole, has been reported to be as high as 50% in *Candida* spp., warranting antifungal stewardship implementation (Gudlaugsson *et al.,* 2003:1172). Fortunately, echinocandins, a newer generation antifungal class has broad spectrum activity against a variation of *Candida* spp. and is indicated for the treatment of invasive candidiasis (Arendup *et al.,* 2011:3300). Examples of this class of antifungals in SA include caspofungin (Cancidas®), anidulafungin (Eraxis®) and micafungin (Mycamine®), all only available in intravenous (IV) formulation.

The echinocandin class of antifungals are especially attractive with strengths such as a good side effect profile, rapid fungicidal activity against most isolates of *Candida* spp. and predictable favourable kinetics allowing a daily dose. There are not a lot of drug interaction concerns with the echinocandins when it is compared with the commonly used azoles. In addition, the

available data also suggests that caspofungin is generally well tolerated and effective in the treatment of invasive aspergillosis and candidiasis and is therefore a promising addition to the antifungal spectrum (Eschenauer *et al.,* 2007:71; Rybowicz & Gurk-Turner, 2002:97).

Antifungal therapy relies on early initiation of antifungal therapy, changing therapy according to available microbiological results, extent of therapy, success and incidence of urgent complications (Wilke, 2011:180). If a susceptible specie is detected, therapy can be de-escalated from an expensive echinocandin to a more reasonable antifungal such as fluconazole after clinical improvement (Andes *et al.,* 2016:17).

Wilke (2014:1199) & Magill (2011:185) both investigated the economic impact of antifungal therapy in critically ill patients and found that some of the cost-effective strategies rely on early specific identification of the causative strain, consistent reviews and early appropriate therapy. In prophylactic treatment, the optimal strategies depend on local epidemiology and resistance patterns. According to Magill *et al.,* (2014:1108), invasive fungal infections have a high morbidity and mortality and are an expensive problem in healthcare settings worldwide. Bouza and colleagues (2015:14, 18) also expressed their concern regarding the inappropriate use of antifungals, increased morbidity and mortality and the significant increase in the cost of antifungal treatment. Antifungals accounted for almost half ($3, 7 million) of the total cost of antimicrobials, in their facility, a tertiary hospital. In Spain, the echinocandins were compared with fluconazole, and the cost of every success with an echinocandin was less than €30,000, the limit considered acceptable in Spain. Anidulafungin was the echinocandin that had the lowest cost per additional success versus fluconazole (Barrueta *et al.,* 2015:533). Another Spanish study published in 2012 also compared the cost per patient for 14 days of treatment on echinocandins. For caspofungin it was €6,404, for anidulafungin it was €5,400, and finally for micafungin €6,000 - €9,000, due to dose increases in certain individuals (Barrueta *et al.,* 2012:210). In Australia, Chen and his co-researchers (2011:28) studied the cost of three available echinocandins and established the following values in Australian dollars as well as in US dollars:

Table 1-1: The cost of echinocandins in Australian and US dollars

Cost	Caspofungin	Micafungin	Anidulafungin
US dollars ($)	70mg: 421,06	50mg: 112,20	50mg: 108,00
	50mg: 405,25	100mg: 224,40	100mg: 216,00
Australian dollars	70mg: 724,63	50mg: 889	50mg: 347,50
	50mg: 631,17	N/A	70mg: 695,00

Chen and his co-researchers studied the comparison of the cost between micafungin and caspofungin in the United Kingdom (UK) and found no substantial difference in cost effect. However, in other studies, the echinocandins were also compared with liposomal amphotericin B for empirical therapy for febrile neutropenia and suspected invasive fungal infection, which consistently reported a cost benefit in favour of echinocandins. Prices are driven by local markets, making a generalisable economic conclusion very challenging because of disparity in the cost between countries and pharmaceutical companies (Chen *et al.,* 2011:33).

However, the future success of fungal treatment is not yet secured. In this regard, certain types of *Candida* are becoming more and more resistant to first- and second-line therapies (Cleveland *et al.,* 2012a:1352; Cleveland *et al.,* 2012b:3435). Approximately 1% of all *Candida* spp. tested at the CDCP already showed echinocandin resistance (Cleveland *et al.,* 2012a:1352). This is of great concern because echinocandins are usually used to treat infections caused by *C. glabrata.* This specie is most often associated with an already established fluconazole resistance (CDCP, 2014). Historically, *C. albicans* was the predominant pathogen among the *Candida* spp., but currently *C. glabrata* and *C. parapsilosis* have been increasingly noticed, especially among critically ill patients (Bassetti *et al.,* 2016:13). This change in specie development has a direct effect on therapy because of the differences in susceptibility to azoles and echinocandins among these spp. It could possibly contribute to the reported increased resistance, worldwide, to azoles and even echinocandins (Bassetti *et al.,* 2016:13). Specific to the SA setting, Govender (2016:1) stated that *C. auris* is the new superbug of fungal infections, which is of particular concern, considering the limited number of available treatment options. This newly discovered specie, that is one of the many *Candida* spp, can be labelled as multi drug resistant *C. auris*, due to its resistance developed to at least three different classes of antifungals. Govender performed a *C. auris* surveillance study in SA over a period of four years (2012-2016) and detected approximately 1500 cases of *C. auris*. Furthermore, *C. auris* infection appeared to be on the increase, since up to 80 new monthly cases have been reported since

April 2016. Most of these spp. were already resistant to fluconazole and voriconazole and alarmingly a small proportion showed resistance to the broad spectrum antifungal amphotericin B as well as against the echinocandins (Govender, 2016).

This study will focus on the prescribing patterns of echinocandins and especially on the duration of treatment, reason for treating with an echinocandin as well as the de-escalation from the IV administration to an oral antifungal. The outcome of this study can be used to develop a hospital-specific echinocandin guideline to optimise antifungal prescribing and also to contribute to antimicrobial stewardship.

1.3 Problem statement

The use of antifungals has increased dramatically nowadays. It is therefore important to promote and ensure that appropriate attention is directed at antifungals. The SA market requires professionals to practise vigilance with the echinocandin class of antifungals in order to ensure their rational use and conservation of their sensitivity for the treatment of invasive fungal infections (Mer, 2014:96).

Currently physicians are being overwhelmed by different international guidelines, and a private hospital group developed an alert on the prescribing of echinocandins, based on one of these guidelines. These guidelines will be discussed and compared to a private hospital's prescribing patterns of echinocandins in SA.

Cornely *et al.,* (2012:19) have proven that empiric therapy or therapy based on a positive fungal blood culture stays controversial. The cost of antifungals is being evaluated against everyday blood tests and blood cultures to confirm the correct antifungal agent for the susceptible specie or to stop antifungal treatment until a negative blood culture has been obtained. Cornely and colleagues also emphasised that the duration of treatment is increasing even though literature states that a patient should be on antifungal treatment for up to 14 days after a negative blood culture has been obtained. It has, however, been proven that after ten days on IV antifungal treatment, the treatment can be de-escalated to an oral antifungal.

In this hospital, the researcher has observed patients being on echinocandins for more than 14 days with no blood tests done in that period. It is important to know with which agent to treat empirically and which ones should be reserved for evidence-based fungal infection.

The current debate is mostly among specialists with regard to the use of antifungal agents, especially echinocandins, as empiric therapy in the critically ill patients. Several studies have shown that a delay in administration of appropriate antifungal therapy in *Candida* bloodstream infections is associated with increased mortality. It is known that the majority of invasive fungal

infections are due to *Candida* spp. and therefore a hospital may benefit from a decent *Candida* scoring system or algorithm that would constantly ensure that the right patients are receiving appropriate antifungal therapy (Andruszko & Ashley, 2016:113). However the challenge of obtaining a positive blood culture and de-escalating therapy according to the blood culture result and clinical improvement is a debate on its own.

Research questions that need to be answered from a South African perspective are:

- What are the general prescribing patterns of echinocandins?
- What are the prescribing patterns of echinocandin treatment with and without blood cultures?
- What is the average treatment period with echinocandin treatment for adult patients?
- What is the average cost of echinocandin treatment per patient per day?
- Are IV echinocandins being de-escalated to an oral agent in adult patients?

1.4 Research aim and objectives

1.4.1 Research aim

The research aim is to investigate the prescribing patterns of echinocandins in hospital patients in a SA private hospital.

1.4.2 Research objectives

The specific research objectives of the literature review include the following:

- to study the pharmacological background and classification of echinocandins;
- to investigate and compare international and national guidelines regarding the prescribing of echinocandins with the focus on dosage, duration, blood tests, cost and de-escalation; and
- to study the clinical effect of incorrect (drug, dose and timespan) prescribing of echinocandins.

The specific research objectives of the empirical study include the following:

- to determine the general prescribing patterns of echinocandins, for example the prescribed daily dose (PDD), loading dose (LD) and type of oral agent if de-escalated, in a SA private hospital in Gauteng Province (the study site);

- to determine whether there is an association between the prevalence of the treatment period, de-escalation of therapy and the availability of blood culture tests of patients treated with echinocandins; and

- to determine the possible difference in the average cost of echinocandin treatment with or without blood cultures when patients are treated.

1.5 Research methodology

The research methodology will include an explanation of the literature review and empirical investigation that will be conducted in order to answer the objectives of this study.

1.5.1 Literature review

Literature and research articles that can be included in the literature review of this study will be selected as stated below:

- conduct an internet search using appropriate database such as Google Scholar® TM, EBSCOHost®, Science Direct® and Scopus®; and

- identifying keywords that can be used in the internet search related to antifungals, prescribing and echinocandins.

Keywords, both in a single entity and in different combinations, which can be used in conducting a literature research on a database, are the following: “echinocandin”, “caspofungin”, “anidulafungin”, “micafungin”, “resistance”, “fungal infection”, “cost of antifungal therapy”, “prescribing”, “patterns”, “dosage”, “duration”, “appropriate, “antifungal stewardship”.

1.5.2 Empirical investigation

The empirical investigation is needed to determine the prescribing patterns of echinocandins by doctors employed at a specific private hospital in the Gauteng province, SA, and the results will be generalisable within the private health care sector of SA. The empirical investigation will include the investigation of the patient files and drawing a conclusion from what is documented in the files. The empirical investigation will be discussed under the following headings: study setting, target population, study population, study design, sample size, data collection tools, and reliability and validity of the data collection tool.

1.5.2.1 Study setting

This study will be conducted at a private hospital in the Gauteng Province of SA. It is the largest private hospital within the group, being a 470 bed hospital, and will provide sufficient data to

draw a conclusion regarding the prescribing patterns of echinocandins. The use of echinocandins should be more likely at this hospital due to its capacity.

1.5.3 Target population

The target population will involve all patients in this private hospital being on antifungal treatment for the period 1 January 2015 to 31 December 2015.

The study population will include all patients who comply with the inclusion criteria. This study will include all adult patients who were admitted to the specific private hospital and who were on antifungal treatment during their hospitalisation.

1.5.3.1 Inclusion criteria

- The first inclusion criterion is all patients 18 years of age and older. This study will focus on adults because of a less frequent use at the hospital's paediatric units, although caspofungin has been approved by the Food and Drug Administration (FDA) for the paediatrics use in children older than three months (Cancidas® PI, 2012). Anidulafungin should be avoided in children until more pharmacokinetic and clinical data becomes available (Van den Bussche & Van Loo, 2010:166).

- The second inclusion criterion is the period during which all patients 18 years of age and older were started on IV echinocandin treatment from 1 January 2015 to 1 January 2016. The specific time period is chosen by the researcher as anidulafungin only became available in South Africa at the end of 2014.

1.5.3.2 Exclusion criteria

- Patients who were admitted while on any antifungal treatment or who used it as chronic therapy is the first criterion applied to exclude people as participants. The chronic therapy is only available as oral or topical agents and echinocandins are only available in an IV form; therefore, possible self-administration of echinocandins would not be possible.

- Pregnant patients will also not be included. Both caspofungin and anidulafungin are classified as category C drugs and should only be used in pregnant patients if the benefit justifies the potential risk to the foetus.

- Patients who change from an IV echinocandin to another IV antifungal will be excluded, since the aim of the study is to determine the cost benefit of switching from IV to oral administration. The cost benefit for the patient when switching from one IV to another IV is unlikely as all the IV echinocandins as well azole IV agents are equally expensive.

1.5.4 Study design

This study will apply quantitative research design methods; it will take the form of an observational, descriptive study because the researcher will be observing retrospective data and there will not be interference from the researcher.

According to Leedy and Ormrod (2001:7), “quantitative research involves looking at amounts, or quantities, of one or more variable, while qualitative research involves looking at characteristics or qualities that cannot easily be reduced to numerical values”. Quantitative research is an objective and systematic process in its ways of using numerical data from only a selected subgroup of a universe to generalise the findings to the universe that is being studied (Maree 2007:145).

Variables such as medication use patterns and adherence, as well as laboratory results such as therapeutic drug levels is being described by a descriptive study (Benner *et al.,* 2007:5).

1.5.5 Sample size

All the patients who adhere to the inclusion criteria will be used. A *priori* power analysis is conducted using the software package G*Power. A sample size of 140 would be sufficient to detect an effect of 0.3 with a power of 80% and an alpha of 0.05 (Faul *et al.,* 2007:175). The study population over a period of twelve months will be a transparent representation of the number of patients on echinocandin treatment.

1.6 Data collection tool

The patient files will be the primary data source and will be studied thoroughly to collect the data needed. The data collection form will contain the following information for each participant:

- demographic information, including age (inclusion criteria states only patients >18 years), gender (to compare use of echinocandins between males and females), and ward admitted in hospital (to comply with inclusion and exclusion criteria);
- the IV echinocandin that the patient was started with;
- LD;
- PDD;
- start date of echinocandin treatment;
- end date of echinocandin treatment;

- de-escalation of therapy;
- if yes, active ingredient of oral agent;
- presence of blood cultures;
- result of blood cultures;
- cost of antifungal treatment (i.e. the total amount that the hospital pharmacy charged the patient for the medication alone); and
- cost of blood tests and blood cultures performed.

The questions on the data collection tool will be determined by the fact that the researcher wants to sketch a picture of a patient who has been on antifungal therapy. These questions contribute to the prescribing patterns of antifungal therapy and will allow the researcher to make a valid conclusion about the prescribing patterns in the specific hospital. The definition of antimicrobial stewardship leads to the questions that were developed to study the prescribing patterns of echinocandins.

The average cost of antifungal therapy will enable the researcher to compare the cost of echinocandin therapy per day for patients with a positive blood culture test with those without a blood culture test. The results of the average cost for the use of echinocandins can be used to motivate prescribing doctors to de-escalate to an oral antifungal, or to do blood culture tests more regularly until a negative culture has been obtained. It is, however, controversial whether blood tests must be performed every day while on echinocandins until a negative culture has been obtained and then stopping the treatment after 14 days or to just treat the patient until he/she is clinically better. The cost of the blood tests is being weighed up against the cost of treatment. In this study, the researcher will compare the cost of blood tests with the average cost of echinocandin treatment. The costs for performing blood tests (to identify the presence of an infection) and blood cultures (to identify the infection) as well as antifungal treatment will be captured from the patient file.

1.6.1 Validity and reliability of data collection tool

A very important consideration when deciding to use patient records is to verify that the dataset appropriately measures the variables. Original patient records consist of information that was not collected for intentional research purposes but for an institutional policy or provider preference. Retrospective chart review is often used as the golden standard for the validation of measures even though it has the potential for unreliability (Kimberlin & Winterstein, 2008:2276).

When evaluating validity during a research study, two aspects, i.e. internal and external validity, need to be taken into consideration. Internal validity refers to the extent to which the researcher's design and data obtained will allow the researcher to draw accurate conclusions about relationships within the data. External validity refers to the extent to which the results obtained during the study can be generalised to other contexts (Leedy & Ormrod, 2001:7).

The preliminary data collection form was checked by the supervisors of the study, a statistician, as well as the hospital's antibiotic stewardship committee, to make sure that the form included all the relevant questions to answer the research questions. The statistician evaluated the face validity of the data collection form and determined whether the data collection form ensured accurate data capturing.

Only the researcher was responsible for the data gathering and capturing. The researcher captured the data in hard copy format and there after the data was captured on an Excel® spread sheet.

The accuracy of the data was subject to the availability of the data provided in the patient records and was able to be generalised to other contexts. Only doctors prescribe echinocandins, as it is a schedule 4 medicine, and therefore the prescription charts were used instead of the nursing notes. Echinocandins are only available in IV formulation, making it useable only in hospital patients. It is also mainly pharmacists or pharmacist assistants who capture the prescription details into the electronic system. The researcher was alone responsible for the capturing of the data from the patients' prescription chart to the data collection form.

Reliability was achieved by standardising the measurement procedure so that the procedure always stays consistent. Regular proof checks were performed by the research team, researcher and supervisors, to ensure accuracy. The statistician and the supervisors both performed random checks on 50% of the original data forms against the electronic captured data. Where outliers were observed in the electronic data, the researcher performed re-collection of the data from the patient file onto the data collection form.

1.7 Data collection process

The researcher used the hospital's electronic system to identify patients who received echinocandin treatment during the study period and recorded the patient file number from the electronic system. The researcher used this list of patient file numbers to collect patient files from the hospital's filing room and determined whether the patient's medical file complies with the inclusion criteria. The relevant patient data was captured by the researcher on a paper data collection sheet (Annexure A) in a private office of the hospital. These hard copies were stored

in a lockable cabinet in the private office for the time that the data was collected (the key to this cabinet will be kept by only the researcher). Data collection took place after working hours (which may include days that the researcher is not on duty in the pharmacy). The researcher captured the data electronically on an Excel® spreadsheet (Annexure B) after completion of the data collection forms. Each patient record was given a number when collecting and analysing the data to ensure that anonymity was being maintained. The researcher did not capture any personal information of the participant. The computer and the Excel® spreadsheet was password protected. Data collection took place over a three-month period, from 1 August 2016 to 31 October 2016 and took place only after ethical approval and permission from the Health Research Ethics Committee (HREC), Faculty of Health Sciences, North-West University (NWU) and the Research Operations Committee of the Netcare Group were obtained. Ethical number: NWU-00361-15-A1.

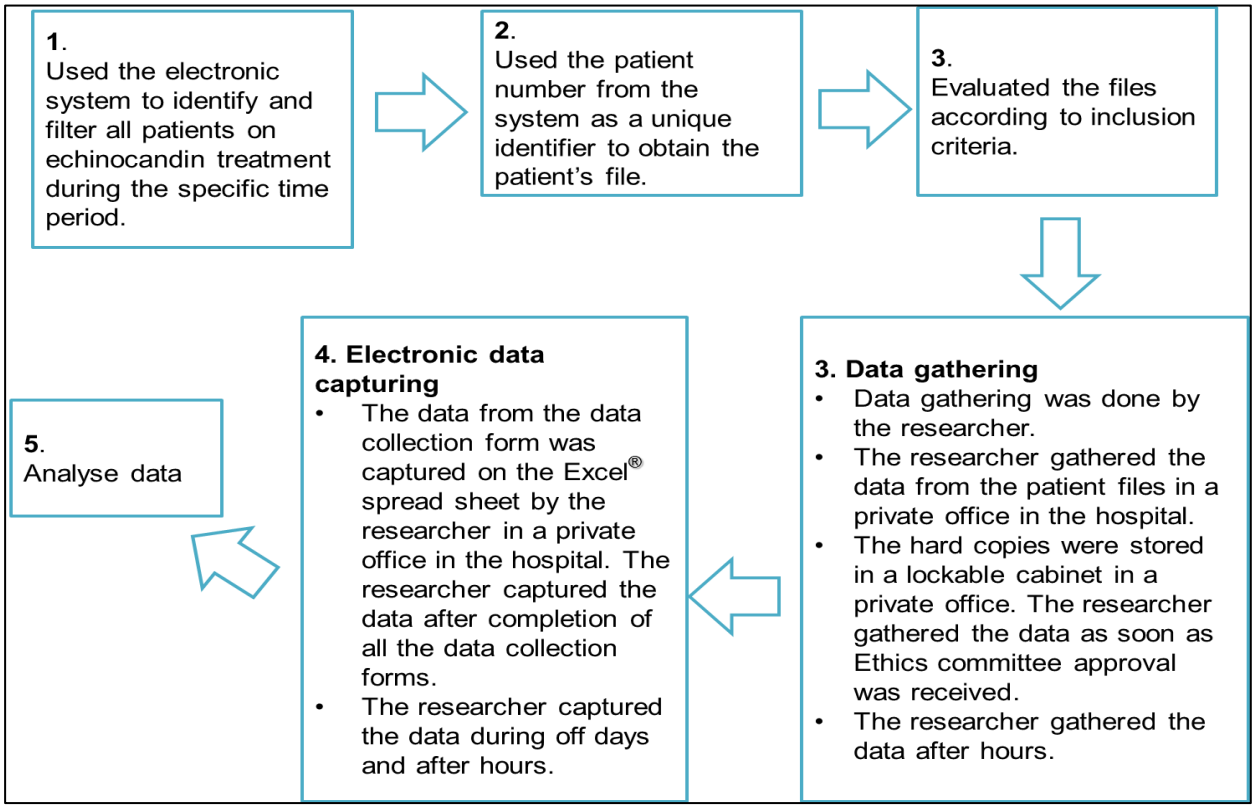

Figure 1-1: Data collection process

- Annexure A: Data collection form that the researcher used to extract the relevant information from the patient files; and
- Annexure B: Data collection sheet on which the data from the data collection form was captured.

1.8 Statistical analysis

The variables for this study are the type of antifungal, the dosage of antifungal treatment, the duration of treatment, the de-escalation of therapy, blood results and cultures and the average cost of antifungal treatment.

The Statistical Analysis System®, SAS 9.3® (SAS Institute Inc., 2009) was used to analyse the data in consultation with the Statistical Consultation Services of the NWU. All variables were expressed using descriptive statistics such as frequencies (n), percentages (%), means, standard deviations (SD), and 95% confidence intervals (CI). The two-sample t-test was utilised to compare the difference between the means of two groups. Cohen's *d*-value was used to determine the practical significance of the results (with $d \geq 0.8$ seen as a large effect with practical significance). Pearson's chi-square test was used to determine the association between two categorical variables. Cramér's *V* was applied to determine the practical significance of the results (with $v \geq 0.5$ defined as a large effect with practical significance).

Table 1-2: Statistical methods

Objective	Independent variable	Dependent variable	Descriptive statistics	Inferential statistics	Effect size
To compare the average duration of treatment between patients with positive blood cultures and patients without blood cultures.	Blood culture (Yes/No)	Duration of treatment	Mean ± SD 95% CI	Independent t-test	Cohen's *d*-value
To describe and compare the average cost between patients with positive blood cultures to the average cost of patients with no blood cultures.	Blood culture (Yes/No)	Cost of treatment	Mean ± SD 95% CI	Independent t-test	Cohen's *d*-value
To determine whether there is an association between de-escalation of therapy and blood culture.	Blood culture (Yes/No)	De-escalation of therapy (Yes/No)	Frequencies and percentages	Chi-square test	Cramér's *V*
To determine whether a LD was prescribed for caspofungin.		LD (Yes/No)	Frequencies and percentages		
To determine whether a LD was prescribed for anidulafungin.		LD (Yes/No)	Frequencies and percentages		
To determine the average PDD for caspofungin.		Daily dosage	Average		
To determine the average PDD for anidulafungin.		Daily dosage	Average		

1.9 Ethical considerations

In this section, ethical considerations such as permission, anonymity, confidentiality, benefit-risk ratio and data management are discussed.

1.9.1 Permission and informed consent

Permission to use the data in patient medical files at a specific private hospital in the Gauteng Province of SA was obtained from:

- the hospital manager;
- the Research Operations Committee of the company's head office; and
- HREC - Faculty of Health Sciences, NWU.

Admission to the private hospital that is used as study setting is subject to terms and conditions as part of the admission contract (Annexure C). This contract requires patient's acknowledgement that the company that owns the hospital and other third parties are allowed to process personal information for the purpose of providing services. The researcher, as a clinical pharmacist of this company, had access to information that is essential in the study on a daily basis as part of normal responsibilities. The contract between the researcher and the employer had a non-disclosure clause regarding confidential information, which included information about the patients admitted to the hospital. Preliminary permission has been obtained from the hospital manager (Annexure D). This study took place after ethical approval has been obtained from the HREC of the Faculty of Health Sciences **(NWU-00361-15-A1),** as well as the Research Operations Committee of the company (application for ethical approval of the latter is subject to approval from the HREC).

1.9.2 Anonymity

The researcher was the only person who collected the data retrospectively from the patients' records. Each patient record was given a number when collecting and analysing the data to ensure that anonymity was maintained. The researcher did not capture any personal information of the participant. No information was published that can cause any participant to be identified.

1.9.3 Confidentiality

Only the researcher, study leaders and the biostatistician did have access to the data collected. The participants were allocated with a number as soon as the data was captured, ensuring

confidentiality and making it impossible to identify a participant in the results. The Excel® data collection spreadsheet was password protected and the data collection forms were stored in a lockable cabinet in a private office at the hospital.

All efforts were made to ensure the privacy of the participants with regard to the safe keeping of their records at the research entity Medicine Usage of South Africa (MUSA).

1.9.4 Storing of data

The data was collected from the patient files using the data collection form. The hard copies were kept safe in a locked cabinet in a private office at the hospital. This data was used to complete the data collection sheet electronically. The electronic data file and computer was password protected with access only to the researcher and study leaders.

The hard copies of the data were taken to the NWU to the office of the research entity MUSA for safe keeping. All electronic data was stored on a dedicated external drive in a safe in a locked room in MUSA's office. The electronic data was deleted from the researcher's computer in the presence of the research assistant of MUSA.

The electronic data and hard copies will be stored for seven years, according to the NWU guidelines, after which the data will be destroyed in the presence of the research assistant of MUSA.

1.9.5 Benefit-risk ratio analysis

1.9.5.1 Anticipated benefits

Direct benefits

There were no direct benefits for the participants in this study because the study was being conducted retrospectively and the researcher did not have any contact with the participants.

Indirect benefits

The following can be seen as indirect benefits for the specific private hospital:

- contribution to the their antibiotic stewardship campaign;
- identifying the prescribing patterns at this specific hospital, the data was specific to this hospital's doctors that can lead to patients receiving more effective therapy, reducing hospital stay and treatment costs;

- development of a hospital-specific guideline for antifungal treatment with the focus on echinocandins; and
- reflection on the average cost of echinocandin therapy and can be used in further investigations in order to curb costs.

1.9.6 Anticipated risks and precautions

1.9.6.1 Anticipated risks to the participants and precautions taken

The anticipated risk for the participants was that their identities may be leaked, but the researcher implemented the following precautions to prevent this from happening:

- keeping their identity anonymous by giving each file a number;
- no personal data was gathered for the completion of this study; and
- the researcher alone was responsible for the data collection and capturing.

1.9.6.2 Anticipated risks to the researcher and precautions taken

There were no anticipated risks for the researcher as the study was conducted retrospectively and there was no personal contact with the participants.

The benefits for conducting the study outweighed the risks associated if anonymity and confidentiality were maintained; therefore, this study can be regarded as medium risk.

1.9.7 Data management

Access to all records took place on the premises of the hospital, based on patient confidentiality procedures of the hospital and the company. Data was collected from the patient files and completed on the data collection form. As stated in section 1.9.4, the data collection forms were kept in a lockable cabinet in the private office where data capturing occurred (and only the researcher had a key to the cabinet). Once data capturing on the data collection forms were completed, the data was entered into an electronic data collection sheet which was password protected. This process was monitored by the case manager of the hospital to ensure that no patient file was removed from the hospital premises.

1.9.8 Dissemination of research results

The results and discussion of this study will be presented in an article format to the NWU as a mini-dissertation. The hospital name was not published in the mini-dissertation to comply with

anonymity and confidentially agreements. The results of the study can be presented at a conference and will be published in a peer-reviewed journal in article format. The results will not be made available to the participants since the data is collected retrospectively. The researcher furthermore can present the results of the study in a presentation to the hospital manager and to the doctors working at this hospital. The results of this study will be useful to develop a guideline for the prescribing of echinocandins.

1.9.9 Chapter summary

This introductory chapter described he background to the study, as well as the research aims and the research methodology. In the next chapter a detailed literature review will be conducted and described regarding the use of echinocandins.

CHAPTER 2: LITERATURE STUDY

2.1 Introduction

Candida spp. have been identified as the most commonly isolated healthcare-associated bloodstream pathogen by a recent multicentre point-prevalence survey (Bamberg *et al.,* 2014:1198; Andes *et al.,* 2016:9), together with other reports that indicate *Candida* spp. to be the major pathogens associated with hospital acquired fungal infections, particularly in the Intensive Care Unit (ICU) globally (Aitken *et al.,* 2015:316, Morris & Villmann, 2006:1693). In the past, *C. albicans* has been the most common pathogen, but now a days non-*albicans Candida* spp. became the most common pathogen particularly: *C. parapsilosis*, *C. glabrata, C. auris* and *C. krusei* have been seen in many centres since the early 2000s (Mer, 2014:95, Aitken *et al.,* 2015:316; Bassetti *et al.,* 2013:263). Recent reports in SA have revealed substantial shifts in the spectrum of *Candida* spp. to non-*albicans* forms, with *C. parapsilosis* and reduced azole susceptibilities being widely documented. This is of great concern since an increase in *Candida* spp. bloodstream infections have been observed, along with a simultaneous increase in non-*Candida albicans* spp. such as C. *glabrata* and a decrease in *C. albicans*-related infections. Unfortunately, *C. glabrata* has inconstant susceptibility to the commonly used antifungal agent fluconazole, which has been the drug of choice since the nineties (Morris & Villmann, 2006:1693). An alarming new superbug, namely *C. auris* is being studied, not only in the SA, but outbreaks have been reported in at least three countries to date (National Institute for Communicable Diseases, 2016; Govender 2016). The National Institute further reported that *C. auris* is the second most common cause of candidemia in the private sector for 2016, with most cases occurring in the Gauteng province in SA (National Institute for Communicable Diseases, 2016).

Fluconazole is an acceptable substitute for echinocandins in stable patients, although it should be used with caution. Fluconazole is not active on strains embedded in biofilms, it is only fungistatic and it has very low to no activity against *C. krusei* and *C. glabrata* (Bassetti *et al.,* 2013:271). Previous exposure to fluconazole or broad spectrum antibiotics is associated with an increased possibility of fluconazole-resistant *Candida* spp. (Bryant *et al.,* 2014:1317).

The emerging incidence of multidrug-resistant *Candida* spp. will complicate the selection of antifungal therapy in the near future, therefore the appropriate prescribing, including cost-evaluation and benefit-risk ratio, of echinocandins should be strongly encouraged (Andes *et al.,* 2016:17).

2.2 Fungal infections and causative organisms

Invasive fungal infection caused by yeast and mould is a growing problem in healthcare. Morris and Villmann (2006:1693) states that from 1980 to 1997, fungal infections have increased from the tenth most common cause of death from infectious diseases to the seventh most common. The incidence of systemic fungal infections has increased as a result of immunosuppression by chemotherapy, transplantation, Human Immunodeficiency Virus (HIV) infections and the prolonged survival of patients. The challenges that are opposed with fungal infections are the significant mortality, difficult early diagnosis and costs of newer antifungal drugs (Bicanic & Harrison, 2013:435).

Candida spp. is a group of fungi of about 150 yeast spp. and is normally harmless on skin and mucous membranes until the environment becomes more heated, wet and more fertile for the *Candida* spp*.* to grow. Factors that can contribute to the more favourable environment includes hot weather, restrictive clothing, poor personal hygiene, infrequent and poor hygiene with diaper changes, the use of broad spectrum antibiotics, inflammatory diseases as well as immunosuppression either from drugs or an illness (Aaron, 2015).

Eight *Candida* spp. are regarded as clinically important pathogens in human disease, namely *C.albicans, C. tropicalis, C. parapsilosis, C. krusei, C. stellatoidea, C. guilliermondii, C. lusitaniae,* and *C. glabrata* (DiPiro *et al.,* 2015:359) of which *C. albicans, C. glabrata, C. tropicalis, C. parapsilosis and C. krusei* are the most common and responsible for more than 90% of invasive diseases (Andes *et al.,* 2016:1). Each of these organisms has unique virulence potential, antifungal susceptibility and epidemiology. The CDCP (2016(a) has published a clinical alert to the USA Healthcare Facilities regarding the worldwide dilemma of invasive infections caused by multidrug-resistant fungi *C. auris.* One of the major concerns of *C. auris,* according to the clinical alert, is the increase in resistance to all antifungals. The organisation recommends that all *C. auris* infections should be reported to the CDCP. Communication should be implemented from different laboratories and their abilities to detect *C. auris* spp. and infection control and environmental cleaning should be of excellent standard.

Candidemia refers to the presence of *Candida* spp. in the blood. Candidemia is the most common manifestation of invasive candidiasis. For many patients candidemia is a manifestation of invasive candidiasis that could have originated in a variety of organs, whereas, for others candidemia originated from an infected indwelling IV catheter (Kaufmann *et al.,* 2017). From all the literature studied and from a very recent presentation by Mer, (2017), it is more likely for candidemia to arise from indwelling devices such as IV lines and catheters because of the fact that it has a biofilm, which provides more favourable growing conditions for fungus spp.

Candida spp. has the ability to create a biofilm on indwelling devices for example pacemakers and intravascular catheters. Because of these biofilms, the indwelling devices act as a source or reservoir for systemic *Candida* infection. A very recent study came to the conclusion that biofilm formation is a key driver of *C. albicans* pathogenicity and is associated with mortality (Borman *et al.,* 2017:328). While the removal of the catheter is instantly recommended, it may not be practicable in certain clinical situations (Cornely *et al.,* 2008:477). Azole antifungals are significantly less active against biofilm associated *Candida* spp. as compared with planktonic cells of the same strain (Cornely *et al.,* 2008:476).

Mortality has been associated to both the timing of therapy and/or source control (Andes *et al.,* 2016:9), implying that the appropriate antifungal treatment should be started as soon as possible together with the removal of the central venous catheter (CVC) or other indwelling devices and drainage of infected material (Andes *et al.,* 2016:9 & Bassetti *et al.,* 2016:16). Candidemia is associated with up to 47% attributable mortality, and in patients with septic shock, this is even higher (Andes *et al.,* 2016:9).

According to a presentation by Mer (2017), intravascular devices are an intrinsic component to modern day medicine, and that it is used to administer emergency medication, fluids, and parenteral nutrition and blood products. Almost all ICU patients need to have intravascular devices and CVCs, as an emergency precaution, in order to administer medication at a high rate when necessary. Intravascular devices and CVCs are important risk factors in the development and diligence of candidemia in non-neutropenic patients. In almost 70% of patients with candidemia a CVC is present at the time that the blood culture is obtained. The relationship of candidemia to CVCs has been assumed on the basis of observation, clinical expertise and an understanding of the role of biofilm in the genesis of bloodstream infections (Andes *et al.,* 2016:19).

Mer has also (2017) presented that source control is a crucial factor when managing a patient with candidemia, together with the appropriate antifungal therapy. In a retrospective study with 224 consecutive patients with septic shock and positive blood cultures for *Candida* spp., adequate source control and appropriate antifungal therapy that was administered within 24 hours of onset of shock, resulted in a mortality rate of 52.8%. Mortality rate for patients who have not attained these goals had a mortality rate of 97.6% (Doherty *et al.,* 2012:1743).

2.3 Antifungals for systemic use available in South Africa

The following antifungals are available in SA and each group will be discussed in the order presented below.

1. Amphotericin B;

2. Azole derivatives (fluconazole, itraconazole, voriconazole, posaconazole and ketoconazole);
3. Flucytosine; and
4. Echinocandins (anidulafungin, micafungin and caspofungin).

2.3.1 Amphotericin B (Ambisone®, Fungizone®)

Amphotericin B is the drug of choice for most severe fungal infections such as aspergillosis, cryptococcosis, blastomycosis, systemic candidiasis, coccidioidomycosis, histoplasmosis, zygomycosis, sporotrichosis (Rossiter *et al.,* 2014:314). However, formulations of amphotericin B is used only if no other alternative is available, due to the risk of toxicity, and an echinocandin would be favored as first line therapy for *C. krusei* and *C. glabrata* over amphotericin B (UpToDate, 2017).

Amphotericin B acts by binding to sterols, particularly ergosterol, in the cell membrane, increasing the permeability of the cell membrane of sensitive fungi. Amphotericin B is available as conventional amphotericin B and liposomal amphotericin B, that is amphotericin B which is encapsulated in liposomes making it less nephrotoxic than conventional amphotericin B (Rossiter *et al.,* 2014:316).

2.3.2 Azole antifungals (Diflucan®, Aspen Fluconazole®, Vfend®, Noxafil®)

The azole antifungals include two classes, imidazoles and triazoles, which share the same mechanism of action except for imidazoles that consist of a two-nitrogen azole ring and the triazole consisting of three nitrogens in the azole ring (Bennett & Zonios, 2008:198).

Azole derivatives for systemic administration include the imidazoles for example ketoconazole and the triazoles (fluconazole, itraconazole and voriconazole). Voriconazole and posaconazole are the newer generation triazoles and has shown efficacy against fluconazole resistant strains of *Candida* (Hidalgo, 2016). Ketoconazole, an agent for topical fungal infections is not recommended for systemic use as it is less effective and more toxic than triazoles (Rossiter *et al.,* 2014:216). The triazoles' spectrum of activity is somewhat limited. Fluconazole is active mainly against *C. albicans* and *Cryptococcus neoformans*. Itraconazole is most active against *Aspergillus* spp. and has greater activity than fluconazole against resistant strains of *Candida* spp. other than *C. albicans* (Greer, 2003:241). Voriconazole and posaconazole can be used for invasive aspergillosis, infections caused by *Candida* spp. that shows resistant to fluconazole and as alternative to amphotericin B in high risk patients (Rossiter *et al.,* 2014:319; Hidalgo, 2016).

2.3.3 Flucytosine

Flucytosine is a fluorinated pyrimidine antifungal agent used in the treatment of systemic fungal infections with the exception of *C. krusei* (Andes *et al.,* 2016:13). It has no intrinsic antifungal capability, but after it has been taken up by susceptible fungal cells it is converted into 5-fluorouracil (5-FU), which is further converted to metabolites that inhibit fungal DNA and RNA (Dankert *et al.,* 2000:171). This antifungal can be imported on a named-patient basis, as it is not freely available in SA.

2.3.4 Echinocandins (Cancidas®, Eraxis®, Mycamine®)

The non-competitive inhibition of β-(1, 3)-D – glucan synthase, a crucial component of the fungi's cell wall is the main mechanism of action of the echinocandins (Morris & Villmann, 2006:1694). Inactivation of the β-(1, 3)-D – glucan synthase additionally entails loss of the cell wall integrity (Graninger *et al.,* 2006:165). As a consequence the fungal cell becomes incapable of resisting intracellular osmotic pressure, ultimately leading to death of the fungal cell. Unlike other classes of antifungal drugs, e.g. the azole antifungals, which act on the cell membranes (Revankar & Sobel, 2014), echinocandins inhibit the synthesis of the cell wall. Thus, cross resistance between echinocandins and conventional antifungals are not expected to occur. Another advantage of echinocandins is the lack of toxicity to mammalian tissues because mammalian cells lack enzymes involved in glucan synthesis. The antifungal range of the individual echinocandins is mostly identical and mostly includes the clinically relevant *Candida* and *Aspergillus* spp. (Cornely *et al.,* 2008:476).

2.4 Risk factors for invasive candidiasis

The risk factors for candidemia are numerous and vary in description depending on author. Therefore, the risk factors according to three different authors are presented and compared in table 2-1 in an attempt to unify the mentioned risk factors (Bryant *et al.,* 2014 1316, Bassetti *et al.,* 2014:265, Bernhardt *et al.,* 2006:351 & Castanheira & Pfaller, 2016:4).

Table 2-1: Risk factors for invasive candidiasis

Factors predisposing patients to candidemia	**Risk factors for invasive candidiasis**	**Underlying pathology/medical care of patients with candidemia**	**Risk factors for invasive** *Candida*
All patients	Hospitalisation in ICU	Surgery	Abdominal surgery
Prior abdominal surgery	Surgery, trauma and burn patients	Burns	Neutropenia
Intravascular catheters	Solid organ transplant	Solid tumour	Solid organ transplant
Parenteral nutrition	Total parenteral nutrition and the use of indwelling catheters	Haematological malignancy	Haematological malignancy
Use of broad spectrum antibiotics	Previous prolonged antibiotic use	Intensive care	Older adult > 70 years
Immunosuppression including corticosteroid use	Immunosuppressive therapy	Steroids	
Acute renal failure	Renal failure requiring haemodialysis or haemofiltration	HIV infection	
Diabetes	Diabetes Mellitus		
Transplantation	Duration of hospital stay		
Haemodialysis	Multiple underlying medical conditions		
Pancreatitis	Multiple site colonisation		
ICU patients	Neutropenia		
Prolonged stay in ICU	Previous *Candida* infection		
Factors predisposing patients to candidemia	**Risk factors for invasive candidiasis**	**Underlying pathology/medical care of patients with candidemia**	**Risk factors for invasive** *Candida*
Candida colonisation	Acute/chronic organ dysfunction requiring intensive care/invasive procedures		
High acute physiology and chronic evaluation II			
Blood transfusions			

In summary it is clear to recognize that the risk factors are equally described by all the authors and that the risk factors that are most commonly identified by the four different authors have been summarised in figure 2-1:

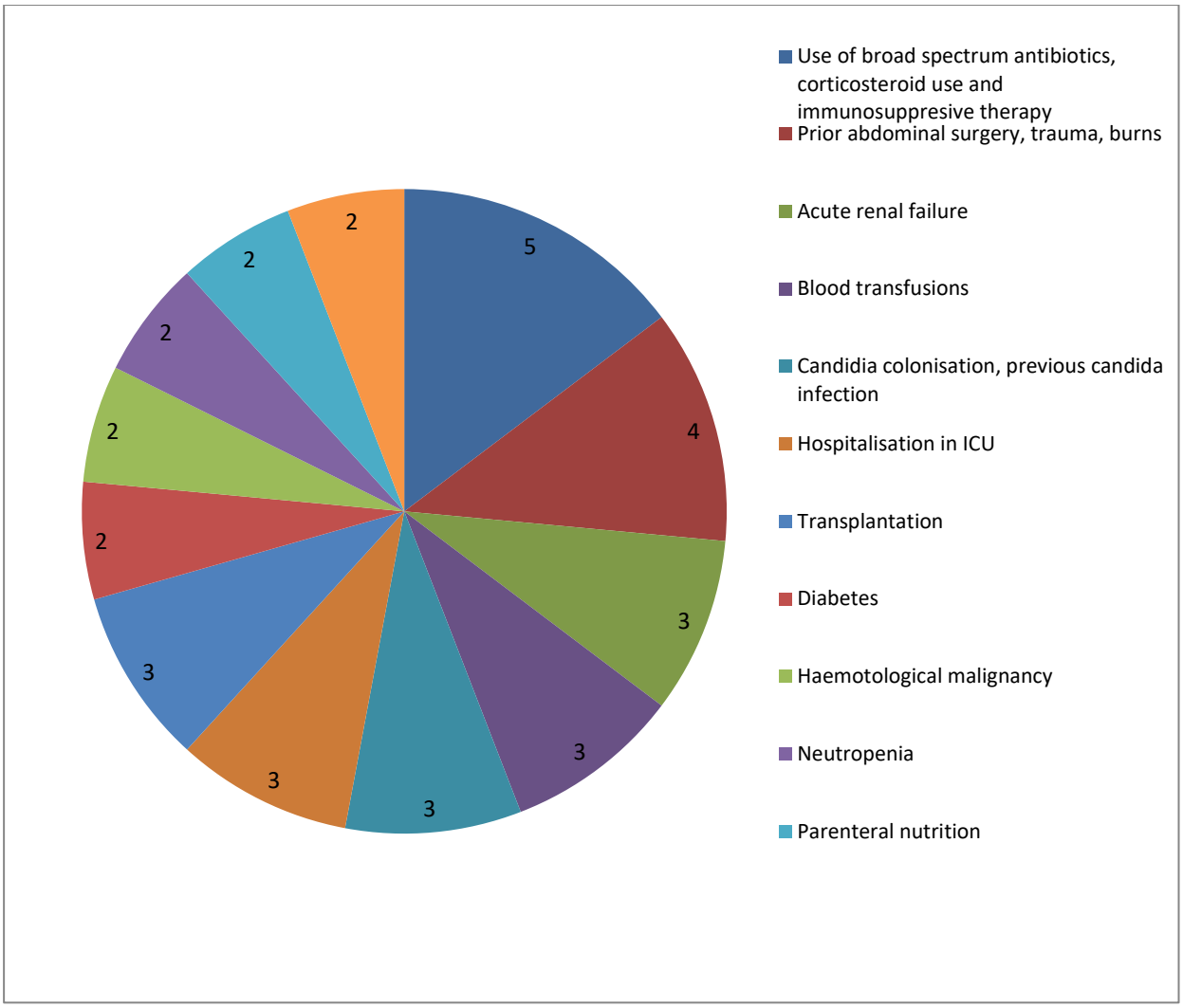

Figure 2-1: The risk factors for invasive candidiasis described in four different studies

The use of broad spectrum antibiotics, corticosteroid use and immunosuppressive therapy was identified as the risk factor that is most commonly identified by the authors. Prior abdominal surgery, trauma and burns were the second most common risk factor from the literature reviewed. From there on, acute renal failure, blood transfusions, *Candida* colonisation and previous *Candida* infection, hospitalisation in ICU and transplantation were the third most common risk factors. Diabetes, solid organ transplant, parenteral nutrition, neutropenia and haematological malignancy were all described as the fourth most common risk factors. Invasive candidiasis' risk factors can be incorporated with a *Candida* scoring system or algorithm to guide intensivists to effective antifungal therapy as soon as possible.

2.5 Invasive candidiasis

The high rate of candidemia and deep seated infections due to *Candida* (i.e. invasive candidiasis) are paralleling the growing difficulty of surgical procedures and the larger patient populations at risk of infection (Bassetti *et al.,* 2013:263). Invasive candidiasis includes bloodstream infections, deep seated tissue infection or both (Bryant *et al.,* 2014:1316).

According to Bassetti and his colleagues (2013:268), an echinocandin should be used as the first line therapy for invasive candidiasis because of it's:

- fungicidal activity;
- action against strains embedded in biofilms;
- activity against fluconazole–resistant and non-*albicans* strains that are resistant to fluconazole;
- good safety profile; and
- low tendency for interactions.

The high rate of *Candida* infections and the challenges that arise from resistant fungal spp. necessitate correct and effective therapy with an echinocandin as a first line therapy.

2.6 Dosing considerations

Historically low doses of antifungals were used to minimalize side effects, but nowadays higher dose are suggested in attempt to prevent further resistance (Bassetti *et al.,* 2016:16). In this regard, the dose adjustments and considerations of the echinocandins (caspofungin, micafungin and anidulafungin), azole antifungals and amphotericin B will be discussed next.

2.6.1 Caspofungin (Cancidas®)

Caspofungin needs a LD of 70mg followed by a 50mg daily dose IV (Cornely *et al.,* 2008:478; Glöckner, 2011:168; Sobel & Vazquez, 2006:220). According to the PI of Cancidas® (2012), as well as the authors and references mentioned above, patients with a body weight more than 80kg must receive 70mg of caspofungin IV daily. Caspofungin have been used in higher doses such as 150mg per day in clinical trials of invasive candidiasis (Glöckner, 2011:168).

All clinical studies done on caspofungin have shown a LD of 70mg and a 50mg once-daily dose will be most effective (Denning, 2002:889).

Caspofungin needs a dose reduction of 35mg per day, following a LD of 70mg, in patients with modest hepatic failure and should be avoided in patients with severe hepatic insufficiency (Glöckner, 2011:168; Graninger *et al.,* 2006:165).

2.6.2 Micafungin (Mycamine®)

Micafungin is administered at 100mg IV per day with no LD required (Cornely *et al.,* 2008:478). No dose adjustments are necessary in hepatic dysfunction, renal dysfunction and age (Graninger *et al.,* 2006:165; Mycamine® PI 2015). Micafungin should be administered IV after reconstitution with 0.9% normal saline or 5% dextrose water over 1 hour (Mycamine® PI, 2015).

Table 2-2: Micafungin dosages

Indication	Body weight more than 40kg
Prophylaxis of *Candida* infection	50mg/day
Invasive candidiasis treatment	100mg/day
Oesophageal candidiasis treatment	150mg/day

2.6.3 Anidulafungin (Eraxis®)

Treatment with anidulafungin starts with a LD of 200mg IV followed by a maintenance dose of 100mg IV per day (Eraxis® PI, 2006). Anidulafungin should be reconstituted with 30 ml of water for injection. The reconstituted vial should be clear and free from visible particulates and should then be diluted with normal saline (0.9%) or with glucose (5%) for infusion (Eraxis® PI, 2006). The infusion solution should be kept in the refrigerator between 2 and 8˚C and should be used within 24 hours. Anidulafungin can be administered with no dose adjustments in hepatic dysfunction (Graninger *et al.,* 2006:165).

In treating oesophageal candidiasis, the LD of anidulafungin is 100mg, followed by 50mg/day. For candidemia and other deep-tissue infections a LD of 200mg followed by 100mg/day thereafter is necessary (Sobel & Vazquez, 2006:219).

2.6.4 Fluconazole (Diflucan®, Aspen Fluconazole®)

The recommended LD of fluconazole is 800mg (12mg/kg), followed by 400mg (6mg/kg) IV daily (Bryant *et al.,* 2014:1319). Fluconazole is available in a ready mixed solution with no preparation necessary (Rossiter *et al.,* 2014:317). Fluconazole has the best activity in the

cerebrospinal fluid (CSF) and also reaches urine concentrations that are 10-20 times of those in serum (Andes *et al.,* 2016:11).

2.6.5 Voriconazole (Vfend®)

Voriconazole is the agent of choice for invasive aspergillosis and can also be used in infections caused by *Candida* spp. Voriconazole however, cannot be used in patients with severe hepatic impairment and use in paediatrics, geriatrics and pregnancy have not been established (Rossiter *et al.,* 2014:319). The LD is a 6mg/kg IV every 12 hours for 24 hours, followed by a maintenance dose of 3mg/kg IV every 12 hours. Voriconazole is available in an oral form with excellent oral bioavailability and, can for this reason, be considered as a step-down agent from an IV agent for patients to continue out of hospital (Andes *et al.,* 2016:12).

2.6.6 Posaconazole (Noxafil®)

Posaconazole is indicated for invasive aspergillosis refractory to amphotericin B as well as for other *Candida* spp. that are resistant to other therapy (Rossiter *et al.,* 2014:318). It can also be used as prophylactic therapy in high risk neutropenic patients. Posaconazole is currently in SA only available in an oral suspension form (Greaves *et al.,* 2006:1180).

2.6.7 Amphotericin B (Ambisone®, Fungizone®)

Amphotericin B deoxycholate (Fungizone®) should be administered as an IV daily dose of 0, 6 - 1mg/kg and liposomal amphotericin (Ambisone®), which is a lipid formulation, IV daily 3-5mg/kg (Andes *et al.,* 2016:11 & Bryant *et al.,* 2014:1319). A test dose of 1mg in 50ml 5% dextrose water is given over 30 minutes with careful monitoring for 4 hours. If no severe adverse events occur, the nurse or the doctor needs to give half of the calculated daily dose over 4 hours and the full dose the following day (Rossiter *et al.,* 2014:215).

2.7 Pharmacodynamics

The echinocandins are concentration-dependant antifungals (Carver *et al.,* 2007:78) so the in-vitro activity of echinocandins against *Candida* spp. is measured by the minimum inhibitory concentration (MIC). The determination of the MICs highly depends on the growth medium applied as well as on the presence or absence of proteins (Graninger *et al.,* 2006:168).

The MIC (µg/ml) of echinocandins against the clinically important spp. of *Candida* is being described in table 2-3 (Graninger *et al.,* 2006:168, Cornely *et al.,* 2008:477).

Table 2-3: Minimum inhibitory concentration (µg/ml) of echinocandins against clinically important spp. of *Candida*

Species	**Caspofungin $_{MIC90}$ (µg/ml)**	**Micafungin $_{MIC90}$ (µg/ml)**	**Anidulafungin $_{MIC90}$ (µg/ml)**
C. tropicalis	1	0.06	0.13
C. glabrata	0.06 - 2	0.015 – 0.06	0.12 – 0.13
C. parapsilosis	1 - 4	2	2
C. krusei	0.12 – 2	0.06 – 0.25	0.06 - 0.13
C. albicans	0.06 - 1	0.03	0.03 – 0.12

The extremely lower MICs of anidulafungin suggest the presence of proteins in growth medium (Graninger *et al.,* 2006:168*).* Interpretive breakpoints that can help guide the clinician are not yet available and will require validation in clinical trials (Carver *et al.,* 2007:74; Cornely *et al.,* 2008:477).

Caspofungin has efficacy against *C.albicans* even when the concentration fall below the MIC. This means that the concentration in the tissue stays high even after the serum concentration has declined and proves that caspofungin has a strong post-antifungal effect (Carver *et al.,* 2007:78).

Echinocandins are characterised by their favourable interaction profile. Caspofungin is partly metabolised via the CYP450 system and therefore interactions with inducers of CYP450, such as rifampin, dexamethasone, phenytoin and carbamazepine have been reported. An increased maintenance dose of 70mg per day is thus recommended if caspofungin is used in patients receiving these drugs (Cornely *et al.,* 2008:479; Carver *et al.,* 2007:80; Glöckner, 2011:169).

The adjunctive use of cyclosporine with caspofungin has shown an increase in hepatic transaminase concentration. Morris and Villmann (2006:1700), suggest that caspofungin did not increase the level of cyclosporine, but the area under the concentration-time curve (AUC) of caspofungin increased by approximately 35%. It has been suggested that this effect is due to inhibition of caspofungin uptake into the hepatocytes by cyclosporine.

Table 2-4 indicates the enzyme mediated drug interactions of antifungals available in SA (Rossiter *et al.,* 2014:315-319, Mycamine® PI, 2015, Eraxis®PI, 2014, Cancidas® PI, 2012, Noxafil ® PI, 2010).

Table 2-4: Interactions with enzyme mediated drugs

Antifungal agent	Enzymes involved	Drugs	Effect
Caspofungin	CYP450	Rifampicin, nevirapine, efavirenz, dexamethasone, phenytoin and carbamazepine.	Increased metabolism of caspofungin. Increase caspofungins' daily dose to 70mg.
	Hepatic transaminase	Cyclosporin, tacrolimus.	No dose adjustment.
Micafungin	Low potential for interaction with substances metabolised via CYP3A mediated pathways.	Cyclosporin, tacrolimus, prednisolone, fluconazole, ritonavir, rifampicin, voriconazole & amphotericin B.	No evidence of altered pharmacokinetics of micafungin.
	N/A	Itraconazole, sirolimus & nifedipine.	Increase AUC of these drugs, therefore toxicity for these drugs should be monitored and the dose may need to be decreased.
Anidulafungin	Not a clinically relevant substrate, inducer or inhibitor of CYP450 enzymes.	N/A	No known clinically relevant drug interactions.
Fluconazole	CYP3A4	N/A	N/A
	CYP450	Phenytoin, cyclosporin, colchicine, fluvastatin, hydrochlorthiazide, midazolam, rifampin and sulphonylureas.	Increased or decreased fluconazole level.

Voriconazole	CYP450	N/A	Increasing plasma levels of substances that are metabolised by these enzymes.
	CYP3A4	N/A	N/A
	CYP2C9	N/A	N/A
	CYP2C19	N/A	N/A
Posaconazole	Substrate for p-glycoprotein	N/A	N/A
	Inhibitor of CYP3A4 mediated reactions	H_2 receptor antagonists, phenytoin, rifabutin.	Posaconazole level decreases.
		Calcium channel blockers.	Posaconazole inhibits it's metabolism that can lead to additive negative inotropic effects.
		Cyclosporin, tacrolimus & sirolimus.	Serum levels of these drugs are increased and a dose reduction is necessary.
		Ergotalkaloids	Concurrent use in contraindicated
		Astemizole, pimozide & quinidine.	Metabolism of these drugs are inhibited, increased plasma levels may lead to cardiotoxicity.
Amphotericin B	No enzyme mediated drug interactions, only drug-drug interactions.	N/A	N/A

The azole antifungals are substrates for some of the CYP450 enzymes and can cause sub-therapeutic levels of the azole when administered with enzyme inducers such as phenytoin, and the azole antifungals are also inhibitors of CYP3A4 and therefore cause an increase in plasma levels of drugs metabolised by this enzyme (Bucker & King, 2015:289). Amphotericin B formulations are associated with pharmacodynamic interactions that primarily affect renal function and electrolyte levels (Cornely *et al.,* 2008:479).

2.8 Activity

The group of echinocandins exhibit good fungicidal activity against *Candida* spp. All three agents display higher MIC's for *C. parapsilosis, C. lusitaniae* and *C. guilliermondii* compared with other *Candida* spp. (Carver *et al.,* 2007*:*74). Echinocandins also have fungi static activity against *Aspergillus* spp. Anidulafungin, micafungin and caspofungin have activity for most isolates of *Candida* spp., including those that are either amphotericin B-resistant or fluconazole- and itraconazole resistant such as *C. glabrata* (Morris & Villmann, 2006:1696). The echinocandins do not have good activity against *C. parapsilosis* and *C. guilliermondii* and no activity against fungi that lack significant β-glucan in their cell walls, such as *Cryptococcus neoformans.* For *Aspergillus* spp., the echinocandins have fungistatic activity similar to or better than that of amphotericin B and the triazoles, however only the latter two have fungicidal activity against *Aspergillus* spp. (Morris & Villmann, 2006:1696).

Labelled indications approved by the FDA for the echinocandins differ slightly (Morris & Villmann, 2006:1701). While all three agents are indicated for the treatment of esophageal candidiasis, caspofungin and anidulafungin are also indicated for the treatment of candidemia and other infections caused by *Candida* spp., including intra-abdominal abscesses and peritonitis. Caspofungin can be used for the treatment of *candidal* pleural space infections, empirical treatment of suspected fungal infections in neutropenic patients and for the treatment of aspergillosis in patients who are intolerant to other antifungal agents (Morris & Villmann, 2006:1696).

Caspofungin is the only echinocandin that is approved for the empiric therapy in patients with febrile neutropenia. Caspofungin will not particularly be the first line therapy in invasive aspergillosis but can be used as a second line therapy and, according to variant studies, will show positive results (Carver *et al.,* 2007:78).

Caspofungin, anidulafungin and micafungin are approved for the treatment of invasive *Candida* infections in adult patients. The labelling of caspofungin includes patients with neutropenia. In addition, caspofungin is licensed for second-line treatment of invasive aspergillosis and empiric treatment of neutropenic patients with fever and suspected fungal infection. Micafungin is approved for invasive candidiasis, oesophageal candidiasis and prophylaxis of *Candida* infections in patients undergoing allogeneic blood stem-cell transplantation or in patients with neutropenia for more than ten days (Cornely *et al.,* 2008:486).

Even though the echinocandins are only available in IV form, their good safety profile, excellent efficacy, limited drug interactions and concerns about fluconazole resistance has led to

clinicians preferring it as first line therapy when candidemia is suspected (Andes *et al.,* 2016:18).

The echinocandins show good fungicidal activity against most *Candida* spp. and all of these agents have shown success in approximately 70-75% of patients in randomised, comparative clinical trials (Andes *et al.,* 2016:18).

Different guidelines have been studied by Bassetti *et al.* (2016:16), in terms of the recommended antifungal to be used as empiric treatment for an infection caused by *Candida* spp. as listed in Table 2-5:

Table 2-5: Recommended antifungal treatment according to different international guidelines

Guideline	Recommended antifungal
Infectious Diseases Society of America (2016)	Fluconazole/Echinocandin
European Society for Clinical Microbiology and Infectious Diseases (2012)	Echinocandin
Australian and New Zealand Consensus Guidelines (2014)	Echinocandin
An Italian consensus for invasive candidiasis management (2013)	Echinocandin
SITI/ISC (2013)	Echinocandin/Amphotericin B
Spanish Society of Infectious Diseases and Clinical Microbiology (2011)	Fluconazole/Echinocandin

The preference of echinocandins over azoles, as recommended by the updated guidelines will likely have a noteworthy impact on prescribing practices in the ICU, encouraging the need for antifungal stewardship and local epidemiology data in individual institutions (Ashley & Andruszko, 2016:113). There is a role for first-line therapy with fluconazole where the patient is clinically stable and the isolate is likely to be susceptible to fluconazole (Bryant *et al.,* 2014:1319).

2.9 Pharmacokinetics of echinocandins

The echinocandins consists of a very low oral bioavailability, high protein binding, relatively low CSF and urine concentrations of the parent drug (Clancy *et al.,* 2015:1069; Glöckner 2011:168). Their poor CSF penetration is largely due to its high protein binding and large molecular weight (Carver *et al.,* 2007:78). Echinocandins achieve therapeutic concentrations in all infection sites

except of the eye, central nervous system and urinary tract (Andes *et al.,* 2016:12). Since urine concentrations of the active metabolites are minimal, echinocandins show poor clinical significance for treating urinary tract infections systemically. All echinocandins demonstrate linear pharmacokinetics following administration of IV dosages and are metabolised predominantly by the liver (Graninger *et al.,* 2006:165). \the metabolised products are excreted slowly over many days via the bile; therefore echinocandins do not require dose adjustments in renal failure.

2.9.1 Pharmacokinetics in special populations

No dose adjustments are based on race and gender (Carver *et al.,* 2007:78). Caspofungin's dose is based on body surface area (50mg/m^2/day) in pediatric patients, whereas anidulafungin can be used as 0.75mg/kg/day after a LD of 1.5mg/kg/day (Carver *et al.,* 2007:79; Cancidas® PI, 2012; Graninger *et al.,* 2006:166). The use of anidulafungin in children is debatable since the PI states that it should not be used in children (Eraxis® PI, 2014). Micafungin should be used in higher doses in the pediatric population because of an observed age related decrease in micafungin clearance (Graninger *et al.,* 2006:166), however, since children are excluded from the study, the dosing schedules for children falls outside the scope of this study.

2.9.1.1 Hepatic insufficiency

Carver *et al.,* (2007:78); Glöckner, (2011:168); as well as Graninger and his co-researchers (2006:165) suggested that caspofungins' maintenance dose should be decreased to 35mg in patients with moderate hepatic impairment. The AUC of caspofungin is significantly increased in patients with moderate hepatic impairment due to the fact that caspofungin is being metabolised by the liver.

The AUC of micafungin is decreased in patients with moderate hepatic insufficiency, most likely due to the lower protein binding in these populations and an increased volume of distribution. Micafungin is however contraindicated in patients with severe hepatic dysfunction because of the development of foci altered hepatocytes and hepatocellular tumours after a treatment period of three months or longer were observed in rats. Mycamine ® PI, 2015).

No dose adjustments are necessary for anidulafungin, most probably because of the fact that anidulafungin is eliminated by a slow chemical degradation rather than hepatic metabolism (Eraxis® PI, 2014; Carver *et al.,* 2007:78).

2.9.1.2 Nursing mothers

It is not known whether echinocandins will be found in the breast milk of humans but it was indeed found in the breast milk of lactating rats and therefore caution should be exercised when echinocandins are administered to nursing woman (Carver *et al.,* 2007:78; Glöckner, 2011:173; Eraxis® PI, 2014). It can thus be concluded that treatment should only be considered when benefits outweighs the risk.

2.9.1.3 Pregnancy

All the echinocandins are categorised as a category C drug, as done by the FDA. Category C indicates that animal studies have shown ADEs and there are no adequate and well controlled studies in pregnant women; or no animal studies have been conducted and there are no adequate or well controlled studies in pregnant women (Rossiter *et al.,* 2014:7). It has been shown to be embryotoxic in rats and rabbits (Morris & Villmann, 2006:1701). Echinocandin use during pregnancy is again only advised when the benefit outweighs the risk (Carver *et al.,* 2007:78; Glöckner, 2011:173, Mycamine® PI, 2015).

2.9.1.4 Geriatrics

Plasma concentrations of caspofungin in healthy older patients were increased slightly compared with young healthy men and a similar effect of age on pharmacokinetics was seen in patients with candidemia or other *Candida* infections. Until further investigation dose adjustments in the elderly are not necessary (Carver *et al.,* 2007:78). The use of echinocandins can thus be considered safe in geriatric patients.

2.10 Safety and adverse effects

All three echinocandins (caspofungin, anidulafungin, micafungin) have a safe profile in comparison to other antifungals such as amphotericin B and the triazoles (Morris & Villmann, 2006:1700; Carver *et al.,* 2007:80). Common adverse effects are listed in Table 2-6 (Carver *et al.,* 2007:81; Cancidas® PI, 2012; Eraxis® PI, 2014 & Mycamine® PI, 2015). Micafungin has a black box warning with regard to liver damage and should be used with extreme caution in patients with severe liver disease (Mycamine® PI, 2015).

Table 2-6: Adverse effects of echinocandins

Parameter		Caspofungin	Micafungin	Anidulafungin
Haematologic	Neutropenia	N/A	1.2%	1.0%
	Leukopenia	N/A	0.9%	0.7%
	Eosinophilia	3%	Rarely related to infusion	N/A
	Thrombocytopenia	<4%	N/A	N/A
	Decreased haemoglobin and haematocrit	3-12%	N/A	N/A
Gastrointestinal	Nausea	<3%	2.4%	1.0%
	Diarrhoea	N/A	N/A	N/A
	Vomiting	<3%	N/A	0.7%
	Dyspepsia	N/A		0.3%
Miscellaneous	Hyperbilirubinemia	N/A	3.3%	N/A
	Increased gamma gluteryl transferase	N/A	N/A	<1%
	Elevated aspartate aminotransferase/alanine aminotransferase	<2%	Rare	N/A
	Hypokalemia	11% after 70mg dose, <4% with 50mg dose	1.8%	2.4-3.1%
	Rash	N/A	N/A	<1%
	Pyrexia	12-26%	N/A	0.7%
	Headache	<3%	N/A	1.3%
	Flushing	<3%	N/A	N/A
	Phlebitis/thrombophlebitis	12-18%	Rare	1.3%
	Infusion related reactions/histamine release	2%	Rare	1 patient flushing with infusion

As there were some concerns regarding the effect of using cyclosporine in combination with caspofungin the PI recommends liver tests regularly. From the literature studied most common side effects are histamine-mediated symptoms with echinocandins (Carver *et al.,* 2007:78).

2.11 Resistance to echinocandins

The development of echinocandin-resistance and the echinocandin/azole-resistant *Candida* spp. especially *C. glabrata*, clearly have been documented, and this discovery seems to be associated with poor clinical outcomes (Andes *et al.,* 2016:18). Fluconazole resistance is a common finding among echinocandin-resistant isolates, further complicating therapeutic options (Andes *et al.,* 2016:18).

C. glabrata has the potential to be cross resistant to both the azole antifungals and the echinocandins. This is due to increased transporter genes, increased expression of efflux pumps and the propensity for biofilm formation (Bryant *et al.,* 2014:1321).

In SA, a recent epidemiology study has proven that a quarter of the tested spp. were fluconazole resistant. According to the hypothesis of Coovadia and colleagues (2016:2002), the overuse of azole antifungals in empiric therapy and treatment of candidemia may have led to the emergence and subsequent nosocomial transmission of these azole-resistant strains. Furthermore, the hypothesis is supported by the emergence of bloodstream *Candida* infections caused by azole-resistant *C. auris*. At the time this study was conducted a very low prevalence of echinocandin resistance was noted, possibly due to the fact that caspofungin was only then released into the SA market and the use was restricted to private healthcare facilities. The epidemiology in SA is unique with a dominance of azole-resistant non – *C. albicans* spp. causing bloodstream infections (Coovadia *et al.,* 2016:2002). In 2016, the CDCP raised the concern of multidrug-resistant *C. auris* worldwide.

C. auris can differentially adhere to polymeric surfaces, form biofilms and resist antifungal agents that are active against its planktonic counterparts. This can lead to caspofungin that can become inactive against *C. auris* biofilms (Bornman *et al.,* 2017:330).

Since *C. auris* was first defined in Japan in 2009, cases have been reported in South Korea, India, Kuwait, Kenya, and SA and more recently in Colombia, Venezuela, Pakistan, the UK and the USA. One of the greatest concerns is the fact that *C. auris* is repeatedly multi-drug resistant and almost all tested *C. auris* spp. are resistant to fluconazole (Centre for Opportunistic, Tropical and Hospital Infections, 2016:1). Especially in SA, *C. auris* was the second most common cause of invasive candidiasis in the private sector in 2016, based on current active,

laboratory-based surveillance for invasive candidiasis, with most cases occurring in the Gauteng province. However, in the public sector *C. auris* was the fourth most common *Candida* specie causing invasive candidiasis, again with the majority of cases in the Gauteng province. A big challenge when fighting a *C. auris* outbreak is to be able to differentiate when a patient has a *C. auris* infection and when a patient has a *C. auris* colonisation. Effective first-line therapy, isolation methods and monitoring of the outbreak will depend on the correct classification of patients. In table 2-7 *C. auris* infection and *C. auris* colonisation is compared (adapted from Centre for Opportunistic, Tropical and Hospital Infections, 2016:3).

Table 2-7: Difference between *C. auris* infection and colonisation

***C. auris* INFECTION**	***C. auris* COLONISATION**
A patient with established or suspected *C. auris* infections identified by a diagnostic laboratory from any sterile body site: • Blood • CVC tip • CSF • Tissue • Fluid from a sterile site • Urine	A patient with established or suspected *C. auris* from any "non-sterile" body site: • Skin • Tracheal aspirate / respiratory secretions • Rectal swab • Nasal swab • Urine

First line treatment should include an echinocandin or amphotericin B deoxycholate as well as removal of indwelling devices such as CVCs which may be the source of *Candida*. Treatment duration should be continued for 14 days after documented clearance of *Candida* from the bloodstream (one blood culture per day until negative culture has been received). The duration of treatment does agree with all other relevant guidelines regarding the treatment of fungal infections (Andes *et al.,* 2016:15, Bassetti *et al.,* 2014:263, Bryant *et al.,* 2014:1315; Cornely *et al.,* 2012:21, Centre for Opportunistic, Tropical and Hospital Infections, 2016:3; Gookool-Sewram *et al.,* 2014:1).

2.12 Global/International guidelines

The Infectious Diseases Society of America (IDSA) published a clinical practice guideline for the managing of candidiasis in 2016. For this guideline, the IDSA Standards and Practice Guidelines Committee assembled a multidisciplinary panel of 12 experts in the management of

candidiasis, and included 11 adult infectious diseases physicians (Andes *et al.,* 2016:10). This guideline followed an evidence review called the Grading of Recommendations Assessment, Development and Education (GRADE) method to support the literature. IDSA adopted this GRADE method that is a systematic approach to guideline development in 2008. In the GRADE system, the guideline panel assigns each recommendation with separate ratings for the underlying quality of evidence supporting the recommendation and for the strength with which the recommendation is made, as illustrated in figure 2-2 (Adapted from Andes *et al.,* 2016:2).

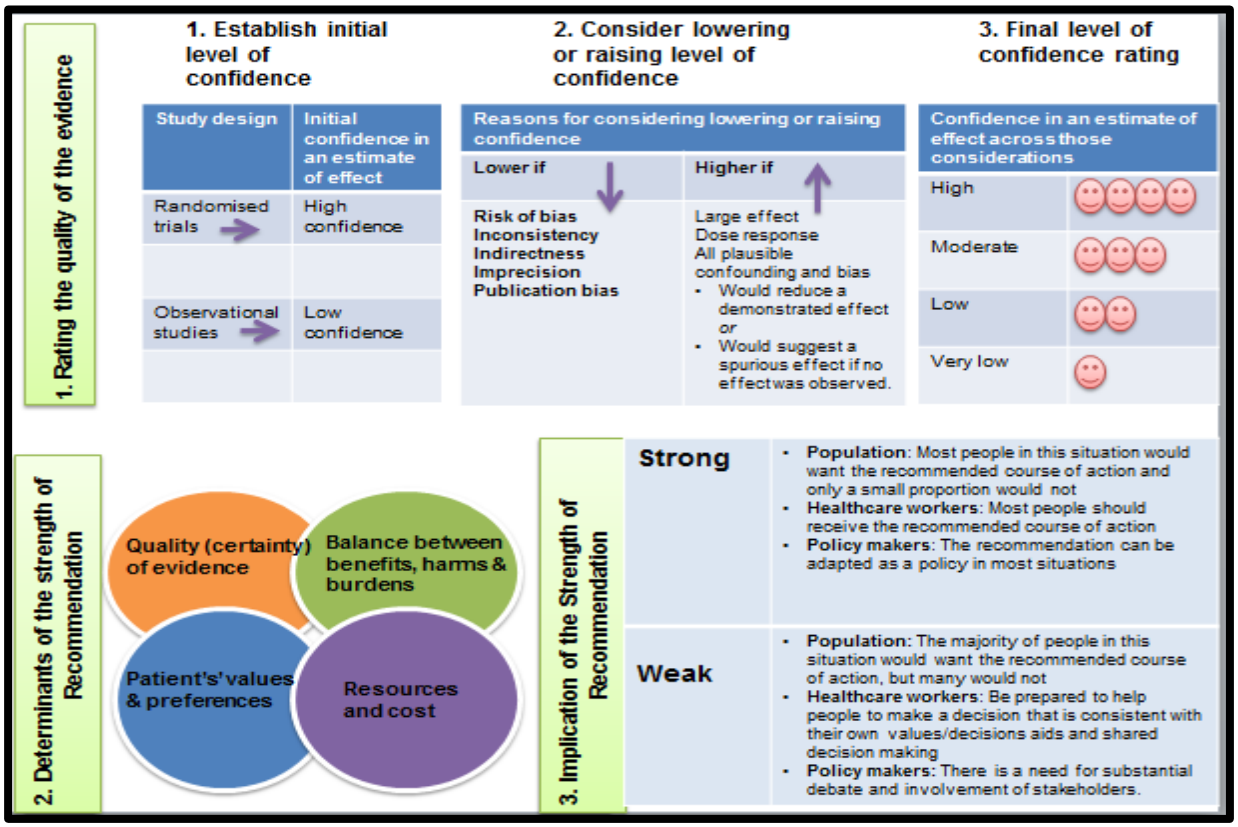

Figure 2-2: The (GRADE) methodology: rating the quality of evidence and strength of recommendations

Data from randomised trials began as “high” quality and data from observational studies began as “low” quality. The strength assigned to the recommendation chiefly reflected the panel’s confidence that the benefits of the following recommendation were expected to outweigh the potential harms.

The European Society for Clinical Microbiology and Infectious Diseases (ESCMID) published a guideline for the diagnosis and management of *Candida* diseases in 2012. An expert panel was set up by the European Fungal Infection Study Group (EFISG) and searched the literature (Cornely *et al.,* 2012:20). To evaluate the literature ESCMID adopted a four-category grading

system for the strength of recommendation (Akova *et al.,* 2012: 4). The definition of the strength of recommendation is given in Table 2-8 as indicated by (Cornely *et al.,* 2012:20).

Table 2-8: Definition of the strength of recommendation according to ESCMID and EFISG

Grade	ESCMID and EFISG
A	Strongly supports a recommendation for use.
B	Moderately supports a recommendation for use.
C	Marginally supports a recommendation for use.
D	Supports a recommendation against use.

The grading of strength of a recommendation cannot simply be applied to diagnostic recommendations and therefore an alternative system was adopted. In table 2-8 the quality of evidence is defined. To ensure the transparency in the evaluation of evidence, they added an index (table 2-9) to the level II recommendations where appropriate (Cornely *et al.,* 2012:20).

Table 2-9: The ESCMID and EFISG definition of the quality of evidence

ESCMID and EFISG	
Level	
I	Evidence from at least one properly designed randomised, controlled trial.
II*	Evidence from at least one well-designed clinical trial, without randomisation, from cohort or case-controlled analytical studies (preferably from >1 centre): from multiple time series or from dramatic results of uncontrolled experiments.
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies or reports of expert committees.
***Added index (for quality of evidence II)**	
r	Meta-analysis or systematic review of randomised controlled trials.
t	Transferred evidence, that is, results from different patients' cohorts, or similar immune-status situation.
h	Comparator group is a historical control.
u	Uncontrolled trial
a	Published abstract (presented at an international symposium or meeting).

The Italian Society of Antimicrobial Therapy, Società Italiana di Terapia Antimicrobica (SITA), approved a national consensus process involving numerous medical disciplines to review the available evidence and created practical, hospital-wide recommendations about the management of severe *Candida* infections in non-immunocompromised patients, excluding patients with haematological diseases and those who had undergone solid organ and hematopoietic stem cell transplants (Bassetti *et al.,* 2013:264).

The consensus panel involved 30 infectious disease consultants, surgeons and intensive care physicians, and a clinical epidemiologist with two external discussants (a microbiologist and a clinical pharmacist). SITA adopted the GRADE profile in order to assess the quality of evidence and strength of recommendations.

Bryant *et al.* (2014:1315) published a consensus guideline for the treatment of yeast infections in the haematology, oncology and intensive care setting in Australia. Their search strategy included a literature study using PubMed® to identify papers published since 2007 that pertained to the treatment of yeast infections.

A private hospital company in SA published a guideline within this study setting to ensure the appropriate use of echinocandins in their hospital group (Gokool-Sewram, 2014:1-5). This guideline is called a Quality Alert and is based on the ESCMID guidelines that will be compared to the international guidelines by IDSA, ESCMID, Italian and Australian guidelines. Annexure E compares the five different guidelines with each other with the focus on the research questions of this study.

2.13 Adjunctive therapies and management of invasive candidiasis

Figure 2-3 was developed from the Australian guideline by Bryant and colleagues *(*2014:1317), and recommends the following ancillary management measures in candidemia:

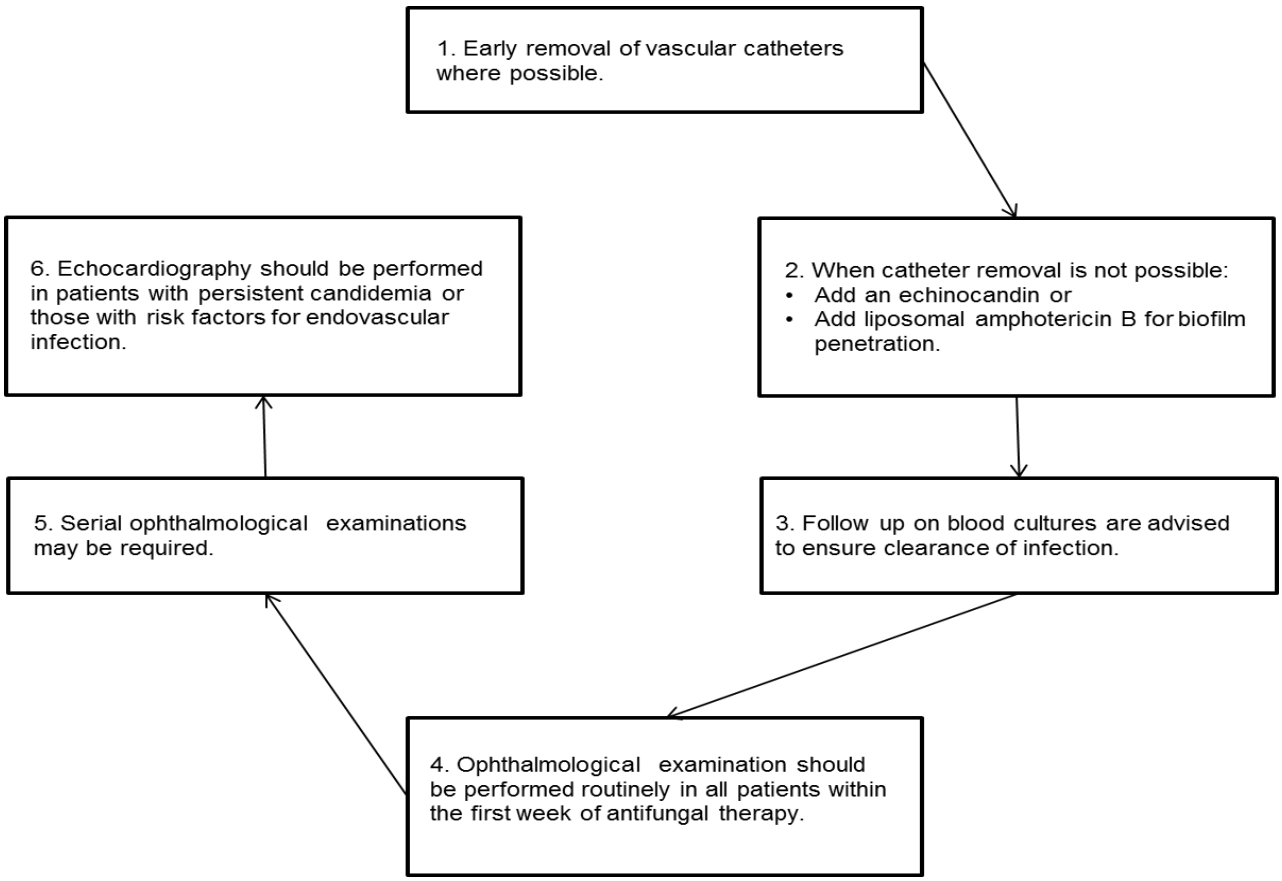

Figure 2-3: Adjunctive therapies and management of invasive candidiasis

The expert panel of IDSA also encourage that CVCs should be removed as soon as possible in the path of illness when the source is assumed to be the CVC and the catheter can be removed safely; the decision should be individualised for each patient (Andes *et al.,* 2016:20).

For all patients with candidemia the expert panel of IDSA as well as the Australian guideline strongly encourage a dilated funduscopic examination, preferably performed by an ophthalmologist, and within the first week after antifungal therapy has been initiated. Recent data suggest that as many as 16% of patients with candidemia have some appearance of ocular involvement, and some of these patients will develop severe, sight-threatening endophthalmitis. All *Candida* spp. that cause candidemia have been reported to cause endophthalmitis as a complication (Andes *et al.,* 2016:31).

Endophthalmitis “is an infection within the eye, usually involving the posterior chamber and sometimes also the anterior chamber” (Egan, 2015).

2.14 Chapter summary

Chapter 2 provided an overview of fungal spp., fungal infections and moreover the echinocandins available in SA. Topics addressed were fungal infections and the causative organisms, antifungals available in SA, risk factors for fungal infections especially invasive candidiasis as well as the dosing considerations and special properties of echinocandins. The specific objectives of the literature review have been answered and the results will be discussed in a manuscript format in the next chapter.

CHAPTER 3: RESULT AND DISCUSSION

3.1 Introduction

This chapter contains the general findings and discussion of the empirical investigation of the study and is represented in the form of one manuscript.

The manuscript, entitled “The general prescribing patterns of echinocandins in adult patients in a private hospital in the Gauteng Province, South Africa” was submitted to the ‘*South African Medical Journal’.*

Instructions to the author can be viewed with the following link:
http://www.samj.org.za/index.php/samj/about/submissions#Guidelines

3.2 Manuscript

Title

The general prescribing patterns of echinocandins in adult patients in a private hospital in the Gauteng Province, South Africa.

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Conflicts of interest

No conflicts of interest have been declared.

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Keywords

Echinocandins; appropriate, candidemia, *Candida,* loading dose, daily dose, appropriate duration, caspofungin, anidulafungin, micafungin.

Abstract

Background: *Candida* species (spp.) are the leading cause of invasive candidiasis worldwide as well as the fourth leading cause of hospital acquired infections. The appropriate use of antifungal agents is one of the most important factors in fighting drug resistance.
Objectives: The specific research objectives include the following: to study the pharmacological background and classification of echinocandins; to investigate and compare international and national guidelines regarding the prescribing of echinocandins. The specific research objectives include the following: to determine the general prescribing patterns of echinocandins, to determine whether there is an association between the prevalence of the treatment period, de-escalation of therapy and the availability of blood cultures of patients treated with echinocandins.
Methods: This study followed a quantitative research design method; it took the form of an observational, descriptive study. The target population involved all patients in this setting being on antifungal treatment for the period 1 January 2015 to 31 December 2015. One hundred and forty six patients complied with the inclusion criteria
Results: 146 patient files were studied, 102 (69.863%) patients received caspofungin and 44 (30.127%) patients received anidulafungin. Out of the 102 patients that received caspofungin 99 (97.058%) patients received a LD of 70mg and 3 (2.941%) patients did not receive a LD at all. Out of the 44 patients that received anidulafungin only 30 (68.181%) received a LD of 200mg and 14 (31.819%) did either not receive a LD or received an inappropriate LD. The PDD for caspofungin is 50mg IV daily whereas in this population 98 (98.078%) patients received 50mg IV per day and 4 (3.922%) patients received 70mg IV per day. The PDD for anidulafungin is 100mg IV per day and the results of this study's data was that 1 (2.273%) patient received 400mg IV per day, 23 (52.273%) patients received 200mg IV per day, 19 (43.182%) patients received 100mg IV per day and 1 (2.273%) patient received only 50mg IV per day. De-escalation is not evident at this setting. The presence of blood cultures did not relate to de-escalation of therapy, but blood cultures are being performed. There was no significant statistics between the duration of treatment and the presence of a positive blood culture.
Conclusion: The results of this study can be used to develop a hospital specific algorithm for patients with *Candida* infections.

Introduction

Candida species (spp.) are the leading cause of invasive candidiasis worldwide as well as the fourth leading cause of hospital acquired infections with dramatic mortality and morbidity rates.[1] Recent reports indicate a change in species distribution patterns of *Candida* infections, resulting in an increase of non-albicans *Candida* spp. such as *C. glabrata* and *C. parapsilosis.* [1-4]

Fungal spp. develops resistance over time as a consequence of inappropriate antifungal use, for example dosages that are too low or treatment courses that are not long enough to reach clinical outcomes. [6, 7] The appropriate use of antifungal agents is one of the most important factors in fighting drug resistance. The Centers for Disease Control and Prevention (CDCP) (2014) have strategies in place to help reduce antifungal resistance, which include the appropriate prescribing of antifungals, assessing antifungals as part of antimicrobial stewardship and documenting the dose, duration and indication for antifungal agents. [17]

It is now evident that the misuse of antifungals has contributed to the global escalation in antifungal resistance, increases in morbidity and mortality and has played a role in the change in the aetiology of invasive fungal infections. [18]

As a result of the changes in the epidemiology of the *Candida* spp. the world is now facing an emergence of antifungal drug resistance spp.[1] Antifungal drug resistance is associated with an uncontrolled distribution and prolonged use of an antifungal agent in recurrent fungal infections. [1, 5, 6, 7]

The changes in species distribution, previous exposure to fluconazole and inherited resistant mechanisms now results in fluconazole resistance and in worst scenarios echinocandin resistant *Candida* spp. [1, 9] Multi-drug resistance was observed in a recent report in South Africa (SA), especially for *C. albicans, C. glabrata* and *C. tropicalis*, indicating a massive threat for the public health sector and reflecting the results of inappropriate antifungal use. [1]

The evolving incidence of multidrug-resistant *Candida* spp. will complicate the selection of antifungal therapy in the near future, therefore the appropriate prescribing that includes: correct dosing, duration of therapy, de-escalation to an oral antifungal, and cost-evaluation and benefit-risk ratio of echinocandins should be strongly encouraged. [8]

Caspofungin needs a loading dose (LD) of 70mg followed by a 50mg daily dose intravenously (IV). [10-13] According to the package insert (PI) of Cancidas® (2012),[13] as well as the authors and references mentioned above, patients with a body weight more than 80kg must receive 70mg of caspofungin IV daily. Caspofungin has been used in higher doses such as 150mg per day in clinical trials of invasive candidiasis. [11] Almost all the caspofungin clinical studies have been at 70mg LD and a 50mg once-daily dose. [14]

Micafungin does not need a LD and should be dosed according to table 3-1. [10, 15]

Table 3-1: Micafungin dosages

Indication	Body weight more than 40kg
Prophylaxis of *Candida* infection	50mg/day
Invasive candidiasis treatment	100mg/day
Oesophageal candidiasis treatment	150mg/day

Treatment with anidulafungin starts with a LD of 200mg IV followed by a maintenance dose of 100mg IV per day. [16] In treating oesophageal candidiasis, the LD of anidulafungin is 100mg, followed by 50mg/day. For candidemia and other deep-tissue infections, a LD of 200mg followed by 100mg/day thereafter is necessary. [12]

Candida infections are not only complicated by the narrow selection of treatment available but also by the fact that these organisms have biofilm activity and is attracted by the biofilms that forms part of indwelling devices and catheters. [19, 20] Because of this unique characteristic of *Candida* spp., mostly all of the guidelines recommend either removal of the indwelling devices, or at least replacing the indwelling devices after a diagnosis of invasive candidiasis or candidemia has been made. [4, 8, 10, 20]

With regard to the de-escalation of therapy and switching from an IV form to an oral antifungal agent, a lot of controversies raised from the available literature. The 2016 guidelines of the Infectious Diseases Society of America (IDSA) recommend that a patient's treatment can be changed from an IV form to an oral agent (fluconazole) usually within 5-7 days for patients who are clinically stable. However, it is imperative that the specie should be susceptible to one of the oral agents available and the patient should have negative repeated blood cultures. [8] The 2012 guidelines by the European Society for Clinical Microbiology and Infectious Diseases (ESCMID), recommend that treatment can be simplified to an oral agent after ten days of IV treatment, if the patient is stable and, able to tolerate an oral form and when the species is susceptible to the treatment. [10]

A local Quality Alert of a national private hospital group in SA based their recommendations on the ESCMID guidelines. It was to be implemented by pharmacists working for this hospital group to ensure the appropriate use of echinocandins.

The duration of therapy for a patient with invasive candidiasis or candidemia remains a big challenge due to the following reasons: [8, 9]

- candidemia is associated with a high mortality rate;
- there are several limitations to early diagnosis;
- there is a geographic species distribution with a variety of different *Candida* spp. each one with unique challenges;
- some spp. have biofilm activity; and
- *Candida* spp. can be deep seated in different organs.

Due to the challenges in treatment of *Candida* infection, the guidelines and literature did not reach an accurate consensus with regard to the duration of therapy. However, it was clear that a course of 14 days of IV treatment should be performed after the first negative blood culture. Therefore, the aim of this study was to determine if doctors are compliant to the guidelines available.

Methods

This study took place at a private hospital in the Gauteng Province of SA.

The target population involved all patients in this private hospital being on antifungal treatment for the period 1 January 2015 to 31 December 2015.

The study population included all patients who complied with the inclusion criteria. This study included all adult patients who were admitted to the specific private hospital and who were on antifungal treatment during their hospitalisation. One hundred and forty six patients complied with the inclusion criteria.

This study was approved by the Health Research Ethics Committee (HREC), Faculty of Health Sciences, North-West University (NWU), Ethical number: NWU-00361-15-A1 and the Research Operations Committee of the private hospital group.

This study followed a quantitative research design method; it took the form of an observational, descriptive study because the researcher was observing retrospective data and there was no interference from the researcher.

The following data fields were captured from patients' medical records using a data collection form: demographic information, including age and ward admitted in hospital; type of the IV echinocandin that the patient was started with; loading dose (LD); prescribed daily dose (PDD); starting date and end date of echinocandin treatment; de-escalation of therapy; and if yes, active ingredient of oral agent; presence and results of blood cultures; cost of antifungal treatment, blood tests and blood cultures performed.

Patients were eligible for inclusion in this study if they met the following criteria: (i) all patients 18 years of age and older and (ii) the period during which all patients 18 years of age and older were started on IV echinocandin treatment from 1 January 2015 to 1 January 2016. The specific time period is chosen by the researcher as anidulafungin only became available in SA at the end of 2014. Patients were excluded if (i) they were admitted while on any antifungal treatment or who used it as chronic therapy, (ii) pregnant patients and (iii) patients who changed from one IV echinocandin to another IV antifungal during their hospital stay.

The variables for this study are the type of antifungal, the dosage of antifungal treatment, the duration of treatment, the de-escalation of therapy, blood results and cultures and the average cost of antifungal treatment.

The Statistical Analysis System®, SAS 9.3® (SAS Institute Inc., 2009) was used to evaluate the data in consultation with the Statistical Consultation Services of the NWU. All variables were expressed using descriptive statistics such as frequencies (n), percentages (%), means, standard deviations (SD), and 95% confidence intervals (CI). The two-sample t-test was used to compare the difference between the means of two groups. Cohen's *d*-value was used to define the

practical significance of the results (with $d \geq 0.8$ seen as a large effect with practical significance). Pearson's chi-square test was used to determine the association between two categorical variables. Cramér's V was used to determine the practical significance of the results (with $V \geq 0.5$ seen as a large effect with practical significance).

Results

The study population consisted of 146 patient files.

General prescribing patterns

With regard to the prescribing patterns of echinocandins it was found that 102 (69.863%) patients received caspofungin and 44 (30.127%) patients received anidulafungin. Out of the 102 patients that received caspofungin 99 (97.058%) patients received a LD of 70mg and 3 (2.941%) patients did not receive a LD at all. Out of the 44 patients that received anidulafungin only 30 (68.181%) received a LD of 200mg and 14 (31.819%) did either not receive a LD or received an inappropriate LD.

The PDD for caspofungin is 50mg IV daily whereas in this population 98 (98.078%) patients received 50mg IV per day and 4 (3.922%) patients received 70mg IV per day. The PDD for anidulafungin is 100mg IV per day and the results of this study's data was that 1 (2.273%) patient received 400mg IV per day, 23 (52.273%) patients received 200mg IV per day, 19 (43.182%) patients received 100mg IV per day and 1 (2.273%) patient received only 50mg IV per day.

To establish if the prescribers prescribed the echinocandins with the appropriate LD, a frequency table indicates the results:

Table 3-2: Frequency and percentage table for the LD of anidulafungin and caspofungin.

Products	Frequency	Percentage
Anidulafungin	Yes: 30	68.182%
	No: 14	31.818%
	n=44	
Caspofungin	Yes: 99	97.058%
	No: 3	2.941%
	n=102	

There are more cases of where the appropriate LD was given than there was for no LD given for both anidulafungin and caspofungin.

From the collected data the average dose for anidulafungin was 200mg IV per day for the majority of patients. One patient was prescribed 50mg IV per day, 19 patients were prescribed

100mg IV per day and 23 patients were prescribed 200mg IV per day. There was only one case where a patient received 400mg IV per day.

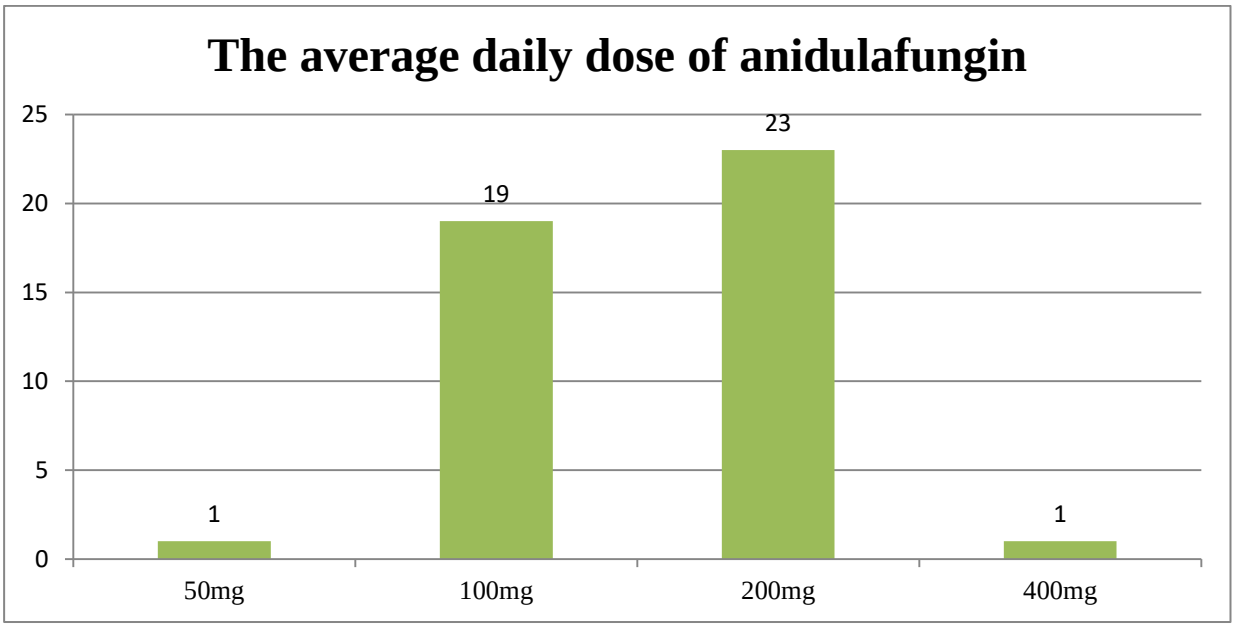

Figure 3-1: Loading doses of anidulafungin

For caspofungin 98 patients received 50mg IV per day and 4 patients received 70mg IV per day.

The association between blood culture and de-escalation of therapy

From table 3-3 the following were observed:

Table 3-3: The association between blood culture and de-escalation of therapy

		Was the patient switched to an oral antifungal?				**Chi-square test (p-value)**	**Cramér's *V***
Was any blood tests performed before treated with an Echinocandin?			**Yes**	**No**	**Total**		
	Yes	Frequency (Per cent) Row % *Col %*	6 (4.11) 4.65 *85.71*	123 (84.25) 95.35 *88.49*	129 (88.36) 100	(0.823)	0.018
	No	Frequency (Per cent) Row %	1 (0.68) 5.88	16 (10.96) 94.12	17 (11.64) 100		

		Col %	*14.29*	*11.51*			
	Total	Frequency (Per cent) Row % *Col %*	7 (4.79) *100*	139 (95.21) *100%*	146 (100)		

- In 6 (4.11%) cases it was observed that both blood cultures performed and de-escalation of therapy occurred.
- In 123 (84.25%) cases it was observed that no de-escalation of therapy was performed but blood cultures occurred.
- In 1 (0.68%) case it was observed that de-escalation of therapy occurred, but no blood cultures were performed.
- In 16 (10.96%) cases it was observed that no de-escalation of therapy was performed and neither was the presence of blood cultures.
- Overall 129 (88.36%) cases had blood cultures performed and 17 (11.64%) cases had no blood cultures performed.
- Overall 7 (4.79%) cases had no blood cultures performed and 139 (95.21%) cases had not been de-escalated.
- Most of the cases did not have de-escalation of therapy but had blood cultures performed.
- Of the 7 cases that had de-escalation of therapy, 6 of them (85.71%) had blood cultures performed.
- For those who did not have de-escalation of therapy, 88.49% had blood cultures performed.
- Nearly all (95.35%) of the patients that had blood cultures, did not have de-escalation of therapy.
- Nearly all (94.12%) of the patients that didn't have blood cultures also didn't have de-escalation of therapy.
- The p-value (0.83) is bigger than 0.05, indicating that there is no association between the two variables.
- Cramér's *V* (0.018) is less than 0.5, indicating a small effect with no practical significance thus no association between de-escalation of treatment and the availability of blood cultures.

The comparison between the average duration of treatment between patients with blood cultures and patients without blood cultures

The comparison between the average duration of treatment between patients with blood cultures and patients without blood cultures was measured by the independent t-test and Cohen's *d* value and is indicated in table 3-4

Table 3-4: The comparison between the average duration of treatment between patients with blood cultures and patients without blood cultures

Statistical measures	Yes (positive blood culture)	No (blood culture)	Independent t-test (p-value)	Cohen's *d* value
n	129	17	-0.141 (0.888)	0.031
Mean (SD*)	9.729 (7.306)	10.00 (8.718)		
Median	8.0	7.0		
95% Confidence interval for mean	8.456; 11.001	5.518; 14.482		
*SD: Standard deviation				

With regard to the duration of therapy it was found that, out of the 146 patients studied, the mean days on therapy were 9.729, regardless of blood cultures performed or not.

Discussion

International guidelines and general prescribing patterns

Three international guidelines and a local Quality Alert by a hospital group in SA were studied as seen in table 3-5, to investigate the correct LD and PDD for echinocandins[4, 8, 10, 21 ,22] The guidelines reached consensus regarding the dosing of echinocandins and the guidelines was used as a standard to measure the compliance of the prescribing patterns of echinocandins in adult patients in a private hospital. In this study setting the researcher observed that the echinocandins were mostly prescribed correctly regarding the LD and PDD. With regards to the general prescribing patterns 98 patients received caspofungin 50mg IV per day and 4 patients received 70mg IV per day. According to the literature [1-8] the daily dose for caspofungin should be 50mg IV per day and for anidulafungin 100mg IV per day. In conclusion most of the patients received the correct caspofungin daily dose but not the correct daily dose for anidulafungin.

The association between blood culture and de-escalation of therapy

In terms of de-escalation of therapy the international guidelines were accepted as the golden standard and the results of this study were measured against the literature in the guidelines (Table 3-5). In this study setting most of the patients indicated no for de-escalation of therapy which in fact means that the prescribing doctors at this study setting were not compliant to the guidelines available. Because of the fact that the literature[8], states that de-escalation can be initiated when a negative blood culture is present it was imperative for the researcher to measure the compliance of de-escalation to the presence of blood cultures as indicated in table 3-3.

The comparison between the average duration of treatment between patients with blood cultures and patients without blood cultures

From the 146 patients studied, 129 patients had a positive blood culture while 17 patients did not have a blood culture. The mean duration of echinocandin therapy for patients with positive blood cultures (9.729%) is lower than the mean duration for patients without a blood culture (10.00%). This mean had to be taken into consideration with the performance of blood cultures as the literature stated that therapy should be stopped after 14 days on IV treatment, after the first negative blood culture.[4, 8, 10]This indicates that the patients with positive blood cultures actually had a lesser time on antifungal therapy than those without a blood culture.

The SD for patients with positive blood cultures is also lower than the SD for patients without a blood culture, indicating that values for the patients with positive blood cultures have less variability than the values for the patients without a blood culture.

Both the medians are smaller than the corresponding means, indicating that the distribution is positive skew; hence the probability density function has a longer tail on the right.

The p-value of 0.888 is greater than the p-value of significance (0.05) meaning that there is no statistical significant difference between the average duration of treatment between patients with blood cultures and patients without blood cultures. When Cohen's *d* value is $\geq$ 0.8, it can be seen as a large effect as discussed in section 1.8. Cohen's *d* value = 0.031 indicating that there is a small effect with no practical significance, which indicates that the duration of echinocandin therapy is not dependant on the presence of a positive blood culture. However a negative blood culture will guide the prescribing doctor on when to de-escalate therapy [4, 8, 10, 21, 22].

This study contributes to the relevance of antifungal stewardship and the practice of using antifungal therapy appropriately. Micafungin became only available in SA after the data collection period which could have influenced the study population. Future research should include the establishment of positive and negative blood cultures and the effect on duration of therapy.

Table 3-5: International guidelines and local Quality Alert of echinocandins

		IDSA guidelines [8]	**ESCMID guidelines** [10]	**An Italian consensus for invasive candidiasis management (ITALIC)**[4]	**Australian consensus guidelines for yeast infections** [21]	**Quality Alert in study setting** [22]
Loading dose (LD) and maintenance dose	**Caspofungin**	A LD of 70mg IV and a daily dose of 50mg IV.	A 70mg IV LD and a maintenance dose of 50mg IV daily for initial targeted treatment of candidemia and invasive candidiasis in adult patients. Caspofungin's dose should be increased to 70mg IV daily instead of 50mg IV daily in patients with a high body weight.	Not discussed.	70mg IV daily for 24 hours, then 50mg IV daily.	A LD of 70mg IV and a daily dose of 50mg IV. A maintenance dose of 70mg IV daily is required for patients of $\geq$ 80kg.

	Micafungin	100mg daily IV			100mg IV daily.	
	Anidulafungin	A LD of 200mg IV and a daily dose of 100mg IV as initial therapy for candidemia in non-neutropenic patients.	Administered as a 200mg IV LD and a 100mg IV maintenance dose for initial targeted treatment of candidemia and invasive candidiasis in adult patients.		200mg IV daily for 24 hours then 100mg IV daily.	LD of 200mg IV and 100mg IV daily.

	IDSA guidelines [8]	ESCMID guidelines [10]	An Italian consensus for invasive candidiasis management (ITALIC)[4]	Australian consensus guidelines for yeast infections [21]	Quality Alert in study setting [22]
De-escalation of treatment	Conversion from an echinocandin to fluconazole (usually within 5-7 days) is suggested for patients who are clinically stable, have isolates that are susceptible to fluconazole, and have negative repeat blood cultures following the beginning of antifungal therapy (strong recommendation; moderate quality evidence).	Treatment can probably be simplified by stepping down to oral fluconazole after 10 days of IV treatment, if the patient is stable, tolerates the oral route and if species are susceptible	De-escalation from echinocandins to fluconazole is advisable, if the isolated *Candida* strain is fluconazole-susceptible and the patient is clinically stable.	Succeeding satisfactory clinical and microbiological response, changing from an IV to oral antifungal therapy is appropriate, assuming susceptibility to the oral agent and a functioning gastrointestinal tract.	If a patient is clinically stable, step down therapy is recommended in acceptable doses bases on results of susceptibility testing. This is usually to fluconazole 800mg IV or oral LD with a 400mg IV or oral maintenance dose. Oral therapy is indicated following 10 days of IV treatment.

	IDSA guidelines [8]	ESCMID guidelines [10]	An Italian consensus for invasive candidiasis management (ITALIC)[4]	Australian consensus guidelines for yeast infections [21]	Quality Alert in study setting [22]
Duration of treatment	Recommended duration of therapy for candidemia without metastatic complications is for two weeks after documented clearance of *Candida* spp. from the bloodstream and resolution of symptoms attributable to candidemia (strong recommendation; moderate quality of evidence).	The duration of treatment depends on the extent of organ involvement, but ESCMID states that a patient should be treated for 14 days after the end of candidemia. To determine the end of candidemia, at least one blood culture per day should be taken until cultures come back negative.	Patients should be treated for at least 14 days after the last positive blood culture.	For *Candida* in the deep tissue, treatment with systemic antifungals is recommended for at least 14 days following the last positive sterile site culture.	Continue therapy for 14 days following the first negative blood culture. Take at least one blood culture per day until candidemia proven negative.

Conclusion

From the results and discussion it can be concluded that the prescribing doctors at this setting are compliant to the international guidelines with regards to the dosing of echinocandins. With regards to de-escalation of therapy the results have indicated that the prescribing doctors at this hospital setting are not compliant to the available guidelines. The duration of therapy had to be considered with the presence of a blood culture, and from the results it has been indicated that the presence of a blood culture did not have a big impact on the duration. Therefore more research has to be conducted to comment on the compliance of duration compared to the guidelines.

According to the international guidelines a few principles are set with regard to the prescribing of echinocandins. [8, 10, 4, 21, 22] The local hospital group set up a Quality Alert in attempt for the pharmacists to ensure the appropriate use of the echinocandins. This Quality Alert was already implemented in 2012; at least 3 years before the echinocandin resistant organisms for example *C. auris* became a reality. [1, 2, 5, 17, 18] It is now evident that echinocandin resistance is on the rise and therefore it should be promoted to use the echinocandins appropriately with special focus on the duration of therapy, correct dosing, the use of blood cultures to lead the clinician to possible de-escalation and the total cost of the echinocandins. [5, 17, 18]

The aim of this study was to investigate the available literature regarding the use of echinocandins and to compare the literature to the prescribing patterns of echinocandins in the private practice. The results of this study can be used to develop a hospital specific algorithm for patients with *Candida* infections. This study has shown the value of guidelines and the effect of implementing it resulting in the wise use of available antifungals.

This study has the following limitations:

- The outcomes of this study depended on the completeness of the prescription charts by doctors'
- The researcher had a lack of clinical data such as when catheters were changed.
- This study relied on a random sample because of the inclusion and exclusion criteria and therefore there might be a possibility of more correct prescription charts.

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CHAPTER 4: CONCLUSION AND RECOMMENDATIONS

4.1 Introduction

This chapter focus on the conclusions from the study with regard to the specific objectives outlined in Chapter 1. A brief overview is provided of the content of the mini-dissertation and a brief summary of the findings. In conclusion the imitations and strengths of the study are listed with recommendations for future studies.

The aim of this study was to investigate the prescribing patterns of echinocandins in hospital patients in a SA private hospital and to evaluate the prescribing patterns to international guidelines regarding the prescribing of echinocandins.

4.2 Content of dissertation

This dissertation consists of four chapters.

Chapter 1 provides a general overview of the study, addressing background, a problem statement, research questions, and the aim of the study, specific objectives and methodology used in the study.

Chapter 2 focuses on the general summary of echinocandins including pharmacology, dosing, side effects and international guidelines.

Chapter 3 represents the results and discussion of the study in manuscript form. One manuscript is presented with the following title:

- The general prescribing patterns of echinocandins in adult patients in a private hospital in the Gauteng Province, South Africa.

4.3 Literature review

The specific research objectives of this study's literature review were:

- to study the pharmacological background and classification of echinocandins;
- to investigate international and national guidelines regarding the prescribing of echinocandins with the focus on dosage, duration, blood tests, cost and de-escalation; and
- to study the clinical effect of incorrect (drug, dose and duration) prescribing of echinocandins.

The conclusion from the literature study is as follows:

4.3.1 The pharmacological background and classification of echinocandins.

Echinocandins are a class of antifungal treatment with its primary mechanism of action being the non-competitive inhibition of β-(1, 3)-D-glucan synthase, an essential component of the fungi's cell wall (Graninger *et al.,* 2006:165). Changes in the fungi's cell wall result in changes in its characteristics, compromising the osmotic stability and cell lysis. Fungal spp. have different glucans in their cell wall, which explains the fact that some antifungals have better activity than other, against certain strains of spp. (Chen *et al.* 2011:15). Echinocandins are currently only available in IV formulations and the reconstitution, dosages and kinetics are being described in section 2.6 – 2.10. According to Bassetti *et al.* (2014:268), echinocandins should be the first line therapy for invasive candidiasis because of its fungicidal activity, activity against strains embedded in biofilms, activity against fluconazole-resistant strains, good safety profile and low tendency for interactions.

Caspofungin was the first echinocandin on the market and was approved in 2002 (Bal, 2010:13). Caspofungin is highly protein bound and displays non-linear kinetics. It undergoes natural disintegration to an open-ring compound that subsequently undergoes peptide hydrolysis and N-acetylation. The dose should be adjusted in patients with impaired liver dysfunction as well as in patients who use certain medication that undergoes metabolism through the liver (Bal, 2010:14). (Refer to section 2.6).

Anidulafungin is also protein bound, but display linear kinetics. Anidulafungin has the advantage of being excreted in the bile without undergoing metabolism in the liver. Therefore, no dose adjustments are required in patients with liver failure or in patients who use medication that can cause an effect in the cytochrome P450 enzymes (Bal, 2010:15).

Micafungin has the ability to demonstrate a prolonged concentration-dependant post antifungal effect. It is metabolised in the liver and excreted in an inactive form into bile and urine (Chandrasekar & Sobel, 2006:1171). Due to the fact that micafungin has a black box warning with regard to liver damage, it should be used with extreme caution in patients with severe liver disease (Refer to section 2.6.2).

4.3.2 The investigation of international and national guidelines regarding the prescribing of echinocandins with the focus on dosage, duration, blood tests, cost and de-escalation.

Four international guidelines were studied as well as a Quality Alert from a SA hospital group regarding the prescribing of echinocandins. The four international guidelines were IDSA guidelines 2016, ESCMID guidelines 2012, Italian guidelines 2014 and Australian guidelines 2014. The Quality Alert 2014 was developed after the hospital group had a tremendous increase in their use of echinocandins and that the authors of the Quality Alert felt that echinocandins must be used responsibly and correct to prevent antifungal resistance.

According to the guidelines as illustrated in Annexure E the following similarities have been noted:

- LD and maintenance dose of echinocandins, which means that there are no inconsistencies among the data available and that practitioners should comply with guidelines in order to preserve the available antifungal agents and use it appropriately;
- de-escalation of therapy: all the guidelines have reached consensus that a patient's therapy may be de-escalated as soon as the patient is clinically stable, the specie is susceptible to an alternative agent and the blood culture has been negative for 14 days; and
- duration of therapy: all the guidelines have indicated that a patient should be treated with an antifungal that is susceptible to the agent for 14 days until a negative blood culture has been received. Blood cultures should, therefore, be performed every consecutive day together with the treatment until a negative culture has been obtained. Treatment should then be continued for another 14 days.

The following inconsistencies have been noted:

- with regard to blood cultures and blood tests, some differences have been noted within the guidelines; it is debatable whether it is financially beneficial for the patient to be on treatment daily and to be charged a set of blood cultures every day. Some authors do feel that it is too costly for a patient and therefor it would be of some guidance to compare the cost of treatment to the cost of blood cultures; and
- empiric therapy guidelines do vary between countries. Andruszko & Ashley (2016:113) studied different guidelines and found that empiric therapy should now include echinocandins to be considered as first line therapy in patients with no reason for a high fever, critical ill patients with a risk for candidemia and for non-neutropenic patients with

risk factors for candidemia. Fluconazole is now only listed as a reasonable alternative for patients with no previous exposure to azole antifungals. (Refer to section 2.1).

The four international guidelines as well as the Quality Alert from the hospital group in SA reached consensus regarding the LD and maintenance dose of echinocandins, the de-escalation of therapy, duration of treatment and blood cultures and blood tests. The use of echinocandins as empiric therapy can be debated as the guidelines have different views and evidence about this matter.

4.3.3 The clinical effect of incorrect (drug, dose and duration) prescribing of echinocandins

The recent increasing incidence of invasive fungal infections and multidrug-resistant *Candida* spp. will complicate the selection of antifungal therapy in the immediate future, thus the appropriate prescribing of echinocandins should be encouraged. The common use of antifungal agents must be evaluated against the cost, the risk of toxicity and the development of resistance Candidemia is associated with up to 47% attributable mortality and authors have demonstrated that mortality is closely linked to both timing of therapy and/or source control. (Refer to section 2.1-2.2).

The poor forecast associated with invasive fungal infections combined with suboptimal diagnostic tools has driven the abuse of antifungal drugs for inpatients. Inappropriate use of antifungals also contributes to the global increase in antifungal resistance and the occurrence of invasive fungal infections due to evolving fungi. According to previous studies, most inappropriate antifungal prescriptions are due to limited awareness of the first line treatment for invasive fungal infection, low switching from IV to oral antifungal agents, no adjustment after microbiology results and excessive length of treatment. (Refer to section 2.2).

Some species of fungi are naturally resistant to certain types of antifungal medications. Other species may be normally susceptible to a particular type of medication, but develop resistance over time as a result of improper antifungal use - for example, dosages that are too low or treatment courses that aren’t long enough. Appropriate use of antifungal agents is one of the most important factors in fighting drug resistance. (Refer to section 2.11).

Antifungal stewardship includes the appropriate use of antifungals by selecting the proper drug, dosage, duration and route of administration. Both antimicrobial resistance and antifungal resistance (a consequence of the use and misuse of antimicrobial medicines) occur when a micro-organism becomes resistant to a drug to which it was previously sensitive. Primary and

secondary resistance to antifungal drugs is known for several pathogenic fungi (e.g. yeasts such as *Candida* spp., and moulds such as Aspergillus spp.). Resistance mechanisms have been extensively described, in particular for *Candida albicans* against fluconazole with potential cross-resistance to other azole antifungals. Current issues related to treatment for invasive *Candida* infections include aspects such as choice of the optimal antifungal drug for candidemia, balance between overuse (empirical therapy) and underuse (waiting until proven disease) of antifungal therapy in severely ill patients, de-escalation strategies, emergence of non-*Candida albicans* infections, the role of non-cultural diagnostic tests and pharmaco-economics. (Refer to section 2.11).

4.4 Empirical study objectives

The specific objectives of the empirical study using patient medical files were to:

- identify prescribing patterns, such as the type of echinocandin, PDD, LD and the type of oral agent if de-escalated (Refer to section 3.2);
- determine whether there is an association between the prevalence of the treatment period, de-escalation of therapy and the availability of blood culture tests of patients treated with echinocandins in a private hospital in Gauteng Province (Refer to section 3.2) and;
- establish the possible difference in the average cost of echinocandin treatment with or without blood cultures when patients are treated in a private hospital in Gauteng Province.

4.4.1 Establish the possible difference in the average cost of echinocandin treatment with or without blood cultures when patients are treated in a private hospital in Gauteng Province.

The cost can be compared to the cost of receiving treatment together with a blood culture every day to the cost of receiving only treatment with no blood cultures as indicated in table 4-1:

Table 4-1: Statistical results of patients with blood cultures and patients without blood cultures

	No blood cultures done	**Blood cultures done**	
n	n = 17	n = 129	
Mean cost (ZAR)	29540.927	31222.525	
Standard deviation (SD)	25014.729	25929.022	
Median	24194.9	24194.9	
95% Confidence interval for mean	16679.540; 42402.314	26705.372; 35739.679	
Independent t-test (p-value)			0.801
Cohen's *d* value			0.065

Of the 146 patients, 129 have a positive blood culture while 17 patients are without blood cultures. The mean cost for patients with positive blood cultures (R31222.525) is higher than the mean cost for patients without blood cultures (R29540.927). The SD for patients with positive blood cultures is also higher than the standard deviation for patients without blood cultures. The higher SD indicates that the values for patients with positive blood cultures have more variability than the values for patients without blood cultures. Both the medians are smaller than the mean, indicating that the distribution is negative skew, meaning that the probability density function has a longer tail on the left. With 95% confidence the mean of the "Yes" group falls between 26705.372 and 35739.679, while for the "No" group the mean falls between 16679.540 and 42402.314. When the p-value (0.801) is considered, it is clear that it is greater than the significant level of p = 0.05 (5%). This indicates that the presence of blood cultures do not differ statistically significantly from one another. The average cost between patients with positive blood cultures and those patients without blood cultures do not differ statistically significantly from one another. Cohen's *d* value is less than 0.8 indicating that there is a small effect with no practical significance. With regard to this study it is evident that there is no significant difference

in cost between patients with positive blood cultures and patients without blood cultures performed. It is also observed that the presence of a positive blood culture does not influence the duration of treatment.

It is however debatable if the literature is very practical in an environment where cost plays such a big role. The physician has to weigh up the cost of both the treatment and a blood culture every day with perhaps having treatment every day but performing a blood culture only alternative day, in order to save costs.

4.5 Limitations of the research

There are several limitations regarding this study.

- The outcomes depended on the prescription charts that were completed by the prescribing doctor.
- The researcher had a lack of clinical data such as when catheters were changed, which was clearly described in the compared guidelines.
- The patients' files were requested from a storage location and there is a chance that the files could have been incomplete.
- Another limitation is that the third echinocandin micafungin became available after the data collection period and therefor this study lacks any data on micafungin use in this setting.

4.6 Strengths

- This was a low-risk study, since the data was collected retrospectively and the patients' identity was not revealed.
- Reliability and validity of data were ensured. (Refer to section 1.6.1). The sample size of 140 patients was a sufficient sample size as discussed in section 1.5.5.
- This study also led to the implementation and validation of the group's Quality Alert.
- This study contributes to the relevance of antifungal stewardship and the practice of using antifungal therapy appropriately.
- A hospital specific algorithm can be extracted from this study and can be used by this hospital's prescribing doctors and ICUs.
- This study has shown the effect of blood cultures on the LOS as well as the implication on total cost of therapy.
- This study provides valuable information for pharmaceutical companies as well as for doctors.

- This study has shown the value of guidelines and the effect of implementing it, and can therefore motivate doctors to continue using guidelines for prescribing medication.

4.7 Recommendations

Future research should focus on the following aspects such as:

- Nursing collaboration on the clinical aspects of candidemia and the role of indwelling devices on the patient's outcome.
- A cost campaign of performing blood cultures should be introduced to doctors and clinical staff.
- More research is needed to establish if there is an effect such as a shorter duration of stay when blood cultures are performed more often.

4.8 Chapter summary

This study is completed by the final chapter by discussing the conclusions drawn from the specific outcomes outlined from the literature review and the empirical investigation. The strengths and limitations of the study were described and recommendations for future research were made.

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ANNEXURE A: DATA COLLECTION FORM

Data collection form **Study ID: _____**

Echinocandins prescribing patterns in adult patients in a private hospital, Centurion, Gauteng Province, South Africa

Patient case number: _____ Ward: _____

Section A

1. Gender:

Male	1
Female	2

2. Ward:

Multi ICU	1
Trauma ICU	2
High care	3
Neuro-vascular high care	4
Cardiac ICU	5
Ward 2C	6
Ward 2B	7
Ward 2A	8
Ward 1E	9
Ward 1D	10
Ward 1B	11
Ground floor	12

Section B

1. With which echinocandin was the patient started with?

Caspofungin	1
Anidulafungin	2

2. Was the appropriate LD give?

Yes	1
No	2

3. What was the daily dose?

Caspofungin	1: 50 mg daily	2: 50 mg twice daily	3: 70 mg daily	4: Other
Anidulafungin	5: 100 mg daily	6: 100 mg twice daily	7: 200 mg daily	8: Other

4. What was the start date for the echinocandin?

D	D	M	M	Y	Y	Y	Y

5. What was the end date for the echinocandin therapy?

D	D	M	M	Y	Y	Y	Y

6. Was the patient switched to an oral antifungal?

Yes	1
No	2

7. If yes, to which oral antifungal was the patient switched to?

Active ingredient		**Dosage**
Fluconazole	1	
Amphotericin B	2	
Itraconazole	3	
Voriconazole	4	
Ketoconazole	5	
Flucytosine	6	
Other	7	

8. Were any blood tests performed while treated with an echinocandin (to identify the presence of an infection)?

Yes	1
No	2

9. Was there a positive fungal culture present in the patient's blood test (after infection was identified by blood test)?

Yes	1
No	2

10. What is the total medicine cost of the patient's antifungal treatment?

Cost of echinocandin treatment:	1
Cost of oral antifungal treatment:	2

Data collected by: Anja Grey **ID:** 9001190131085

Signature: _____

ANNEXURE B: DATA COLLECTION SHEET

Study ID:	Male / Female	Ward:	1. With which echinocandin was the patient started with?	2. Was the appropriate LD given? Yes / No	3. What was the daily dose?	4. What was the start date for echinocandin treatment?	5. What was the end date for the echinocandin treatment?	Total days	6. Was the patient switched to an oral antifungal?	7. If yes, to which oral antifungal was the patient switched to?	8. Were any blood tests perform while treated with an echinocandin?	9. Was there a positive fungal culture present in the patients' blood test?	10. What is the total medicine cost of the patients' antifungal treatment (echinocandin + oral antifungal if relevant)?
								0					
								0					
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ANNEXURE C: PATIENT CONSENT FORM

Terms and Conditions

The Guarantor	Means any person who signs these terms and conditions, independently from the patient, parent(s) or guardian, and who accepts full responsibility for payment of [redacted]'s invoice. The Guarantor remains liable for full outstanding balance/s, unless settled in full by the patient, parent/guardian, main member, medical aid or any other party.
[redacted]	Means [redacted] Hospitals (Pty) Ltd, its holding, subsidiary and associated companies and all of those companies' directors, officers, employees and/or agents, as well as any hospital, clinic or medical facility owned and/or operated by [redacted].
Signatories	Includes the patient, guarantor, parent(s) and guardian where the patient is a minor, together or separately where the person has signed in that capacity.
Third Parties	"Third parties", include but are not limited to medical practitioners, doctor's, radiologists, physiotherapists, pathologists, specialists, medical aid and other service providers who are not employed by [redacted] but are involved in the provision of various services to the patient.
Payment of account	I/we, the undersigned, will be responsible for and agree to make payment of the [redacted] fee ("the fee") for the use of the [redacted] facility and health services rendered, as charged by [redacted] from time to time. Details of the fee structure as applicable from time to time are available in writing on request, and form part of this [redacted] Contract.
Recovery of costs	In the event where you have failed to pay the fee mentioned above, [redacted] have the right to recover any legal costs to recover the amount due. Attorney's fees will be recovered by the attorney directly from you.
Signatories personally responsible	I/we, the undersigned, signatory(ies), will be personally responsible for payment of the fee, whether the invoice has been submitted to my medical scheme or any other party for payment. The person who signed these terms and conditions, as the person responsible for payment of the fee, will remain solely responsible for the full outstanding amount.
Deposit / Guarantee	We, [redacted] may request a deposit or guarantee from you, which must be provided immediately. Acceptable payment methods will be provided to you with the request.
Invoice due and payable	The fee becomes due and payable immediately upon presentation of a final invoice.
Consent to access credit information	I/we, the undersigned, consent to [redacted] obtaining from any credit bureau, or any other institution with whom I/we, the undersigned, may have financial dealings any information concerning my credit profile and payment history.
Patient's consent	I acknowledge that in providing health and/or medical services ("Services") to me, it is necessary for [redacted] and third parties that are involved in the provision of services, to process my personal information. "I provide my express consent to [redacted] to process my personal information as defined in legislation for purposes of providing service and to share such personal information with "third parties" in order to provide various medical and related services to me".
Consent to Magistrates Court	I/we, the undersigned, hereby consent and submit in terms of section 45 of the Magistrates' Courts Act to the jurisdiction Jurisdiction of the appropriate Magistrate's Court in respect of all actions or other proceedings which might be brought against me/us by or on behalf of [redacted] arising out of my/our failure to pay the fee or other breach of the [redacted] Contract, irrespective of the value of the claim against me/us.
South African Jurisdiction and Law	This [redacted] Contract and the use of [redacted] Facility and any health services provided by [redacted] to the patient shall be governed by and construed in accordance with the laws of the Republic of South Africa.
Address for Notices	The addresses provided in the details section above are the chosen addresses for all purposes, including the serving of any court documents such as summonses or notices, the payment of any amount and any communication between the parties in terms of this agreement. A party may change their chosen address by 30 days written notice to the other party.
Verification of Address & Employment	[redacted] reserves the right to verify address and employment details.
Notice	Every notice, consent, invoice or other communication required or permitted in terms of this contract, must be in writing. Notices may be delivered: • by hand to the address referred to in the details section or any other address chosen in writing; • by telefax or e-mail to the addressees telefax number or e-mail address, an acknowledgement of receipt from the recipient must be given to the sender; or • by prepaid registered post to the address referred to in the details section or any other address chosen in writing.
Disclosure	I/we, the undersigned, authorises [redacted], or any attending doctor, or any other attending healthcare professional to disclose the nature of the patient's diagnosis and/or any health services rendered to the patient and all and any records or copies of records in relation thereto to the patient's medical aid.
Medical Practitioners	I/we, the undersigned, understand and accept that the medical practitioners, doctors, radiologists, physiotherapists, specialists and other such practitioners who treat the patient are independent contractors who are not employed by [redacted] and that [redacted] is not responsible for their invoices or treatment.
Disclaimer in respect of property	I/we, the undersigned, understand, accept and agree that [redacted] will not be liable or responsible for any loss of, damage or destruction to, any property, including money and valuables, belonging to the patient, or in possession of the patient, or given to [redacted] for safekeeping, even if [redacted] is/was negligent in any way and no matter how the loss, damage or destruction was caused.
Minor patients	Where the patient is a minor, that is unmarried and below the age of 18 years, both the minor's parents and/or guardians sign these terms and conditions in both their personal and representative capacities and in so doing accept responsibility for payment of the fee in full.
Accounts and invoices	I/we, the undersigned, hereby confirm that [redacted] may use the email addresses as indicated in the patient/guarantor details for communication purposes on accounts and/or invoices. [redacted] may use my personal information for purposes of collecting and recovering any amounts owed by myself to [redacted].
Terms and conditions read, understood and agree	I/we, the undersigned, warrant that I/we, the undersigned, have read, understood and agree to these terms and conditions, and the **Disclaimer in respect of property** set out herein and contracts on such terms, conditions and the **Disclaimer in respect of property.**

SIGNED AT..... ON THIS..... DAY OF..... 2.....

Please tick ✓ applicable box	(Full name(s))	(Signature(s))
PATIENT ☐ PARENT(S) OR GUARDIAN(S) (if minor child) ☐		
MAIN MEMBER / GUARANTOR: (where the signatory(ies) is a person other than the patient or the patient's parent(s) and/or guardian(s)	(Full name)	(Signature)
[redacted] STAFF MEMBER:	(Full name)	(Signature)

ANNEXURE D: ETHICS APPROVAL

26 May 2015

LETTER CONFIRMING KNOWLEDGE OF CLINICAL MEDICATION OR NON-MEDICATION RELATED TRIAL RESEARCH TO BE CONDUCTED IN THIS [redacted] FACILITY

Dear A Esterhuizen

RE: THE PRESCRIBING PRACTICES OF ECHINOCANDINS IN ADULT PATIENTS IN A PRIVATE HOSPITAL

We hereby confirm knowledge of the above named research application to be made to the [redacted] Research Committee and in principle agree to the research application for [redacted] Hospital, subject to the following:

i) That the research may not commence prior to receipt of FINAL APPROVAL from the Academic Board of [redacted] (Research Committee).

ii) A copy of the research report will be provided to [redacted] once it is finally approved by the tertiary institution, or once complete.

iii) [redacted] has the right to implement any Best Practice recommendations from the research.

iv) That the Hospital Management reserves the right to withdraw the approval for research at any time during the process, should the research prove to be detrimental to the subjects / [redacted] or should the researcher not comply with the conditions of approval.

We wish you success in your research.

Yours faithfully

[redacted]

Hospital Manager

26/05/15

Date

ANNEXURE E: INTERNATIONAL GUIDELINES

Comparison of four different guidelines regarding the diagnosis and management of *Candida* diseases as well as the use of echinocandins in *Candida* diseases.

		IDSA guidelines (Andes *et al.*, 2016:15-23).	**ESCMID guidelines (Cornely *et al.*, 2012:21-25).**	**An Italian consensus for invasive candidiasis management (ITALIC) (Bassetti *et al.*, 2014: 263-279).**	**Australian consensus guidelines for yeast infections (Bryant *et al.*, 2014:1315-1332).**	**Quality Alert in study setting (Gokool-Sewram *et al.*, 2014:1-5).**
Loading dose (LD) and maintenance dose	**Caspofungin**	A LD of 70mg IV and a daily dose of 50mg IV.	A 70mg IV LD and a maintenance dose of 50mg IV daily for initial targeted treatment of candidemia and invasive candidiasis in adult patients. Caspofungin's dose should be increased to 70mg IV daily instead of 50mg IV daily in patients with a high body weight.	Not discussed.	70mg IV daily for 24 hours, then 50mg IV daily.	LD of 70mg IV and a daily dose of 50mg IV. A maintenance dose of 70mg IV daily is required for patients of $\geq$ 80kg.

LD and maintenance dose	**Anidulafungin**	LD of 200mg IV and a daily dose of 100mg IV as initial therapy for candidemia in non-neutropenic patients.	A 200mg IV LD and a 100mg IV maintenance dose for initial targeted treatment of candidemia and invasive candidiasis in adult patients.	Not discussed.	200mg IV daily for 24 hours then 100mg IV daily.	LD of 200mg IV and 100mg IV daily.
	Micafungin	100mg daily IV and	Not discussed	Not discussed.	100mg IV daily.	Not discussed.

	IDSA guidelines (Andes *et al.,* 2016:15-23).	**ESCMID guidelines (Cornely *et al.,* 2012:21-25).**	**An Italian consensus for invasive candidiasis management (ITALIC) (Bassetti *et al.,* 2014: 263-279).**	**Australian consensus guidelines for yeast infections (Bryant *et al.,* 2014:1315-1332).**	**Quality Alert in study setting (Gokool-Sewram *et al.,* 2014:1-5).**
De-escalation of treatment	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, and have negative repeat blood cultures following initiation of antifungal therapy (strong recommendation; moderate quality evidence). (Andes *et al.,* 2016:17).	Treatment can probably be simplified by stepping down to oral fluconazole after ten days of IV treatment, if the patient is stable, tolerates the oral route and if species are susceptible (Betts *et al.,* 2002:2021 & Arnold *et al.,* 2007:884).	De-escalation from echinocandins to fluconazole is advisable, if the isolated *Candida* strain is fluconazole-susceptible and the patient is clinically stable.	Following satisfactory clinical and microbiological response, changing from an IV to oral antifungal therapy is appropriate, assuming susceptibility to the oral agent and a functioning gastrointestinal tract.	If a patient is clinically stable, step down therapy is advised in adequate doses bases on results of susceptibility testing. This is usually to fluconazole 800mg IV or oral LD with a 400mg IV or oral maintenance dose. Oral therapy is indicated following ten days of IV treatment.

	IDSA guidelines (Andes *et al.*, 2016:15-23).	**ESCMID guidelines (Cornely *et al.*, 2012:21-25).**	**An Italian consensus for invasive candidiasis management (ITALIC) (Bassetti *et al.*, 2014: 263-279).**	**Australian consensus guidelines for yeast infections (Bryant *et al.*, 2014:1315-1332).**	**Quality Alert in study setting (Gokool-Sewram *et al.*, 2014:1-5).**
Duration of treatment	Recommended duration of therapy for candidemia without metastatic complications is for two weeks after documented clearance of *Candida* spp from the bloodstream and resolution of symptoms attributable to candidemia (strong recommendation; moderate quality of evidence).	The duration of treatment depends on the extent of organ involvement, but ESCMID states that a patient should be treated for fourteen days after the end of candidemia. To determine the end of candidemia, at least one blood culture per day should be taken until cultures come back negative.	Patients should be treated for at least 14 days after the last positive blood culture.	For *Candida* in the deep tissue, treatment with systemic antifungals is recommended for at least 14 days following the last positive sterile site culture.	Continue therapy for fourteen days following the first negative blood culture. Take at least one blood culture per day until candidemia proven negative.

	IDSA guidelines (Andes *et al.,* 2016:15-23).	**ESCMID guidelines (Cornely *et al.,* 2012:21-25).**	**An Italian consensus for invasive candidiasis management (ITALIC) (Bassetti *et al.,* 2014: 263-279).**	**Australian consensus guidelines for yeast infections (Bryant *et al.,* 2014:1315-1332).**	**Quality Alert in study setting (Gokool-Sewram *et al.,* 2014:1-5).**
Blood cultures and blood tests	With regards to the diagnosis of candidiasis Andes and colleagues proved that both positive cultures of a blood sample and nonculture diagnostic tests such as antigen, antibody, or β-D-glucan detection assays, and polymerase chain reaction (PCR) are now being used to reach a diagnosis (Andes *et al.,* 2016:15). Blood cultures are however limited by slow turnaround times (median time to positivity of 2-3 days, ranging from 1 - ≥7 days). Follow-up blood cultures should be performed every day or every other day to establish the time point at which candidemia has been cleared (strong recommendation; low quality of evidence). Testing for echinocandin susceptibility should be considered in patients who had prior treatment with an echinocandin and among those who have infection with *C.glabrata* or *C.parapsilosis* (strong recommendation; low quality of evidence).	ESCMID recommends that *Candida* isolation from the respiratory secretions should never trigger treatment, but should rather be interpreted as one site of colonisation. (1,3)-β-D-glucan detection in serum or plasma prompting antifungal treatment is marginally supported.	The isolation of a *Candida* from a non-sterile body site for example bronchial aspirate, tracheal aspirate, bronchoalveolar lavage fluid or sputum, should not prompt any treatment in the asymptomatic patient, and should be considered as colonisation. As a general rule, at least two blood cultures should be obtained in patient with signs and symptoms of infection. One of the two blood cultures should be obtained from a peripheral vein and one from a central vein and from the central catheter, if present. The β-D-glucan test as a diagnostic test in a patient with signs and symptoms of infection might be effective in the early diagnosis of invasive candidiasis.	The detection in serum of the fungal cell wall component β-(1,3) – D-glucan for the diagnosis of candidiasis is well studied and has been used as a pre-emptive diagnostic marker.	The quality alert states that appropriate cultures such as blood specimen samples (60ml) and fungitell assays should be taken prior to initiation of treatment.

	IDSA guidelines (Andes *et al.*, 2016:15-23).	**ESCMID guidelines (Cornely *et al.*, 2012:21-25).**	**An Italian consensus for invasive candidiasis management (ITALIC) (Bassetti *et al.*, 2014: 263-279).**	**Australian consensus guidelines for yeast infections (Bryant *et al.*, 2014:1315-1332).**	**Quality Alert in study setting (Gokool-Sewram *et al.*, 2014:1-5).**
Empiric therapy	The failure of empiric therapy in patients that have septic shock due to *Candida* species and who don't have adequate source control or antifungal therapy begun within 24 hours can result in a mortality rate that approaches 100%. Prompt initiation of appropriate antifungal therapy has been associated with as much as a 50% reduction in mortality. The initiation of therapy is often delayed because of the waiting period for a blood culture, the relative insensitivity of blood cultures and the lack of clinical signs and symptoms. Risk factors are basically the only reason to initiate empiric therapy and include; *Candida* colonization, severity of illness, exposure to broad spectrum antibiotics, recent major surgery, particularly abdominal surgery, necrotizing pancreatitis, dialysis, parenteral nutrition, corticosteroids and the use of CVCs.	Fluconazole prophylaxis against invasive candidiasis is recommended in patients who recently underwent abdominal surgery and had recurrent gastrointestinal perforations or anastomotic leakages. ESCMID defined empiric therapy as a fever driven approach in the clinical situation of a patient at risk for invasive candidiasis who is persistently febrile with no microbiological evidence of infection, but in fever driven therapy no data exists for which antifungal agent should be used. *Candida* isolated from a single peripheral blood culture or a single central-line blood culture defines candidemia (Bennett *et al.,* 2008:1818). Candidemia with echinocandins is strongly recommended.	Prophylaxis is according to the Italian consensus, the administration of drug to a patient without clinical signs and symptoms of infection but has risk factors for invasive candidiasis as described in the consensus. In conclusion the Italian consensus does not recommend any prophylaxis treatment in non-immunocompromised patients. Empiric therapy means administration of an antifungal drug in the absence of any indication other than fever and compatible symptoms, while presumptive or pre-emptive implies the existence of additional factors increasing the likelihood that a fungal infection is present.	Initial therapy with an echinocandin is favoured in the hemodynamically unstable or critical ill patient, as well as in the neutropenic patient, or where a biofilm infection or azole resistance is suspected. There is a role for initial therapy with fluconazole where the patient is clinically stable and the isolate is likely to be susceptible to fluconazole.	N/A

	The use of antifungal agents should be balanced against the cost, the risk of toxicity and the emergence of echinocandin or azole resistance. The empiric therapy should be considered in critically ill patients with risk factors and no other known cause of fever. According to the Expert Panel in this study fluconazole should only be used as first line therapy in patients that are stable, have no previous history of azole use, and who not belong in a group at high risk for *C.glabrata* infection, including those who are elderly, have underlying malignancy, or are diabetic.				

ANNEXURE F: THE HEALTH RESEARCH ETHICS COMMITTEE CERTIFICATE

NORTH-WEST UNIVERSITY
YUNIBESITI YA BOKONE-BOPHIRIMA
NOORDWES-UNIVERSITEIT
POTCHEFSTROOM CAMPUS

Private Bag X6001, Potchefstroom
South Africa 2520

Tel: 018 299-1111/2222
Web: http://www.nwu.ac.za

Ethics Office
Tel: 018-285 2291

Email: Wayne.Tovers@nwu.ac.za

07 March 2016

Dr M Julyan
MUSA

Dear Dr Julyan

HREC APPROVAL OF YOUR APPLICATION

Ethics number: NWU-00361-15-S1

Kindly use the ethics reference number provided above in all correspondence or documents submitted to the Health Research Ethics Committee (HREC) secretariat.

Project title: The prescribing patterns of echinocandins in adult patients in a private hospital

Project leader/supervisor: Dr M Julyan

Student: A Grey

Application type: Full Single

Risk level descriptor: Medium

You are kindly informed that at the meeting held on 19/11/2015 of the HREC, Faculty of Health Sciences, the aforementioned was approved.

The period of approval for this project is from 07/03/2016 to 06/03/2017.

After ethical review:

Translation of the informed consent document to the languages applicable to the study participants should be submitted to the HREC (if applicable).

The HREC requires immediate reporting of any aspects that warrants a change of ethical approval. Any amendments, extensions or other modifications to the protocol or other associated documentation must be submitted to the HREC prior to implementing these changes. Any adverse/unexpected/unforeseen events or incidents must be reported on either an adverse event report form or incident report form.

A progress report should be submitted within one year of approval of this study and before the year has expired, to ensure timely renewal of the study. A final report must be provided at completion of the study or the HREC must be notified if the study is temporarily suspended or terminated. The progress report template is obtainable from Carolien van Zyl at

Carolien.VanZyl@nwu.ac.za. Annually a number of projects may be randomly selected for an external audit.

Please note that the HREC has the prerogative and authority to ask further questions, seek additional information, require further modification or monitor the conduct of your research or the informed consent process.

Please note that for any research at governmental or private institutions, permission must still be obtained from relevant authorities and provided to the HREC. Ethics approval is required BEFORE approval can be obtained from these authorities.

The HREC complies with the South African National Health Act 61 (2003), the regulations on Research with Human Participants of 2014 of the Department of Health and Principles, the Declaration of Helsinki, 2013, the Belmont Report and the Ethics in Health Research: Principles, Structures and Processes (SANS document).

We wish you the best as you conduct your research. If you have any questions or need further assistance, please contact the Ethics Office at Carolien.VanZyl@nwu.ac.za or 018 299 1206.

Yours sincerely

Dr Wayne Towers

HREC Chairperson

Prof Minrie Greeff

Ethics Office Head

Current details: (12686417) C:\Users\13210572\Documents\HREC\HREC - Applications\2015 Applications\Applications 10 - 19 November 2015\NWU-00361-15-S1 (M Julyan-A Grey)\NWU-00361-15-S1 (M Julyan-A Grey) - AL\NWU-00361-15-S1 (M Julyan-A Grey) - AL.docm
7 March 2016

File reference: 9.1.5.3

ANNEXURE G: THE SOUTH AFRICAN MEDICAL JOURNAL

Author Guidelines

Please view the Author Tutorial for guidance on how to submit on Editorial Manager.

Please take the time to familiarise yourself with the policies and processes below. If you still have any questions, please do not hesitate to ask our editorial staff (tel.: +27 (0)21 532 1281, email: submissions@hmpg.co.za).

SAMJ policies

- Types of articles considered by the SAMJ
- Article Processing Charges
- Authorship
- Conflict of interest
- Research ethics committee approval
- Clinical trials
- Protection of patient's rights to privacy
- Copyright notice
- Privacy statement
- Ethnic classification
- CPD

Manuscript preparation

- Preparing an article for anonymous review
- General article format/layout
- Preparation notes by article type
- Illustrations
- Tables
- References

From submission to acceptance

- Submission and peer-review
- Production process
- Changing contact details or authorship

Publication

- Online versus print
- Errata and retractions
- Indexing

SAMJ Policies

Type of articles considered by the SAMJ

The *SAMJ* will no longer limit the articles accepted to those that have 'general medical content', but is intending to capture the spectrum of medical and health sciences, grouped by relevance to the country's burdens of disease. This content will include research in the social sciences and economics that is relevant to the medical issues around our burden of disease. Please see 'A new vision for the *SAMJ*– and a call for papers'for a full discussion of the new directions for the *SAMJ*.

We accept the following types of articles:

Research
Reviews
Clinical trials
Editorials
In Practice (Previously Forum incl. Case Reports)
Correspondence
Obituaries
Book reviews
Ad hoc supplements e.g. guidelines, conference/congress abstracts, Festschrifts*

The following articles are by invitation only:

Guest editorial
Continuing Medical Education (CME)

*Contact claudian@hmpg.co.za for information on submitting ad hoc/commissioned supplements, including guidelines, conference/congress abstracts, Festschrifts, etc.

Publication Fees

All articles published in the *South African Medical Journa*l are open access and freely available online upon publication. This is made possible by applying a business model to offset the costs of peer review management, copyediting, design and production, by charging a publication fee of R5 000 (ex vat) for each research article published. The charge applies only to **Research** articles submitted after 1 March 2017. The publication fee is standard and does not vary based on length, colour, figures, or other elements.

When submitting a Research article to the *SAMJ*, the submitting author must agree to pay the publication fee should the article be accepted for publication. The publication fee is payable when your manuscript is editorially accepted and before production commences for publication. The submitting author will be notified that payment is due and given details on the available methods of payment. Prompt payment is advised; the article will not enter into production until payment is received.
Queries can be directed to claudian@hmpg.co.za.

Please refer to the section on 'Sponsored Supplements' regarding the publication of supplements, where a charge is applicable. Queries can be directed to dianes@hmpg.co.za or claudian@hmpg.co.za

Authorship

Named authors must consent to publication. Authorship should be based on: (*i*) substantial contribution to conceptualisation, design, analysis and interpretation of data; (*ii*) drafting or critical revision of important scientific content; or (*iii*) approval of the version to be published.

These conditions must all be met (uniform requirements for manuscripts submitted to biomedical journals; refer to www.icmje.org)

If authors' names are added or deleted after submission of an article, or the order of the names is changed, all authors must agree to this in writing.

Please note that co-authors will be requested to verify their contribution upon submission. Non-verification may lead to delays in the processing of submissions.

Author contributions should be listed/described in the manuscript.

Conflicts of interest

Conflicts of interest can derive from any kind of relationship or association that may influence authors' or reviewers' opinions about the subject matter of a paper. The existence of a conflict – whether actual, perceived or potential – does not preclude publication of an article. However, we aim to ensure that, in such cases, readers have all the information they need to enable them to make an informed assessment about a publication's message and conclusions. We require that both authors and reviewers declare all sources of support for their research, any personal or financial relationships (including honoraria, speaking fees, gifts received, etc) with relevant individuals or organisations connected to the topic of the paper, and any association with a product or subject that may constitute a real, perceived or potential conflict of interest. If you are unsure whether a specific relationship constitutes a conflict, please contact the editorial team for advice. If a conflict remains undisclosed and is later brought to the attention of the editorial team, it will be considered a serious issue prompting an investigation with the possibility of retraction.

Research ethics committee approval

Authors must provide evidence of Research Ethics Committee approval of the research where relevant. Ensure the correct, full ethics committee name and reference number is included in the manuscript.

If the study was carried out using data from provincial healthcare facilities, or required active data collection through facility visits or staff interviews, approval should be sought from the relevant provincial authorities. For South African authors, please refer to the guidelines for submission to the National Health Research Database. Research involving human subjects must be conducted according to the principles outlined in the Declaration of Helsinki. Please refer to the National Department of Health's guideline on Ethics in Health research: principles, processes and structuresto ensure that the appropriate requirements for conducting research have been met, and that the HPCSA's General Ethical Guidelines for Health Researchershave been adhered to.

Clinical trials

As per the recommendations published by the International Committee of Medical Journal Editors (ICMJE), clinical trial research is any research that assigns individuals to an intervention, with or without a concurrent comparison/control group to study the cause-and-effect relationship between the intervention and health outcomes. All clinical trials should be registered with the appropriate national clinical trial registry (or any international primary register, if relevant), and the trial registration number should be cited at the end of the abstract. All clinical trial reports must also contain a data sharing statement as per the recommendations of the ICMJE. Statements are to indicate:

- whether individual deidentified participant data will be shared;
- what data in particular will be shared; whether additional, related documents will be available;
- when the data will become available and for how long; by what access criteria data will be shared.

Please see the ICJME announcement for further details and illustrative examples of data sharing statements: ICMJE Data Sharing Statements for Clinical Trials

Since 1st December 2005, all clinical trials conducted in South Africa have been required to be registered in the South African National Clinical Trials Register. The SAMJ therefore requires that clinical trials be registered in the relevant public trials registry at or before the time of first patient enrollment as a condition for publication. The trial registry name and registration number must be included in the manuscript.

Please refer to the general guidelines for all papers at the top of this article for additional requirements with respect to ethics approval, funding, author contributions, etc. The format of original research articles should be followed for reporting of clinical trial results.

Protection of rights to privacy

Patient

Information that would enable identification of individual patients should not be published in written descriptions, photographs, and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) has given informed written consent for publication and distribution. We further recommend that the published article is disseminated not only to the involved researchers but also to the patients/participants from whom the data was drawn. Refer to Protection of Research Participants. The signed consent form should be submitted with the manuscript to enable verification by the editorial team.

Other individuals

Any individual who is identifiable in an image must provide written agreement that the image may be used in that context in the *SAMJ.*

Copyright notice

Copyright remains in the Author's name. The work is licensed under a Creative Commons Attribution - Noncommercial Works License. Authors are required to complete and sign an Author Agreement form that outlines Author and Publisher rights and terms of publication. The **Author Agreement form** should be uploaded along with other submissions files and any submission will be considered incomplete without it.

Material submitted for publication in the *SAMJ* is accepted provided it has not been published or submitted for publication elsewhere. Please inform the editorial team if the main findings of your paper have been presented at a conference and published in abstract form, to avoid copyright infringement. The *SAMJ* does not hold itself responsible for statements made by the authors.

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If an image/figure has been previously published, permission to reproduce or alter it must be obtained by the authors from the original publisher and the figure legend must give full credit to the original source. This credit should be accompanied by a letter indicating that permission to reproduce the image has been granted to the author/s. This letter should be uploaded as a supplementary file during submission.

Privacy statement

The *SAMJ* is committed to protecting the privacy of its website and submission system users. The names, personal particulars and email addresses entered in the website or submission system will not be made available to third parties without the user's permission or due process. By registering to use the website or submission system, users consent to receive communication from the *SAMJ* or its publisher HMPG on matters relating to the journal or associated publications. Queries with regard to privacy may be directed to publishing@hmpg.co.za.

Ethnic/race classification

Use of racial or ethnicity classifications in research is fraught with problems. If you choose to use a research design that involves classification of participants based on race or ethnicity, or discuss issues with reference to such classifications, please ensure that you include a detailed rationale for doing so, ensure that the categories you describe are carefully defined, and that socioeconomic, cultural and lifestyle variables that may underlie perceived racial disparities are appropriately controlled for. Please also clearly specify whether race or ethnicity is classified as reported by the patient (self-identifying) or as perceived by the investigators. Please note that is not appropriate to use self-reported or investigator-assigned racial or ethnic categories for genetic studies.

Continuing Professional Development (CPD)

SAMJ is an HPCSA-accredited service provider of CPD materials. Principal authors can earn up to 15 CPD continuing education units (CEUs) for publishing an article; co-authors are eligible to earn up to 5 CEUs; and reviewers of articles can earn 3 CEUs. Each month, *SAMJ* also publishes a CPD-accredited questionnaire relating to the academic content of the journal. Successful completion of the questionnaire with a pass rate of 70% will earn the reader 3 CEUs. Administration of our CPD programme is managed by Medical Practice Consulting. To complete questionnaires and obtain certificates, please visit MRP Consulting

Manuscript preparation

Preparing an article for anonymous review

To ensure a fair and unbiased review process, all submissions are to include an anonymised version of the manuscript. The exceptions to this are Correspondence, Book reviews and Obituary submissions.

Submitting a manuscript that needs additional blinding can slow down your review process, so please be sure to follow these simple guidelines as much as possible:

- An anonymous version should not contain any author, affiliation or particular institutional details that will enable identification.
- Please remove title page, acknowledgements, contact details, funding grants to a named person, and any running headers of author names.
- Mask self-citations by referring to your own work in third person.

General article format/layout

Accepted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction, which will delay publication.

General:

- Manuscripts must be written in UK English.
- The manuscript must be in Microsoft Word format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes).
- Please make your article concise, even if it is below the word limit.
- Qualifications, ***full*** affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.
- Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.

- Include sections on Acknowledgements, Conflict of Interest, Author Contributions and Funding sources. If none is applicable, please state ‘none’.
- Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dL).
- Litres is denoted with an uppercase L e.g. 'mL' for millilitres).
- Units should be preceded by a space (except for % and ºC), e.g. '40 kg' and '20 cm' but '50%' and '19ºC'.
- Please be sure to insert proper symbols e.g. µ not u for micro, a not a for alpha, b not B for beta, etc.
- Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160.
- Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'
- Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.
- If you wish material to be in a box, simply indicate this in the text. You may use the table format –this is the *only* exception. Please DO NOT use fill, format lines and so on.

SAMJ is a generalist medical journal; therefore for articles covering genetics, it is the responsibility of authors to apply the following:

- Please ensure that all genes are in italics, and proteins/enzymes/hormones are not.

- Ensure that all genes are presented in the correct case e.g. TP53 not Tp53.

**NB: Copyeditors cannot be expected to pick up and correct errors wrt the above, although they will raise queries where concerned.

- Define all genes, proteins and related shorthand terms at first mention, e.g. ‘188del11’ can be glossed as ‘an 11 bp deletion at nucleotide 188.’

- Use the latest approved gene or protein symbol as appropriate:

- Human Gene Mapping Workshop (HGMW): genetic notations and symbols
- HUGO Gene Nomenclature Committee: approved gene symbols and nomenclature
- OMIM: Online Mendelian Inheritance in Man (MIM) nomenclature and instructions
- Bennet et al. Standardized human pedigree nomenclature: Update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Counsel 2008;17:424-433: standard human pedigree nomenclature.

Preparation notes by article type

- Research
- Editorials
- CME
- In Practice and Case reports
- Reviews
- Clinical trials
- Correspondence
- Obituaries

- Book reviews
- Guidelines

Research

Guideline word limit: 4 000 words

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text.

Do not replicate data in tables and in text .

Structured abstract

- This should be 250-400 words, with the following recommended headings:
  - **Background:** why the study is being done and how it relates to other published work.
  - **Objectives:** what the study intends to find out
  - **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.
  - **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
  - **Conclusion:** must be supported by the data, include recommendations for further study/actions.
- Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors.
- Do not include any references in the abstracts.

Here is an example of a good abstract.

Main article

All articles are to include the following main sections: Introduction/Background, Methods, Results, Discussion, Conclusions.

The following are additional heading or section options that may appear within these:

- Objectives (within Introduction/Background): a clear statement of the main aim of the study and the major hypothesis tested or research question posed

- Design (within Methods): including factors such as prospective, randomisation, blinding, placebo control, case control, crossover, criterion standards for diagnostic tests, etc.
- Setting (within Methods): level of care, e.g. primary, secondary, number of participating centres.
- Participants (instead of patients or subjects; within Methods): numbers entering and completing the study, sex, age and any other biological, behavioural, social or cultural factors (e.g. smoking status, socioeconomic group, educational attainment, co-existing disease indicators, etc)that may have an impact on the study results. Clearly define how participants were enrolled, and describe selection and exclusion criteria.
- Interventions (within Methods): what, how, when and for how long. Typically for randomised controlled trials, crossover trials, and before and after studies.
- Main outcome measures (within Methods): those as planned in the protocol, and those ultimately measured. Explain differences, if any.

Results

- Start with description of the population and sample. Include key characteristics of comparison groups.
- Main results with (for quantitative studies) 95% confidence intervals and, where appropriate, the exact level of statistical significance and the number need to treat/harm. Whenever possible, state absolute rather than relative risks.
- Do not replicate data in tables and in text.
- If presenting mean and standard deviations, specify this clearly. Our house style is to present this as follows:
- E.g.: The mean (SD) birth weight was 2 500 (1 210) g. Do not use the ± symbol for mean (SD).
- Leave interpretation to the Discussion section. The Results section should just report the findings as per the Methods section.

Discussion

Please ensure that the discussion is concise and follows this overall structure – sub-headings are not needed:

- Statement of principal findings
- Strengths and weaknesses of the study
- Contribution to the body of knowledge
- Strengths and weaknesses in relation to other studies
- The meaning of the study – e.g. what this study means to clinicians and policymakers
- Unanswered questions and recommendations for future research

Conclusions

This may be the only section readers look at, therefore write it carefully. Include primary conclusions and their implications, suggesting areas for further research if appropriate. Do not go beyond the data in the article.

Editorials

Guideline word limit: 1 000 words

These opinion or comment articles are usually commissioned but we are happy to consider and peer review unsolicited editorials. Editorials should be accessible and interesting to readers without specialist knowledge of the subject under discussion and should have an element of topicality (why is a comment on this issue relevant now?) There should be a clear message to the piece, supported by evidence.

Please make clear the type of evidence that supports each key statement, e.g.:

- expert opinion
- personal clinical experience
- observational studies
- trials
- systematic reviews.

CME (by invite only)

CME is intended to provide readers with practical, up-to-date information on medical and related matters. It is aimed at those who are not specialists in the field.

From January 2016, all CME articles will be printed in full in the *SAMJ*. Please try to adhere strictly to the guidelines on word count as we have a page limit for the print issue of the *SAMJ*. We reserve the right to place some tables and reference lists online if this is necessary for space.

In practice, this means that each CME topic usually covers two issues of the print issue of the *SAMJ*.

The guest editor, in consultation with the editor, is responsible for convening a team of authors, deciding on the subjects to be covered and for reviewing the manuscripts submitted. The suggestion is for 4 - 5 articles, although there is some room for flexibility contingent on discussions with the editor.

For queries about these guidelines please feel free to contact the CME editor, Dr Bridget Farham, by email (ugqirha@iafrica.com) or telephone (+27 (0)21 789 2331).

Review process

The guest editor reviews the articles and returns them to the CME editor for review and final approval.

Guest editorials

Guideline word limit: 1 000 words

- Include the guest editor's personal details (qualifications, positions, affiliation, e-mail address, and a short personal profile (50words)).
- If possible, include a photograph of the author(s) at high enough resolution for print. It is preferable to provide two guest editorials, one for each issue, so that the content of the articles in each issue is covered.

Articles

Guideline word limit: 2 000 - 3 000 words

- Each article requires an abstract of ±200 words.
- The editor reserves the right to shorten articles but will send a substantially shortened article back for author approval.

Personal details

Please supply: Your qualifications, position and affiliations and MP number (used for CPD points); Address, telephone number and fax number, and your e-mail address; and a short personal profile (50words)and a few words about your current fields of interest.

In Practice

Guideline word limit: 2 000 - 3 000words

This section includes articles that would previously have been accepted into the Forum section, and case reports.

In practice articles are those that draw attention to specific issues of clinical, economic or political interest regarding medicine and healthcare in southern Africa. They are assigned to a topic:

Case report

Clinical practice

Clinical alert

Issues in medicine

Issues in public health

Healthcare delivery

Consensus/Position statement

Medicine and the environment

Medicine and the law

Cochrane corner

An In Practice article should follow the following format – sub-headings are not necessary, but may be used for clarity:

- Author affiliations and qualifications: to be the same as for Research. Provide all authors' names and initials, qualifications and full affiliations, and corresponding author.
- Short abstract: does not need to be structured, but should capture the essential features of the article
- Introduction: the reason for the article and the issue being addressed
- Recent research, discussion, local policy around the issue – include your own research where appropriate
- All statements should be referenced and, if opinion only, this should be stated
- Discussion: how this article adds to the discussion around a particular topic
- If a clinical practice or policy point is at issue, this needs to be emphasised, using a box with highlights if appropriate.

Essentially In practice is an opportunity for a more discursive approach to topics of clinical, economic or political importance in southern African health systems. It is not an opportunity to put forward unsubstantiated opinions!

Case reports

The *SAMJ* has recently started to accept case reports. The cases must come from Africa, preferably southern Africa unless the condition is common to all African countries, and must be either a completely new description of a clinical condition or result (use Google!) or a case that highlights important practice or management issues.

Please use the following format for case reports:

- Title of case: do not include the words 'a case report' in the title
- Summary/abstract: up to 150 words summarising the case presentation and outcome
- Background: why is this case important and why did you write it up?
- Case presentation: presenting features, medical, social, family history as appropriate
- Case management: should be according to best practice, and if not, please explain why
- Investigations, if relevant: save space by simply saying 'normal' if, for example, renal function was completely normal, rather than listing normal results, highlight the abnormal – or indeed the normal if this is clinically significant
- Differential diagnosis, if relevant
- Treatment, if relevant
- Outcome and follow-up
- Discussion – a VERY BRIEF review of similar published cases
- Teaching points: 3 - 5 bullet points
- References: as per the *SAMJ* house style
- Tables and figures: keep to a minimum. Use clinical images where relevant – we need hi-res versions for print, and identifiable persons must have a consent form
- Patient consent: please include a statement about patient consent to a written case report. This should be uploaded as a supplementary file.

Clinical trials

Guideline word limit: 4000 words

As per the recommendations published by the International Committee of Medical Journal Editors (ICMJE), clinical trial research is any research that assigns individuals to an intervention, with or without a concurrent comparison/control group to study the cause-and-effect relationship between the intervention and health outcomes. All clinical trials should be registered with the appropriate national clinical trial registry (or any international primary register, if relevant), and the trial registration number should be cited at the end of the abstract. Since 1st December 2005, all clinical trials conducted in South Africa have been required to be registered in the South African National Clinical Trials Register. The *SAMJ* therefore requires that clinical trials be registered in the relevant public trials registry at or before the time of first patient enrollment as a condition for publication. The trial registry name and registration number must be included in the manuscript.

Please refer to the general guidelines for all papers at the top of this article for additional requirements with respect to ethics approval, funding, author contributions, etc. The format of original research articles should be followed for reporting of clinical trial results.

Review articles

Guideline word limit: 4 000 words

These are welcome, but should be either commissioned or discussed with the Editor before submission. A review article should provide a clear, up-to-date account of the topic and be aimed at non-specialist hospital doctors and general practitioners.

Please ensure that your article includes:

- Abstract: unstructured, of about 100-150 words, explaining the review and why it is important
- Methods: Outline the sources and selection methods, including search strategy and keywords used for identifying references from online bibliographic databases. Discuss the quality of evidence.
- When writing: clarify the evidence you used for key statements and the strength of the evidence. Do not present statements or opinions without such evidence, or if you have to, say that there is little or no evidence and that this is opinion. Avoid specialist jargon and abbreviations, and provide advice specific to southern Africa.
- Personal details: Please supply your qualifications, position and affiliations and MP number (used for CPD points); address, telephone number and fax number, and your e-mail address; and a short personal profile (50 words) and a few words about your current fields of interest.

Correspondence (Letters to the Editor)

Guideline word limit: 500 words

Letters to the editor should relate either to a paper or article published by the SAMJ or to a topical issue of particular relevance to the journal's readership

- May include only one illustration or table
- Must include a correspondence address.

Book reviews

Guideline word limit: 400 words

Should be about 400 words and must be accompanied by the publication details of the book. Provide a hi-res image of the cover if possible (with permission from the copyright holder).

Obituaries

Guideline word limit: 400 words

Should be offered within the first year of the practitioner's death, and may be accompanied by a photograph.

Guidelines

Guidelines should always be discussed with the Editor prior to submission.

Because of the intensive review process required to ensure Guidelines are independent, evidence-based and free from commercial bias, they are usually published as a supplement to the *SAMJ*, the costs of which must be covered by sponsorship, advertising or payment by the guideline authors/association. We will provide a quote based on the expected length of the guideline and whether it is to appear online only, or in print, which must be accepted by the body putting the guidelines together before submitting the work to the SAMJ.

The Editor reserves the right to determine the scheduling of supplements. Understandably, a delay in publication must be anticipated dependent upon editorial workflow.

All guidelines should include a clear, transparent statement about all sources of funding and an explicit, clear statement of conflicts of interest of any of the participants in the guidelines about industry funding for lectures, research, conference participation etc.

All guidelines should be structured according to Agree II.

Please access this website before putting the guidelines together, download the Agree 11 instrument and use this to put the guidelines together.

All submitted guidelines will be sent to the local Agree II appraisal committee for review and must be endorsed by an appropriate body prior to consideration and all conflicts of interest expressed.

A structured abstract not exceeding 400 words (recommended sub-headings:*Background, Recommendations, Conclusion*) is required. Sections and sub-sections must be numbered consecutively (e.g. 1. Introduction; 1.1 Definitions; 2.etc.) and summarised in a Table of Contents.

Illustrations/photos/scans

- If illustrations submitted have been published elsewhere, the author(s) should provide consent to republication obtained from the copyright holder.
- Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'.
- Each figure must have a caption/legend: Fig. 1. Description (any abbreviations in full).
- All images must be of high enough resolution/quality for print.
- All illustrations (graphs, diagrams, charts, etc.) must be in PDF or jpeg form.
- Ensure all graph axes are labelled appropriately, with a heading/description and units (as necessary) indicated. Do not include decimal places if not necessary e.g. 0; 1.0; 2.0; 3.0; 4.0 etc.
- Scans/photos showing a specific feature e.g. *Intermediate magnification micrograph of a low malignant potential (LMP) mucinous ovarian tumour. (H&E stain).* –include an arrow to show the tumour.
- Each image must be attached individually as a 'supplementary file' upon submission (not solely embedded in the accompanying manuscript) and named Fig. 1, Fig. 2, etc.

Tables

- Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged.
- Large tables will generally not be accepted for publication in their entirety. Please consider shortening and using the text to highlight specific important sections, or offer a large table as an addendum to the publication, but available in full on request from the author
- Embed/include each table in the manuscript Word file - do not provide separately as supplementary files.
- Number each table in Arabic numerals (Table 1, Table 2, etc.) and refer to consecutively in the text.
- Tables must be cell-based (i.e. not constructed with text boxes or tabs) and editable.
- Ensure each table has a concise title and column headings, and include units where necessary.
- Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

Do not: Use [Enter] within a row to make ‘new rows’:

Rather:

Each row of data must have its own proper row:

Do not: use separate columns for *n* and %:

Rather:

Combine into one column, *n* (%):

Do not: have overlapping categories, e.g.:

Rather:

Use <> symbols or numbers that don't overlap:

References

NB: *Only complete, correctly formatted reference lists in Vancouver style will be accepted. Reference lists must be generated manually and not with the use of reference manager software. Endnotes must* ***not*** *be used.*

- Authors must verify references from original sources.
- Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,[2] and others.[3,4-6]
- All references should be listed at the end of the article in numerical order of appearance in the Vancouver style (not alphabetical order).
- Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus.
- Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al.
- Volume and issue numbers should be given.
- First and last page, in full, should be given e.g.: 1215-1217 **not** 1215-17.
- Wherever possible, references must be accompanied by a digital object identifier (DOI) link). Authors are encouraged to use the DOI lookup service offered by CrossRef:
  - On the Crossref homepage, paste the article title into the 'Metadata search' box.
  - Look for the correct, matching article in the list of results.
  - Click Actions > Cite
  - Alongside 'url =' copy the URL between { }.
  - Provide as follows, e.g.: https://doi.org/10.7196/07294.937.98x

Some examples:

- *Journal references:* Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355. http://dx.doi.org/10.1000/hgjr.182
- *Book references:* Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101.
- *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.
- *Internet references:* World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: WHO, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).

- Legal references

  • Government Gazettes:

  National Department of Health, South Africa. National Policy for Health Act, 1990 (Act No. 116 of 1990). Free primary health care services. Government Gazette No. 17507:1514. 1996.

  In this example, 17507 is the Gazette Number. This is followed by :1514 - this is the notice number in this Gazette.

  • Provincial Gazettes:

  Gauteng Province, South Africa; Department of Agriculture, Conservation, Environment and Land Affairs. Publication of the Gauteng health care waste management draft regulations. Gauteng Provincial Gazette No. 373:3003, 2003.

  • Acts:

  South Africa. National Health Act No. 61 of 2003.

  • Regulations to an Act:

  South Africa. National Health Act of 2003. Regulations: Rendering of clinical forensic medicine services. Government Gazette No. 35099, 2012. (Published under Government Notice R176).

  • Bills:

  South Africa. Traditional Health Practitioners Bill, No. B66B-2003, 2006.

  • Green/white papers:

  South Africa. Department of Health Green Paper: National Health Insurance in South Africa. 2011.

  • Case law:

  Rex v Jopp and Another 1949 (4) SA 11 (N)

  Rex v Jopp and Another: Name of the parties concerned

  1949: Date of decision (or when the case was heard)

  (4): Volume number

  SA: SA Law Reports

  11: Page or section number

  (N): In this case Natal - where the case was heard. Similarly, (C) would indicate Cape, (G) Gauteng, and so on.

  NOTE: no. after the v

- *Other references (e.g. reports) should follow the same format:* Author(s). Title. Publisher place: Publisher name, year; pages.
- Cited manuscripts that have been accepted but not yet published can be included as references followed by '(in press)'.
- Unpublished observations and personal communications in the text must **not** appear in the reference list. The full name of the source person must be provided for personal communications e.g. '(Prof. Michael Jones, personal communication)'.

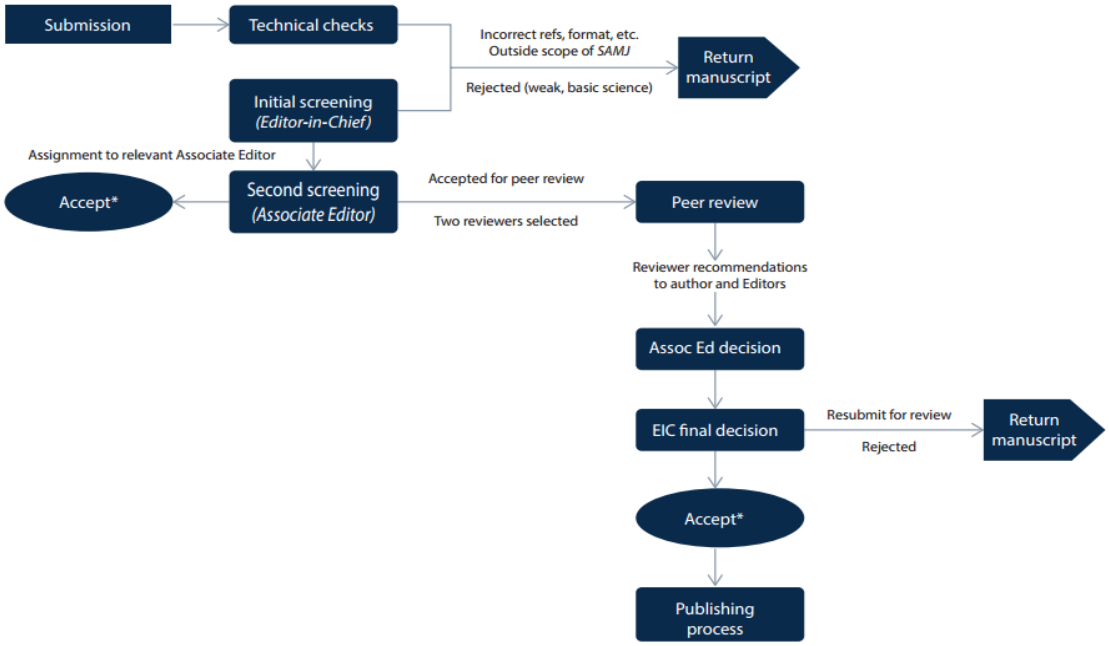
From submission to acceptance

Submission and peer-review

To submit an article:

- Please ensure that you have prepared your manuscript in line with the SAMJ requirements.
- All submissions should be submitted via Editorial Manager
- The following are required for your submission to be complete:
  - Anonymous manuscript (unless otherwise stated)
  - Author Agreement form
  - Manuscript
  - Any supplementary files: figures, datasets, patient consent form, permissions for published images, etc.
- Once the submission has been successfully processed on Editorial Manager, it will undergo a technical check by the Editorial Office before it will be assigned to an editor who will handle the review process. If the author guidelines have not been appropriately followed, the manuscript may be sent back to the author for correcting.

Peer-review process



*Manuscripts accepted at this point are limited to Editorials, Correspondence, Obituaries, Book reviews, Abstracts, CME
**Some minor revisions may be requested

Production process

The following process will follow:

1. An accepted manuscript is passed to a Managing Editor to assign to a copyeditor (CE).
2. The CE copyedits in Word, working on house style, format, spelling/grammar/punctuation, sense and consistency, and preparation for typesetting.

3. If the CE has an author queries, he/she will contact the corresponding author and send them the copyedited Word doc, asking them to solve the queries by means of track changes or comment boxes.
4. The authors are typically asked to respond within 1-3 days.Any comments/changes must be clearly indicated e.g. by means of track changes. Do not work in the original manuscript - work in the copyedited file sent to you and make your changes clear.
5. The CE will finalise the article and then it will be typeset.
6. Once typeset, the CE will send a PDF of the file to the authors to complete their final check, while simultaneously sending to the 2nd-eye proofreader.
7. The authors are typically asked to complete their final check and sign-off within 1-2 days. No major additional changes can be accommodated at this point.
8. The CE implements the authors' and proofreader's mark-ups, finalises the file, and prepares it for the upcoming issue.

Changing contact details or authorship

Please notify the Editorial Department of any contact detail changes, including email, to facilitate communication.

Publication

Online v. print

The *SAMJ* is an online journal. The online version of the journal is the one that has the widest circulation, is indexed by bibliographic databases including PubMed and SciELO, and is accessible in academic libraries. A printed edition , containing material selected by the Editor is also published each month and distributed to the membership of the South African Medical Association.

Online

- The full text of all accepted articles is published in full online, open access, within 4 - 6 weeks of acceptance.
- Citation information of each article is based on its online publication.
- You may want to make use of the advantages of online publication e.g. specify web links to other sources, images, data or even a short video.

Print

- Not all articles will be selected for print.
- An article may be selected for print in a different month from that in which it was published online.
- Research articles will appear *in abstract form only*, if selected for a print edition.

Errata and retractions

Errata

Should you become aware of an error or inaccuracy in yours or someone else's contribution after it has been published, please inform us as soon as possible via an email to publishing@hmpg.co.za,including the following details:

- Journal, volume and issue in which published

- Article title and authors
- Description of error and details of where it appears in the published article
- Full detail of proposed correction and rationale

We will investigate the issue and provide feedback. If appropriate, we will correct the web version immediately, and will publish an erratum in the next issue. The correction will be indexed, as PubMed has a function for linking errata back to the original article. All investigations will be conducted in accordance with guidelines provided by the Committee on Publication Ethics (COPE).

Retractions

Retraction of an article is the prerogative of either the original authors or the editorial team of HMPG. Should you wish to withdraw your article before publication, we need a signed statement from all the authors.

Should you wish to retract your published article, all authors have to agree in writing before publication of the retraction.

Send an email to publishing@hmpg.co.za, including the following details:

- Journal, volume and issue to which article was submitted/in which article was published
- Article title and authors
- Description of reason for withdrawal/retraction.

We will make a decision on a case-by-case basis upon review by the editorial committee in line with international best practices. Comprehensive feedback will be communicated with the authors with regard to the process. In case where there is any suspected fraud or professional misconduct, we will follow due process as recommended by the Committee on Publication Ethics (COPE), and in liaison with any relevant institutions.

When a retraction is published, it will be linked to the original article.

Indexing

The *SAMJ* has an impact factor of 1.5.

Published articles are covered by the following major indexing services. As such articles published in the *SAMJ* are immediately available to all users of these databases, guaranteed a global and African audience:

- Index Medicus (Medline/PubMed)
- ExcerptaMedica (EMBASE)
- Biological Abstracts (BIOSIS)
- Science Citation Index (SciSearch)
- Current Contents/Clinical Medicine
- Scopus
- AIM
- AJOL
- Crossref
- Sabinet
- Scielo

Sponsored supplements

Contact claudian@hmpg.co.za for information on submitting ad hoc/commissioned supplements, including guidelines, conference/congress abstracts, Festschrifts, etc.

Submission Preparation Checklist

As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines.

1. Named authors consent to publication and meet the requirements of authorship as set out by the journal.
2. The submission has not been previously published, nor is it before another journal for consideration.
3. The text complies with the stylistic and bibliographic requirements in **Author Guidelines**.
4. The manuscript is in Microsoft Word document format. The text is single-spaced, in 12-point Times New Roman font, and contains no unnecessary formatting.
5. Illustrations/figures are high resolution/quality (not compressed) and in an acceptable format (PDF or jpeg). These must be submitted individually as 'supplementary files' (not solely embedded in the manuscript).
6. For illustrations/figures or tables that have been published elsewhere, the author has obtained written consent to republication from the copyright holder.
7. Where possible, references are accompanied by a digital object identifier (DOI).
8. An abstract has been included where applicable.
9. The research was approved by a Research Ethics Committee (if applicable)
10. Any conflict of interest (or competing interests) is indicated by the author(s).

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Material submitted for publication in the *SAMJ* is accepted provided it has not been published or submitted for publication elsewhere. Please inform the editorial team if the main findings of your paper have been presented at a conference and published in abstract form, to avoid copyright infringement.

Privacy Statement

The *SAMJ* is committed to protecting the privacy of the users of this journal website. The names, personal particulars and email addresses entered in this website will be used only for the stated purposes of this journal and will not be made available to third parties without the user's permission or due process. Users consent to receive communication from the *SAMJ* for the stated purposes of the journal. Queries with regard to privacy may be directed to publishing@hmpg.co.za.

ANNEXURE H: SUBMISSION OF MANUSCRIPT

ANNEXURE I: PROOF OF LANGUAGE EDITING

DECLARATION

I, C Vorster (ID: 710924 0034 084), Language editor and Translator and member of the South African Translators' Institute (SATI member number 1003172), herewith declare that I did the language editing of a mini-dissertation written by Ms A Grey from the North-West University (student number 21698295).

Title of the mini-dissertation: The prescribing practices of echinocandins in adult patients in a private hospital

C Vorster — 16 November 2017

C Vorster — Date