TOWARDS COST-EFFECTIVE UTILISATION OF HIGH-COST ANTIFUNGAL AGENTS IN AUSTRALIAN HOSPITALS

A THESIS

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To my parents, Majed and Rima

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LIST OF ABBREVIATIONS

AIDS	Acquired immune deficiency syndrome
ALL	Acute lymphoid leukaemia
AML	Acute myeloid leukaemia
AR-DRG	Australian-Refined Diagnosis-Related Groups
C&S	Culture and sensitivity
CT	Computer tomography
DNA	Deoxyribonucleic acid
ELISA	Enzyme-linked immunosorbent assay
FAB	French/American/British
FDA	Food and Drug Administration
G-CSF	Granulocyte-colony stimulation factors
HDPE	High-density polyethylene
HIV	Human immunodeficiency virus
HPLC	High-performance liquid chromatography
HSC	Hematopoietic stem-cell
ICU	Intensive care unit
IFI	Invasive fungal infection
IV/iv/i.v.	Intravenous
LAmB/LAMB	Liposomal amphotericin B
MIC	Minimum inhibitory concentration
MIC_{50}	Minimum concentration at which 50% of isolates are inhibited
MIC_{90}	Minimum concentration at which 90% of isolates are inhibited
PCR	Polymerase chain reaction
PO/po/p.o.	Oral
RCT	Randomised clinical trials
RMH	Royal Melbourne Hospital
RVEEH	Royal Victorian Eye and Ear Hospital
SD/S.D.	Standard deviation
ULN	Upper limit of normal

ABSTRACT

The expenditure on antifungal therapy has risen sharply throughout hospitals in Australia and many other countries over the last decade. This increase is due largely to the recent introduction of new and more expensive antifungal agents, and is consuming a growing portion of limited financial resources. The focus of this thesis was to assess various high-cost antifungals for their ability to produce the highest level of effectiveness at the lowest possible cost in the Australian hospital setting. Antifungal agents were addressed in the context of three treatment strategies: empirical, prophylactic and targeted.

From the empirical standpoint, pharmacoeconomic comparisons among voriconazole, liposomal amphotericin B (LAmB) and caspofungin in febrile neutropenia were performed. Decision analytic models were constructed based on underlying probabilities and patterns derived directly from trial data and expert panels. Cost inputs were obtained from the latest Australian sources. Sensitivity and Monte Carlo uncertainty analyses were undertaken. Caspofungin was the most cost beneficial, with cost savings of AU$798 and AU$7,245 per patient over voriconazole and LAmB, respectively. LAmB had cost savings over voriconazole in the order of AU$1,422 per patient.

Within the context of prophylaxis, an evaluation of the economics of posaconazole versus voriconazole as prophylaxis against invasive fungal infections in patients with acute myeloid leukaemia (AML) was undertaken. A decision analytic model was developed using data extracted from a six-year review of AML patients at an Australian tertiary hospital. Cost inputs were obtained from the latest Australian sources. Sensitivity and uncertainty analyses were undertaken. A total of 94 patients were evaluated. Posaconazole was associated with a net cost saving of AU$17,458 per patient over voriconazole. The posaconazole group was associated with less mortality and lower probability of discontinuation because of possible infections or intolerance, but with more proven infections.

The targeted therapy investigated was the use of extemporaneous voriconazole eye drops for the treatment of fungal keratitis. A number of approaches were evaluated as means to optimise the utilisation of the eye drops. These were concerned with the long-term stability of the eye drops, the clinical success of the eye drops as monotherapy, and the usefulness of higher concentrations of the eye drops. One-percent and 2% voriconazole eye drops were shown to be stable for at least three months at 2-8 ºC. The 1% voriconazole eye drops demonstrated potential effectiveness as monotherapy in fungal keratitis, either as first-line or salvage therapy. In 13 human subjects, 2% voriconazole eye drops resulted in an ocular trough voriconazole concentration (1.67 ± 0.97 µg/mL) similar to that reported with 1%

voriconazole eye drops. It appears that the corneal penetration of topical voriconazole is concentration independent.

In summary, the results from this thesis provide suggestions on how practices can mitigate the cost associated with high-cost antifungals in particular indications in Australian hospitals. The work suggests that greater cost-benefits can be achieved by improving on the current utilisation of caspofungin in the empirical therapy, and on the use of voriconazole eye drops, and by the wider application of posaconazole in prophylaxis.

LIST OF PUBLICATIONS

Work undertaken in preparation for this thesis has resulted in the following publications:

1. **Al-Badriyeh D**, Liew D, Stewart K *et al*. Cost-effectiveness evaluation of voriconazole versus liposomal amphotericin B as empirical therapy for febrile neutropenia in Australia. *J Antimicrob Chemother* 2009; **63**: 197-208.
2. **Al-Badriyeh D**, Liew D, Stewart K *et al*. Economic impact of caspofungin as compared with liposomal amphotericin B for empirical therapy in febrile neutropenia in Australia. *J Antimicrob Chemother* 2009; **63**: 1276-85.
3. **Al-Badriyeh D**, Stewart K, Kong D *et al*. Stability of extemporaneously prepared voriconazole ophthalmic solution. *Am J Health Syst Pharm* 2009; **66**: 1478-83.
4. **Al-Badriyeh D**, Leung L, Davies GE *et al*. Successful salvage treatment of *Scedosporium apiospermum* keratitis with topical voriconazole after failure of natamycin. *Ann Pharmacother* 2009; **43**:1139-42.
5. **Al-Badriyeh D**, Leung L, Roydhouse T *et al*. Prospective open-label study of the administration of two-percent voriconazole eye drops. *Antimicrob Agents Chemother* 2009; **53**: 3153-5.
6. **Al-Badriyeh D**, Leung L, Davies GE *et al*. Successful use of topical voriconazole 1% alone as first-line antifungal therapy against *Candida albicans* keratitis. *Ann Pharmacother* 2009; **43**: 2103-2107.
7. **Al-Badriyeh D**, Slavin M, Thursky K *et al*. Pharmacoeconomic evaluation of voriconazole versus posaconazole for antifungal prophylaxis in acute myeloid leukaemia. *J Antimicrob Chemother* 2010; **65**: 1052-1061.
8. **Al-Badriyeh D**, Neoh CF, Stewart K *et al*. Voriconazole eye drops in the treatment of ophthalmic mycoses. *Journal of Clinical Ophthalmology* 2010; **4**: 391-405. (Invited review).
9. **Al-Badriyeh D**, Heng SC, Neoh CF *et al*. Pharmacoeconomics of voriconazole in the management of invasive fungal infections. *Experts Reviews - Pharmacoeconomics and Outcomes Research* 2010, in review. (Invited review).
10. **Al-Badriyeh D**, Liew D, Stewart K *et al*. Pharmacoeconomic analysis of voriconazole versus caspofungin in the empirical antifungal therapy of febrile neutropenia in Australia. *Value in Health* 2010, in review.
11. **Al-Badriyeh D**, Jhanji V, Leung L *et al*. Penetration of 1% topical voriconazole into the human aqueous humor – a clinical study. *Antimicrob Agents Chemother* 2010, in preparation.

LIST OF CONFERENCES

The work in this thesis has resulted in the following presentations at conferences:

1. **Al-Badriyeh D**, Leung L, Roydhouse T, Daniell M, Davies GE, Stewart K and Kong DCM. 2% Voriconazole eye drops for the management of ophthalmic fungal keratitis. 13th International Congress on Infectious Diseases (May, 2008). Kuala Lumber, Malaysia.
2. **Al-Badriyeh D**, Liew D, Stewart K and Kong D. Pharmacoeconomics of high-cost empirical antifungal therapy. The 48th ICAAC/46th IDSA Annual Meeting (October, 2008). Washington DC, USA.
3. **Al-Badriyeh D**, Leung L, Roydhouse T, Fullinfaw R, Daniell M, Davies GE, Stewart K and Kong DCM. Topical administration of 2% voriconazole for the management of fungal keratitis. Australasian Pharmaceutical Science Association Annual Meeting (December, 2008). Canberra, Australia.
4. **Al-Badriyeh D**, Liew D, Stewart K and Kong D. The cost benefit of voriconazole versus caspofungin as empirical therapy for febrile neutropenia. Australasian Society of Infectious Diseases Annual Meeting (February, 2009). New South Wales, Australia.
5. **Al-Badriyeh D**, Liew D, Stewart K and Kong D. Pharmacoeconomic evaluation of caspofungin versus liposomal amphotericin B as empirical therapy for febrile neutropenia in Australia. Australian Society of Antimicrobials Annual Meeting (March, 2009). Victoria, Australia.

DECLARATION FOR THESIS BASED OR PARTIALLY BASED ON CONJOINTLY PUBLISHED OR UNPUBLISHED WORK

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

The core theme of the thesis is the optimal utilisation of high-cost systemic antifungal agents in Australian hospitals. This thesis includes seven original papers published in peer reviewed journals and one unpublished publications. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the candidate, working within the Department of Pharmacy Practice at the Faculty of Pharmacy and Pharmaceutical Sciences, under the supervision of Dr David CM Kong and A/Prof Kay Stewart. The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.

In the Chapters Four, Five, Six, Eight, Ten, Eleven, Twelve and Thirteen, my contribution to the work involved the following:

Chapter	Publication title	Status	Nature and extent of candidate's contribution.
Four	Cost-effectiveness evaluation of voriconazole versus liposomal amphotericin B as empirical therapy for febrile neutropenia in Australia	Published	Conception and design. Literature search. Data collection. Statistical experience. Analysis and interpretation. Writing the article. Critical revision of the article. Extent, 85%.
Five	Economic impact of caspofungin as compared with liposomal amphotericin B for empirical therapy in febrile neutropenia in Australia	Published	Conception and design. Literature search. Data collection. Statistical experience. Analysis and interpretation. Writing the article. Critical revision of the article. Extent, 85%.

Six	Pharmacoeconomic analysis of voriconazole versus caspofungin in the empirical antifungal therapy of febrile neutropenia in Australia	In review	Conception and design. Literature search. Data collection. Statistical experience. Analysis and interpretation. Writing the article. Critical revision of the article. Extent, 85%.
Eight	Pharmacoeconomic evaluation of voriconazole versus posaconazole for antifungal prophylaxis in acute myeloid leukaemia	Published	Conception and design. Literature search. Data collection. Statistical experience. Analysis and interpretation. Writing the article. Critical revision of the article. Extent, 60%.
Ten	Stability of extemporaneously prepared voriconazole ophthalmic solution	Published	Conception and design. Literature search. Data collection. Statistical experience. Analysis and interpretation. Writing the article. Critical revision of the article. Extent, 85%.
Eleven	Successful salvage treatment of Scedosporium apiospermum keratitis with topical voriconazole after failure of natamycin	Published	Conception and design. Literature search. Data collection. Analysis and interpretation. Writing the article. Critical revision of the article. Extent, 80%.
Twelve	Successful use of topical voriconazole 1% alone as first-line antifungal therapy against Candida albicans keratitis	Published	Conception and design. Literature search. Data collection. Analysis and interpretation. Writing the article. Critical revision of the article. Extent, 80%.
Thirteen	Prospective open-label study of the administration of two-percent voriconazole eye drops	Published	Conception and design. Literature search. Statistical experience. Data analysis and interpretation. Writing the article. Critical revision of the article. Extent, 65%.

I have renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

Candidate's signature _____ Date_____

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TOWARDS COST-EFFECTIVE UTILISATION OF HIGH-COST ANTIFUNGAL AGENTS IN AUSTRALIAN HOSPITALS

CHAPTER ONE: GENERAL INTRODUCTION

1.1 FUNGAL INFECTION: A CONTINUED THREAT

Fungi can be classified into yeasts and moulds. Yeasts (e.g. *Candida* species) have spheroid structures and multiply by budding. Moulds (e.g. *Aspergillus* species) consist of hyphae and grow by division of the hyphae.[1, 2, 3]

Fungal infection, also called mycosis, is classified as endemic or opportunistic. Endemic fungal infections are the result of breathing in pathogenic airborne fungal spores, which exist in many geographical areas where there is high fungi occurrence associated with particular types of soil, vegetation and weather conditions.[4, 5] This type of fungal infection is a key threat to public health in many developing countries.[6-12] Opportunistic fungi are those recognised as significant pathogens when diagnosed as producing infection in populations with suppressed immune systems.[13, 14, 15] In the last few decades, the incidence of these infections has been increasing drastically, which is anticipated given that the number of immunocompromised patients has been increasing. Ironically, this is mainly due the recent progress in medical procedures and techniques, whereby, patients have been, more than ever, exposed to intensive chemotherapy and radiation (for treating malignancies), or myelosuppressive therapies (for undergoing organ or bone marrow transplantations), which can greatly suppress immunity.[16-22] In Europe, for instance, there are almost 20,000 newly diagnosed leukaemia cases every year, and about 100,000 will receive therapy for haematological cancers, while about 19,000 will experience a transplantation procedure.[23] Other factors that have added to the elevated susceptibility to infectious fungal complications include the excessive use of broad-spectrum antibiotic therapies, resulting in over-kill of colonising bacteria and, as a result, allowing for excessive growth of fungi. The overuse of corticosteroids is another factor that may result in the emergence of susceptibility to fungal infections. Old age is a further factor, in which the immune system weakens, permitting infections.[24-26] The increasing rate and duration of survival in individuals with the human immunodeficiency virus (HIV) is also another factor.[16, 27]

The change in incidence of fungal infections has been accompanied by a change in the spectrum of pathogenic fungi. *Aspergillus*, *Candida*, *Fusarium*, *Scedosporium* and zygomycetes are all causative fungi of common fungal infections;[16] however, a study that investigated the prevalence of these fungi between the late 1980s and early 2000s in the United States, demonstrated that, while the occurrence of *Aspergillus* infections significantly increased by about 6%, *Candida* infections decreased in incidence by about 10%, while the rate of *Fusarium* and *Scedosporium* infections remained stable. In addition, at the start of the

study, zygomycetes had a less than 1% rate of occurrence; however, by the end of the study, and with a four-fold increase in prevalence, zygomycetes emerged as one of the clinically important pathogenic fungi.[28]

Infections caused by pathogenic fungi vary from systemic bloodstream and invasive infections (e.g. aspergillosis and candidiasis) to localised infections (e.g. fungal keratitis).[29-31] According to the US Food and Drug Administration, while bacterial infections came under control by new wide-range of antibiotics, fungal infections are emerging as a common cause of morbidity and mortality, especially in immunocompromised patients, and are increasingly recognised as an important cause of reduced quality and length of life.[32]

1.2 ANTIFUNGAL THERAPY AND COST

Medications with antifungal activity were introduced more than half a century ago. The first antifungal agent to be introduced was griseofulvin in 1939.[33] Not long after, in 1944 and 1949,[34, 35] respectively, the first azole and polyene were isolated. In 1959, amphotericin B, a polyene, was introduced as a superior agent against severe systemic fungal infections, and was considered as the gold standard of therapy for the next four decades.[36,] In 1969, the topical antifungal azoles miconazole and clotrimazole were introduced, followed by econazole in 1974,[37-39] and the intravenous formulation of miconazole in late 1970.[40, 41] However, it was only in the late 1980s,[42, 43] with the introduction of the new generation azoles (triazoles) fluconazole and itraconazole, followed by terbinafine (an allylamine) in early 1990s,[44] that the pharmaceutical market for antifungal agents started its marked and steady growth, driven largely by the significant expansion in the population of immunocompromised patients.[32]

Despite their variety, these antifungal agents were limited by inadequate spectra of activity, drug resistance, toxicities and drug interactions, particularly when used against invasive fungal infections (IFIs).[45, 46] Subsequently, more effective antifungal agents (or new formulations), with improved safety profiles, became available.[47, 48] Liposomal formulations of amphotericin B were introduced in 1996,[49] caspofungin, micafungin and anidulafungin, from the echinocandins class, were introduced around the early 2000s,[50-52] and newer triazole agents (i.e. voriconazole and posaconazole) were introduced in 2002 and 2006, respectively.[49] Consequently, physicians now have a wider choice of effective and safe treatment options. Newer antifungal agents, however, including newer formulations of older agents (i.e. the liposomal formulation of amphotericin B), are significantly more expensive than older antifungal products, which is not surprising, given the increasing development cost associated

with innovative products and techniques.[53] The estimated antifungal market in the United States increased from US$2.1 billion in 1999 to US$3.3 billion in 2003, with sales of azoles constituting 52% of the total cost.[54, 55] Globally, in 2007-08, antifungal agents held a share of the pharmaceutical market with a value of US$11.2 billion. This is expected to increase to as high as US$14 billion by 2012, with an annual growth of 4.5%.[54] In the developed world, a significant part of healthcare spending is associated with costs of medication;[56] therefore, it is no surprise that the increased cost of antifungal agents has increased the overall cost of managing fungal infections. In 1996, the estimated cost of aspergillosis in the US was US$62,426 per case, and US$633.1 million per year.[57] In 1997, the average cost of treating a case of blood stream *Candida* infection was US$34,123-44,536, making a total of US$216-281 million per year.[58] A similar burden was reported in Australia. In 1999, aspergillosis was associated with an average cost of AU$9,333 per case, and a total annual cost of AU$42.8 million. The cost of disseminated candidiasis was AU$33,274 per case, and AU$17.7 million per year.[59]

With such considerable healthcare costs and resources allocated to fungal infections, the choice of antifungal treatment has become extremely pertinent.

1.3 EFFICIENCY OF THERAPY

Relative health returns of any expensive therapies must be scrutinised in relation to their high cost. In a sense, spending resources on a particular preventive or therapeutic antifungal intervention can be characterised as a substitution of increased economic burden for a reduced incidence of infections. Recognising this, and given the increasing prevalence of infections and the associated cost and burden to hospitals, it is worthwhile to ask whether this substitution is being made efficiently, where a maximal overall output is being achieved from the input resources expended. While it is tempting to think that the cost of a therapeutic intervention is the price of that intervention, from an economic point of view, the actual cost of an intervention includes the cost of resources consumed during the application of that intervention.

Resource scarcity and, ultimately, incapacity to generate all desired outputs, necessitates that choices have to be taken to achieve highest efficiency. Efficiency concerns itself with choice, and requires the linking between inputs and outputs (i.e. costs and consequences). Pharmacoeconomics is the branch of economics related to achieving efficiency in relation to the use of pharmaceuticals. It is a comparative evaluation of alternative options of action in terms of their costs and consequences.[60-62]

The key aim of all efforts to achieve efficiency is to guide the use of limited resources to yield maximum value to patients and healthcare payers, as well as society in general.

1.4 OUTLINE OF THESIS

The main objective of this thesis was to assess the efficiency of various high-cost antifungal agents in the context of the Australian hospital system, and to generate information which will lead to the efficient use of these agents. The studies were directed to cover antifungal agents used empirically, prophylactically and for targeted therapy. The empirical therapy explored was the use of antifungal agents for IFIs in patients with febrile neutropenia. The prophylactic strategy was the use of antifungal agents in patients with acute myeloid leukaemia to prevent against IFIs. The targeted therapy was directed against the localised fungal infection, with the focus of interest being the use of an extemporaneous preparation of an antifungal agent for the fungal infection occurring in the cornea of the eye (i.e. fungal keratitis).

The body of this thesis constitutes 14 chapters; the remaining chapters are presented in the following manner.

Chapter Two provides background information to the introductions in **Chapters Three** and **Seven** regarding empirical therapy and prophylaxis, whereby, it gives an overview of IFIs in terms of incidence, risk factors, aetiology, diagnosis and management. This chapter also describes the different types of economic evaluations, and the general methodology involved, providing some background to the economic evaluations reported in **Chapters Four**, **Five**, **Six** and **Eight**.

Chapter Three provides a brief introduction to febrile neutropenia and explains the use of empirical antifungal therapy, including a review of the use of the current empirical antifungal agents. It is an introduction to the work reported in **Chapters Four**, **Five** and **Six**.

Chapter Four presents an economic evaluation comparing voriconazole with liposomal amphotericin B as empirical therapies in febrile neutropenia. **Chapter Four** has been published in the Journal of Antimicrobial Chemotherapy.

Chapter Five reports an economic analysis of caspofungin versus liposomal amphotericin B for empirical use in patients with febrile neutropenia. This chapter has also been published in the Journal of Antimicrobial Chemotherapy.

Chapter Six presents the results of an economic evaluation of voriconazole versus caspofungin for empirical therapy in febrile neutropenia. **Chapter Six** is in review for publication in the Journal of Antimicrobial Chemotherapy.

Chapter Seven introduces acute myeloid leukaemia, and provides a description of the prophylactic antifungal therapies, followed by a review of voriconazole and posaconazole, the current prophylactic antifungal agents. It provides an introduction to the study reported in **Chapter Eight**.

Chapter Eight reports an economic evaluation of voriconazole versus posaconazole as first-line prophylactic agents in acute myeloid leukaemia. The chapter is published in the Journal of Antimicrobial Chemotherapy.

Chapter Nine describes fungal keratitis, including corneal anatomy, infection trends and aetiology, and current therapies. A particular emphasis has been placed on reviewing the use of voriconazole eye drops in fungal keratitis. **Chapter Nine** provides a general introduction to studies reported in **Chapters Ten**, **Eleven**, **Twelve** and **Thirteen**.

Chapter Ten discusses the formulation and stability of preserved 1% and 2% voriconazole eye drops as potential therapy for fungal keratitis. **Chapter Ten** has been published in the Journal of American Health-System Pharmacy.

Chapter Eleven reports the clinical success of 1% voriconazole eye drops as salvage monotherapy in fungal keratitis. The chapter was published in the Annals of Pharmacotherapy.

Chapter Twelve reports the clinical success of 1% voriconazole eye drops as primary monotherapy in fungal keratitis. **Chapter Twelve** has also been published in the Annals of Pharmacotherapy.

Chapter Thirteen describes a prospective clinical study to examine the penetration of 2% voriconazole eye drops into the aqueous humour of the eye. This chapter has been published in the journal Antimicrobial Agents and Chemotherapy.

Chapter Fourteen summarises the overall goals and findings of the previous chapters, discusses their place in clinical practice, and gives suggestions for future directions in research.

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CHAPTER TWO: INVASIVE FUNGAL INFECTIONS IN IMMUNOCOMPROMISED PATIENTS – AN OVERVIEW

As discussed in **Chapter One**, **Chapter Two** provides background information to **Chapters Three** and **Seven** regarding empirical therapy and prophylaxis, and to the economic evaluations in **Chapters Four**, **Five**, **Six** and **Eight**.

2.1 INVASIVE FUNGAL INFECTIONS AND INCIDENCE

Invasive fungal infection (IFI) is a major cause of morbidity and mortality in patients with suppressed immunity, especially in those with haematological malignancies associated with prolonged and severe neutropenia. There are two patient groups with haematological malignancy that are at particularly high risk for IFIs; these are patients undergoing allogeneic stem cell transplant, and patients receiving intensive chemotherapy for acute leukaemia.[1, 2] These haematology patients are followed, in terms of risk for IFIs, by patients with lymphoma and solid tumours.[3, 4]

The incidence of fungal infection has been rising in recent years with the introduction of more intensive chemotherapy regimens and with the advent of stem cell and solid organ transplants.[5] It is difficult to determine the exact incidence of IFI because of the difficulty in diagnosing systemic fungal infections, especially in the early stages. Up to 50% of patients with haematological malignancies can have evidence of fungal infection at autopsy.[6] For patients with acute leukaemia, this rate has been reported at about 25%.[7, 8] The incidence of IFI in patients undergoing myelosuppressive chemotherapy for acute leukaemia is around 14%, and the risk is higher in allogeneic transplant recipients.[9] For patients undergoing chemotherapy, mortality rates ranging from 50-90% have been associated with documented IFI.[10]

2.2 SOURCES OF IFI IN CLINICAL SETTING

The way in which recent changes in medical management and healthcare practices have led to increases in the immunocompromised populations and, ultimately, accelerated spread of fungal infections in general, is well established (see **Chapter One**). The risk factors that

predispose the immunosuppressed host to exposure to fungal organisms, resulting in the development of the IFI, are equally important, and several of them have been identified. Building and restoration areas, especially when used for housing immunocompromised patients, pose a significant risk, particularly increased respiratory exposure to moulds. This has resulted in a number of mandatory protocols in relation to accommodating high risk patients at hospitals, such as efficient air decontamination systems, directed air flow, securely closed lodges, and separators between care areas.[10] Complete intravenous nourishment can provide a medium for fungal colonisation and is another possible predisposing factor for IFIs, especially with the administration of lipids.[11] The yeasts that usually colonise mucosal and skin barriers are another important factor; rigorous chemo- and radiotherapies may affect the integrity of such barriers and, therefore, allow superficial fungal colonies to become invasive. The chronic use of catheters also increases the risk of exposure to fungi. This is because fungal colonies build up over time on the catheter, and when the catheter penetrates the skin, the fungi are exposed to the systemic circulation.[12, 13]

2.3 COMMON TYPES OF IFI

A number of fungi can cause IFIs in immunocompromised patients, including *Aspergillus*, *Candida*, *Cryptococcus*, *Fusarium*, *Acremonium*, *Paecilomyces*, *Scedosporium* and zygomycetes species. *Aspergillus and Candida* species, however, are by far the most common IFI-causative fungi in Australia, as well as in most other countries.[14-20]

2.3.1 ASPERGILLOSIS

There are 300 *Aspergillus* species, with new ones still being defined.[21] Less than 20 of these species result in human infections. *Aspergillus fumigatus* is the most common species identified clinically. It represents most of the *Aspergillus* species identified in patients and is implicated in 90% of systemic aspergillosis, with a survival rate of 40-90%.[22, 23] *Aspergillus fumigatus* is particularly a major cause of the usually deadly invasive aspergillosis occurring in the respiratory tract.[23-25] Other key, but less common, species that have been reported to cause invasive aspergillosis are *Aspergillus flavus*, *Aspergillus terreus*, *Aspergillus niger* and *Aspergillus nidulans*.[26, 27] In immunocompromised populations, the occurrence of invasive aspergillosis is firmly correlated with the duration and severity of neutropenia.[28] Invasive

aspergillosis does not usually develop in short-term neutropenia. In long-term neutropenia, however, the likelihood of developing certain types of aspergillosis (e.g. pulmonary aspergillosis) can increase by over 300%.[28] During the 1980s and 1990s, the occurrence of invasive aspergillosis increased by more than 400% in the United States.[5]

2.3.2 CANDIDIASIS

The most common of the isolated *Candida* species is *Candida albicans*, while *Candida tropicalis*, *Candida glabrata*, *Candida parapsilosis* and *Candida krusei*, in addition to more recent species such as *Candida lusitaniae*. The *Candida* species are usually present in the mouth or intestine, but may develop into invasive candidiasis that can affect many of the organs of immunosuppressed patients.[29] The mortality rate associated with disseminated candidiasis can be up to about 50%.[30, 31] During the past two decades, the incidence of candidiasis has increased significantly to the extent that *Candida albicans* is now considered the most important cause of nosocomial infections.[32] The occurrence of other *Candida* species, such as *Candida krusei* and *Candida glabrata*, has also been increasing. A two-fold increase in systemic infections caused by *Candida krusei* was reported in 1993.[33]

2.4 CLASSIFICATION OF IFI

The European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group classified IFIs according to three definitions that are based on different levels of diagnostic probability,[34] these being:

i. Proven, defined by positive culture obtained by sterile procedure from a sterile and clinically (or radiologically) abnormal site consistent with infection.
ii. Probable, defined by at least one host criterion, with one microbiological criterion and one major or two minor clinical criteria from an abnormal site consistent with infection.
iii. Possible, defined by at least one criterion from the host section, with one microbiological or one major or two minor clinical criteria from an abnormal site consistent with infection.

2.5 DIAGNOSIS OF IFI

Diagnosis of IFIs in clinical setting remains difficult, as symptoms of IFIs are often nonspecific. Several diagnostic tools are used. Blood cultures can be used to diagnose *Candida* infections in many cases; however, sensitivity may depend on whether the patient received antifungal prophylaxis or not.[35] Unless prophylactic antifungal agents are inactivated in culture bottles, using blood cultures as diagnostic tool for fungus may produce false negative results.[35] In addition, *Candida* blood cultures only have a sensitivity of 20-50% for detecting *Candida* fungi in the blood, which is not very useful in the clinical setting. For *Aspergillus* infections, blood cultures are of even less value in diagnosis due to a very low test sensitivity of about 1%.[26] Histological evidence of aspergillosis requires biopsy, which is often inappropriate and too invasive and, hence, mostly only used post-mortem.[34] A newer method, the galactomannan antigen detection test, is widely used for diagnosis of *Aspergillus* infections, whereby, the antigen galactomannan is detected via an enzyme-linked immunosorbent assay (ELISA). With over 85% consistency, ELISA is specific, but it has variable sensitivity of around 65% and is not always clinically practical.[36, 37] The polymerase chain reaction (PCR) is another antigen detection test that detects fungal deoxyribonucleic acid (DNA) in biological samples. This test enables early detection of fungal infections, compared to other diagnostic tests, and can be used to monitor the success of the antifungal therapy. Its sensitivity, however, is highly affected by the use of antifungals by patients, which may reduce the sensitivity to a low 40%.[38-41] Lesions of invasive *Aspergillus* and *Candida* infections can be characterised at early stages via imaging procedures such as computer tomography (CT). The lesions, however, especially with pulmonary *Aspergillus* infections, might be the result of a variety of fungal species, and other infectious and non-infectious conditions.[34, 42] In summary, existing diagnostic tools to detect fungal infections remain inadequate.

2.6 THERAPIES FOR IFI

Current treatment of IFIs is generally limited by the relatively low number of available antifungal drugs.[43, 44] Four classes of systemic antifungal agents have been used for the treatment of IFIs. These are polyenes (conventional amphotericin B and lipid formulations of

amphotericin B), triazoles (fluconazole, itraconazole, voriconazole and posaconazole), echinocandins (caspofungin and anidulafungin) and allylamines (terbinafine).

2.6.1 POLYENES

Conventional amphotericin B (**Figure 2-1**) is amphotericin B deoxycholate (Fungizone®, Bristol-Myers Squibb), and was first used in 1960.[45] It is a highly effective broad-spectrum antifungal agent that was the gold standard for the treatment of IFIs for a long time. The interaction of amphotericin B with the ergosterol in the membrane of the fungus results in the formation of pores containing a hydrophobic link between the amphotericin B molecules and the fungal membrane sterols, leading to altered permeability, leakage of vital cytoplasm components, and oxidative damage and death of the fungus.[46] Conventional amphotericin B, however, is known for its clinically significant side effects, limiting its clinical efficacy. Over 50% of patients receiving amphotericin B experience infusion-related events such as fever, chills, nausea, dyspnoea or hypotension. The majority of these side effects can be lowered by reducing the rate of infusion and by premedication. Nephrotoxicity is also a major adverse effect that includes reduced glomerular filtration, and potassium and magnesium wasting, limiting the prolonged use of this antifungal agent. Over 50% of patients prescribed amphotericin B experience a two-fold increase in serum creatinine levels, with up to 10% requiring haemodialysis.[47-50] These events often results in the administration of suboptimal doses to patients.[47] Higher doses, on the other hand, led to a reported significant increase in mortality as well as treatment costs in patients receiving conventional amphotericin B.[47]

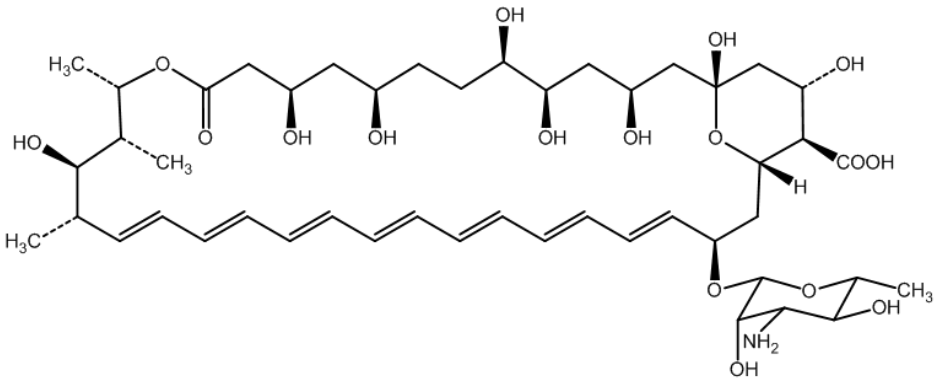

Figure 2-1. Chemical structure of conventional amphotericin B.[14]

Colloidal dispersions, lipid complex and liposomal preparations were developed as lipid formulations of amphotericin B to reduce the toxicity profile of amphotericin B and, ultimately, achieve a more beneficial therapeutic outcome.

Amphotericin B colloidal dispersion (Amphocil®/Amphotec®, Intermune Pharmaceuticals) is a preparation of amphotericin B enclosed in a stable complex with sodium cholysteryl sulphate, forming a colloidal aqueous suspension.[51,52] It is approved for use in the treatment of invasive aspergillosis in patients with renal failure and/or in whom conventional amphotericin B was not successful.[14] Amphotericin B colloidal dispersion has also been used successfully in cases of candidiasis, coccidioidomycosis, cryptococcosis in normal and immunocompromised hosts.[53-55] While the colloidal preparation of the amphotericin B is associated with significantly lower renal toxicity than conventional amphotericin B, it is still associated with an equivalent level of infusion-related side effects.[56, 57]

The amphotericin B lipid complex (Abelcet®, Enzon Pharmaceuticals) is made of a biodegradable phospholipid matrix of dimyristoyl-phosphatidyl chloride and dimyristoyl-phosphatidyl glycerol, and has proven to be effective against aspergillosis. It is approved for use after failure of conventional amphotericin B and/or in patients with renal failure. Amphotericin B lipid complex has also been used successfully in salvage therapy for cases of candidiasis, aspergillosis and cryptococcosis.[58-62] Similarly to conventional amphotericin B, amphotericin B lipid complex is associated with nephrotoxicity, but at a much lower rate (i.e. occurring in up to about 28% of patients). This trend extends to associated infusion-related events as well, with chills, fever and nausea as the most common.[63]

Liposomal amphotericin B (LAmB, Ambisome®, Gilead Science) is a formulation containing amphotericin B encased in unilamellar liposomes made up of hydrogenated soy phosphatidylcholine, distearoyl phosphadidylglycerol and cholesterol.[64] LAmB was demonstrated to be safer than, and at least equally effective as, conventional amphotericin B.[65, 66] A study of LAmB versus conventional amphotericin B as primary therapy in proven and suspected fungal infections, displayed higher success and better overall outcomes for LAmB, particularly in patients with advanced underlying malignancies.[66] In a randomised controlled clinical trial, the effectiveness of the 3 mg/kg dose of LAmB as primary antifungal agent in invasive aspergillosis resulted in a 50% response rate and a 72% survival rate. A dose of 10 mg/kg, however, did not result in higher efficacy and led to a higher rate of renal failure.[67] LAmB is often recommended for use as salvage therapy against aspergillosis and candidiasis, as well as in cases of cryptococcosis in AIDS who are unable to tolerate conventional amphotericin B. It has also been used successfully against blastomycosis.[66, 68, 69] Importantly, LAmB produces significantly less nephrotoxicity and infusion-related chills and fever, compared to conventional amphotericin B and its other lipid formulations. Nonetheless,

increased creatinine levels and hypokalaemia are still a concern with LAmB, especially when compared to azoles.[70, 71]

2.6.2 AZOLES

All triazole antifungals are fungistatic and work by interfering with the synthesis of ergosterol in the membrane of the fungus, by binding to and inhibiting lanosterol demythylase. In patients, all triazoles inhibit the main metabolising liver enzyme CYP3A4.[72]

Itraconazole (**Figure 2-2**; Sporanox®, Janssen-Cilag) is relatively safe and effective against *Aspergillus* species. It has a highly variable gastrointestinal penetration and an uncertain bioavailability and, hence, is less favourable as treatment of choice in acute aspergillosis. Nonetheless, itraconazole can be used in chronic aspergillosis and as alternative to conventional amphotericin B in acute cases.[73, 74] Itraconazole has also demonstrated success against histoplasmosis, paracoccidioidomycosis and blastomycosis, as well as cases of cryptococcosis in AIDS.[75-77] The use of itraconazole against *Candida* species is limited by potential post-fluconazole resistance and the fact that it has not been well investigated against candidiasis.[78] Itraconazole has major limitations because of its interactions with a wide variety of usually co-administered medications, including immunosuppressants, benzodiazepines, prednisolone and digoxin.[73, 74] In addition, it has a well-recognised gastrointestinal side-effect profile, including nausea and diarrhoea. Headache and dizziness are reported occasionally. Hypokalemia, hypertension and oedema may also manifest. Mild increases of liver enzymes are reported with itraconazole, but not as serious hepatotoxicity.[79-83]

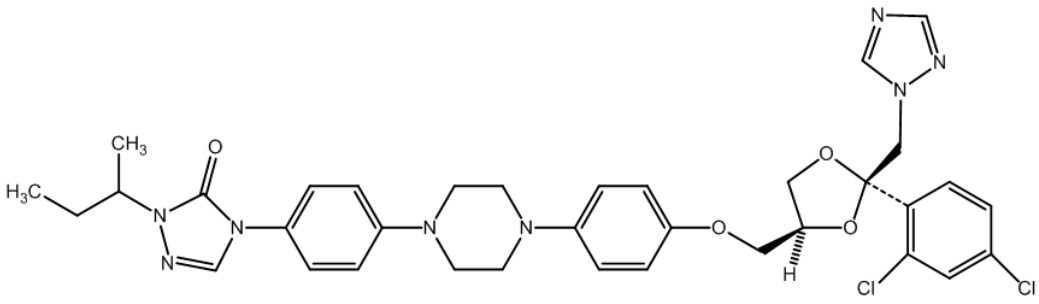

Figure 2-2. Chemical structure of itraconazole.[14]

Fluconazole (**Figure 2-3**; Diflucan/Trican®, Pfizer) is an extremely safe azole antifungal, except for some rare and minor side effects relating to nausea, abdominal pain and liver

toxicity. Skin rashes were also reported.[84] It is indicated for the treatment of invasive *Candida* infections, especially infections caused by *Candida albicans*. In a randomised controlled clinical trial that investigated the effectiveness of fluconazole versus conventional amphotericin B in the treatment of candidemia, equal efficacy was reported, with the conclusion that candidemia without evidence of deep infection may be managed by fluconazole alone if the patient has not received prior azole prophylaxis.[85] A similar outcome was reported against candidiasis, but with the necessity for a longer duration of therapy (i.e. six months).[86, 87] FIuconazole is also useful in the prolonged treatment of cryptococcosis cases in AIDS. Fluconazole, however, lacks the efficacy against *Aspergillus* species. Its use is also limited by resistance commonly developed by some *Candida* species, such as *Candida glabrata*, *Candida krusei* and *Candida albicans*.[14, 88-91]

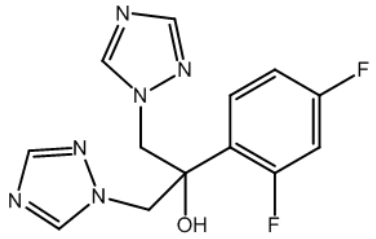

Figure 2-3. Chemical structure of fluconazole.[14]

Voriconazole (**Figure 2-4**; Vfend®, Pfizer) is a derivative of fluconazole.[92] Its excellent systemic bioavailability and high activity against *Aspergillus* has made it the standard of care for the treatment of invasive aspergillosis.[92, 93] Voriconazole was compared with conventional amphotericin B in a randomised trial in patients with invasive aspergillosis,[92] where it resulted in higher success (53% versus 31%), higher survival and fewer severe side effects. It is recommended for use against aspergillosis and candidiasis, including that caused by *Candida* with reduced sensitivity to fluconazole, as well as against *Fusarium* and *Scedosporium* species.[71, 72, 92, 94] Similarly to itraconazole, voriconazole interacts with a large number of medications, presenting a major challenge in the treatment of significantly deteriorating patients.[95] The most common side effects associated with voriconazole use are visual disturbances in up to 30% of patients. These, however, are reversible and rarely lead to therapy discontinuation. Other adverse effects, which may lead to therapy discontinuation, include skin rashes, hallucinations and, mainly, reversible hepatotoxicity.[92, 95-97]

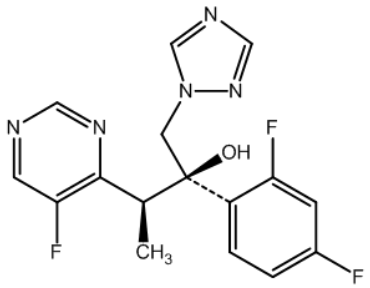

Figure 2-4. Chemical structure of voriconazole.[14]

Posaconazole (**Figure 2-5**; Noxafil®, Schering-Plough) is the most recent triazole and has broad-spectrum activity against a variety of fungi, including some that are resistant to other antifungal agents. Randomised clinical trials investigating the effectiveness of posaconazole against IFIs are lacking, however, studies have proven it to be well tolerated and effective against a variety of infections such as aspergillosis, candidiasis, fusarioses and zygomycosis.[98-100] Posaconazole was shown to be particularly successful for prophylaxis in patients with neutropenia and severe graft-versus-host disease.[102, 103] It is effective as an alternative to unsuccessful initial antifungal therapy.[104] It also has fewer side effects and drug interactions than itraconazole and voriconazole.[102, 103, 105] The major adverse effects of posaconazole are limited to gastrointestinal events, including diarrhoea, nausea and vomiting. Rashes have also been reported.[100] The absorption of posaconazole is particularly problematic, requiring high fat meals for best absorption.[106]

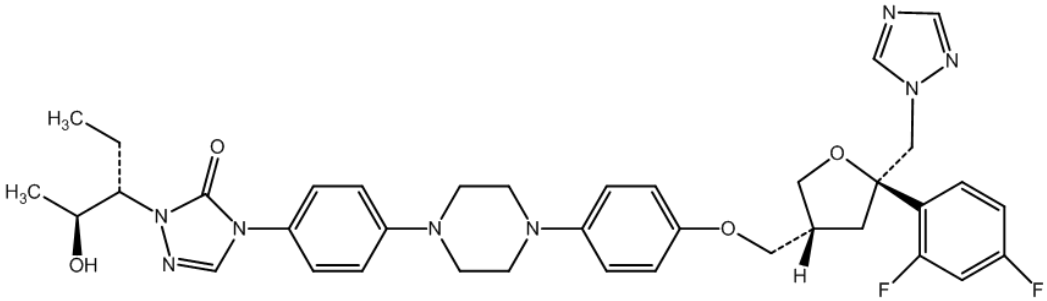

Figure 2-5. Chemical structure of posaconazole.[14]

2.6.3 ECHINOCANDINS

Caspofungin (**Figure 2-6**; Cancidas®, Merck), like amphotericin B, is fungicidal in activity. It has broad-spectrum activity and acts by inhibiting the synthesis of β-D-glucan synthase enzyme, which is responsible for synthesising glucan polymers in the fungal cell wall. This leads to the disruption and instability of the fungal cell wall and, ultimately, the death of the fungus. There are no randomised trials on the use of caspofungin against invasive aspergillosis, but caspofungin was demonstrated to be an effective alternative salvage therapy in patients with aspergillosis.[107] A randomised clinical trial was performed to compare caspofungin against conventional amphotericin B for the treatment invasive candidiasis.[108] Although the survival rate was similar between the two antifungals, caspofungin had a higher success rate (72% versus 63%), and was associated with fewer side effects. Caspofungin is licensed for use against invasive aspergillosis and candidiasis; however, its activity is not sufficient against coccidioidomycosis, and it is not effective against *Fusarium*, *Paecilomyces*, *Scedosporium,* cryptococci, and zygomycetes.[108] It has a very favourable safety profile, with few drug interactions, and is generally well tolerated.[108-110] The side effects are limited to minor events of fever, nausea, headache, and phlebitis at the infusion site. Rare cases of rashes have also been reported. Mild to moderate increases in transaminases were reported in about 17% of patients.[108, 113]

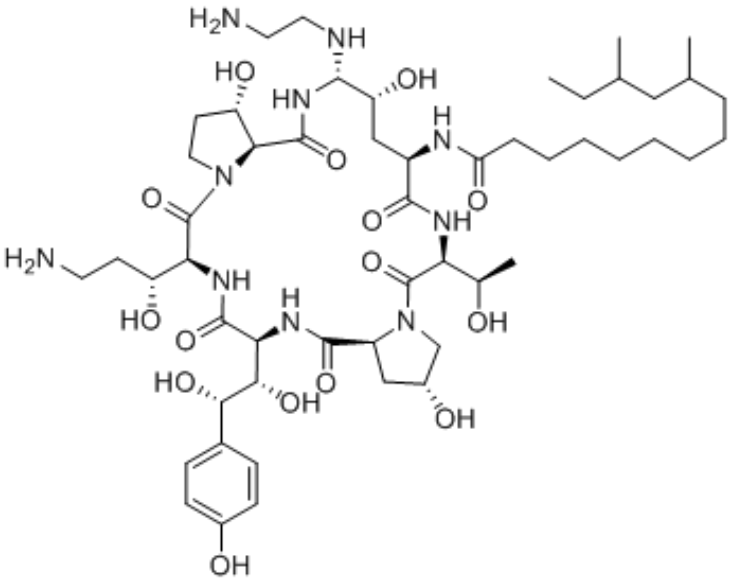

Figure 2-6. Chemical structure of caspofungin.[14]

Anidulafungin (Eraxis®, Pfizer) is another echinocandin, which was only approved for use in Australia in 2009; hence, clinical experience is limited. It is active against *Aspergillus* and *Candida* infections, and has a favourable safety profile. Similarly to caspofungin, anidulafungin has very few side effects. The most common side effects reported include infusion reactions in the form of flushing, urticaria and rash at the infusion site. This is in addition to mild elevations in transaminases enzymes.[114, 115] It is only available for intravenous administration.[116]

2.6.4 ALLYLAMINES

Terbinafine (**Figure 2-7**; Lamisil®, Novartis) is fungicidal against many moulds, but only a few types of yeast. It inhibits ergosterol biosynthesis at the early step of squalene epoxidation. As a result, the sterol precursor squalene accumulates, increasing the fungal membrane permeability and, ultimately, the death of the fungal cell.[117] Because squalene epoxidase is not a cytochrome P-450 enzyme, terbinafine is less toxic than azoles.[118] Despite its broad-spectrum activity, clinical efficacy and use are limited by its pharmacokinetic characteristics.[119, 120] Because of its poor systemic pharmacokinetics, terbinafine works only against dermatophytes. Against aspergillosis, however, terbinafine is used successfully in combination with other fungal ergosterol synthesis inhibitors (e.g. voriconazole), producing a synergistic effect.[72, 118]

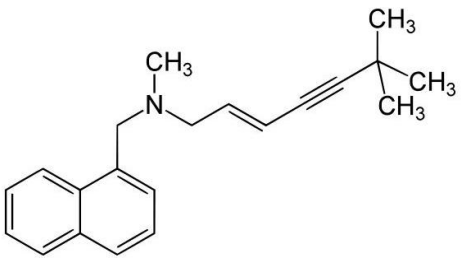

Figure 2-7. Chemical structure of terbinafine.[14]

The available antifungal agents, and their preparations, as used in Australia, as well as their recommended doses are shown in **Tables 2-1** and **2-2**.

Table 2-1. Recommended doses of antifungals for invasive mould infections[44]

Agent	Preparation	Recommended dose
Amphotericin B deoxycholate[a]	Intravenous	1-1.5 mg/kg/day
Liposomal amphotericin B	Intravenous	3-5 mg/kg/day
Amphotericin B lipid complex	Intravenous	3-5 mg/kg/day
Voriconazole	Intravenous	6 mg/kg bd[b] for 1 day, followed by 4 mg/kg bd
	Oral (maintenance), or	200 mg bd
	Intravenous (maintenance)	200 mg bd
Caspofungin	Intravenous	70 mg daily for 1 day, followed by 50 mg daily
Posaconazole	Oral	200 mg qid[c], or 400 mg bd
Itraconazole	Oral, Intravenous	200 mg bd
Terbinafine	Oral	250 mg daily

[a]Conventional amphotericin B.

[b]bd, twice daily.

[c]qid, four times daily.

Table 2-2. Recommended doses of antifungals for invasive *Candida* infections[44]

Agent	Preparation	Recommended dose
Amphotericin B deoxycholate[a]	Intravenous	0.6-1 mg/kg/day
Liposomal amphotericin B	Intravenous	3-5 mg/kg/day
Amphotericin B lipid complex	Intravenous	3-5 mg/kg/day
Voriconazole	Oral, Intravenous	6 mg/kg bd[b] for 1 day, followed by 4 mg/kg bd
Fluconazole	Oral, Intravenous	400 mg (6-12 mg/kg) daily
Caspofungin	Intravenous	70 mg daily for 1 day, followed by 50 mg daily

[a]Conventional amphotericin B.

[b]bd, twice daily.

2.7 RESISTANCE TO ANTIFUNGAL AGENTS

A resistant fungus is a fungus that continues producing clinical disease despite being exposed to high concentrations of an active antifungal agent at the site of infection. It can be primary,

occurring at the onset of antifungal therapy, or secondary, developing during therapy.[14] Several mechanisms can result in resistance to antifungals. These include alterations in the target of therapy (e.g. binding site), deficient or reduced drug entry into the cell, reduced intracellular drug accumulation, and alterations in sterol biosynthesis.[14, 121, 122]

Resistance to antifungal therapy is particularly an issue with triazoles, especially fluconazole, given the increased use of these agents.[123] Unlike other groups of antifungals, where usually a single mechanism is behind the development of resistance, resistance to azoles can be due to multiple mechanisms, making the occurrence of resistance more likely.[14, 124-129] In addition, azoles are increasingly being used as agricultural fungicides,[14] which may result in the spread of azole-resistant fungi, except for *Candida albicans* which lives on mucosa. Exposure to triazoles may produce resistance, which is a problem in patients with long-term exposure to therapies such as in the case with prophylaxis. Fluconazole prophylaxis has been shown to result in considerable reduction in invasive candidiasis; however, this was associated with increased incidence of less susceptible opportunistic yeasts, such as *Candida krusei* and *Candida glabrata* that caused colonisation and breakthrough IFI.[89-91, 130] While *Candida krusei* has an intrinsic resistance to fluconazole, *Candida albicans* often develops multi-drug resistance upon exposure to fluconazole. Because the mechanisms of resistance are similar between azoles, fluconazole-resistant isolates of *Candida albicans* have a low susceptibility to other triazole derivatives as itraconazole, voriconazole and posaconazole, but to different extents. Cross-resistance is important when considering the combination of fluconazole and itraconazole. Although concerns were reported regarding the combination of fluconazole and amphotericin B, fluconazole-resistant *Candida albicans* is usually susceptible to amphotericin B (and vice versa) because of differences in the mechanisms of resistance to the two agents.[14] Resistant *Aspergillus fumigatus* was reported after treatment with itraconazole, with the mechanism of resistance being similar to that against posaconazole, but not voriconazole. Cross-resistance between itraconazole and posaconazole has been reported. Some resistance by *Aspergillus fumigatus* has also been reported against voriconazole.[131] Breakthrough IFIs with voriconazole included resistant *Aspergillus*, *Candida* and zygomycetes species, but with a rate lower than comparators.[132] Resistance is also reported against polyenes and echinocandins. Emerging lower susceptibility was reported by *Aspergillus terreus* and *Scedosporium* species toward amphotericin B. Other reported breakthrough infections because of resistance against amphotericin B included *Fusarium*, *Candida* and *Geotrichum* species. [73, 133-136] *Cryptococcus neoformans* is an example of isolates that can develop resistance to caspofungin.[14]

Resistance patterns are best investigated through reporting breakthrough IFIs as they occur, because clinical resistance does not necessarily directly correlate with in vitro susceptibility profiles reported at the laboratory level.[73, 137]

In general, resistance to antifungals is more relevant and problematic in cases where organisms have low susceptibility to antifungal agents with fungistatic activity against them, such as *Candida* species with azoles and terbinafine. Here, the efficacy of the antifungals is easily affected.[14]

2.8 STRATEGIES TO AVOID IFI

There are three strategies that are being used to avoid or manage anticipated IFIs in patients with neutropenia. One strategy is empirical antifungal therapy (see **Chapter Three**), which is commenced before diagnosis of IFI, but when persistent fever of unknown origin, involving proven/possible IFI, develops.[138] The aim of this strategy is to manage fungal infection at a very early stage, that is, as soon as the infection is suspected. The rationale behind this strategy is that early diagnosis of the IFI has been challenging due to insensitive diagnostic tools.[26, 34-41] In addition, targeted antifungal therapy that is initiated after the IFI is established is often ineffective.[138] The disadvantage of empirical therapy, however, is that fever is a poor predictive surrogate for IFI. As the incidence of IFI in neutropenic patients with persistent fever is only about 15%,[139] empirical therapy may result in unnecessary drug-related side effects and therapy costs. Another strategy is pre-emptive therapy, whereby, the antifungal agent is commenced when there is early suspicion of fungal infection and, more commonly, when fungal colonisation exists, but without fever or other clinical signs of infection.[140] This strategy is similar in principle to the empirical strategy, aiming to manage fungal infection at a very early stage, before the IFI is established. Pre-emptive therapy is a more refined approach, however, whereby the onset of antifungal therapy is delayed until neutropenic patients show microbiological or radiological signs of infection. Compared to empirical therapy, pre-emptive therapy will expose fewer patients to unnecessary drug toxicity and cost. However, pre-emptive therapy requires the availability of diagnostic tests that are sufficiently sensitive to accurately detect clinical and radiological markers of fungal infections, early enough to avoid the disease becoming established, but late enough to avoid prescribing antifungal agents to patients who do not have IFI. Employing this strategy is challenging, given that reliable sensitive diagnostic tools of fungal infections are not well developed,[141-144] and that consensus on the diagnostic factors that should be used to guide the pre-emptive therapy has not yet been established.[139, 145, 146] The third approach is antifungal prophylaxis (see **Chapter Seven**), where an antifungal agent is commenced at the onset of neutropenia to prevent the development of fungal infection.[147] IFI is, as discussed previously, difficult to treat once the infection has become established, and is associated with a high mortality rate.

Antifungal prophylaxis is given to patients at risk of IFI over the period of risk. This strategy has been the first option to consider in a number of settings, particularly for haematological patients. But while the risk factors for IFI are recognised, the time during which particular risk factors affect a patient is less well established.[148, 149] This is important, as prolonged exposure to antifungals can be associated with development of resistance. Since the early 1990s, fluconazole prophylaxis has been associated with cases of colonisation and breakthrough IFIs caused by less opportunistic *Candida* species, such as *Candida glabrata* and *Candida krusei*.[89, 90] Other examples include reported emergence of less susceptible *Aspergillus fumigatus* with prolonged exposure to itraconazole, voriconazole and caspofungin.[131] Potential limitation in the antifungal spectrum of activity is another possible disadvantage. At the time when fluconazole was the standard for the prophylaxis antifungal therapy, infections caused by *Candida* species were significantly reduced in incidence. This, however, correlated with a considerable change in the epidemiology of IFI, as infections due to *Aspergillus* species (which is inherently insensitive to fluconazole) became increasingly common.[150] Newer antifungals with broad-spectrum activity, such as voriconazole and caspofungin, have been more commonly used. These, however, are significantly more expensive, especially as long-term prophylactic agents. Understanding the local epidemiology of IFI at an institution is crucial for the optimal selection of antifungal prophylaxis. For instance, in settings where patients have multiple risk factors to particularly develop invasive candidiasis, fluconazole can be recommended.[151]

In summary, IFIs are often associated with mortality and morbidity in immunocompromised patients. The diagnosis of an IFI is difficult given poor and inadequate diagnostic tools. Thus, an exact incidence of occurrence of IFIs is difficult to elucidate. IFIs are classified into proven, probable and possible, with aspergillosis and candidiasis as the main types of infections. For decades, conventional amphotericin B was the primary antifungal agent used. Now, however, less toxic formulations of amphotericin B, new triazoles and the echinocandins have become available for clinical use as effective and less toxic alternatives.

2.9 ECONOMICS OF TREATMENTS FOR IFI

As discussed in **Chapter One**, recently available antifungal agents (i.e. LAmB, voriconazole, posaconazole and caspofungin) are significantly more expensive than older agents (i.e. conventional amphotericin B, fluconazole and itraconazole). No central source of antifungals prices is available in Australia. The prices for commonly used antifungals in Australia, drawn

from a number of sources, are shown in **Table 2-3**. Given the large price differences, economic considerations relating to the use of these agents are of particular interest. This is illustrated by the fact that developers of local hospital policies may consider the cost of therapies when making decisions, especially when equivalency in effect between different medications is demonstrated.[152, 153] These consist mainly of policies restricting the use of expensive antifungal agents to specific indications or populations. Examples include reserving the more expensive LAmB for patients with low tolerance to the less expensive and more toxic agents, such as conventional amphotericin B.[154] Unfortunately, the policies seem to have been designed to focus mainly on acquisition cost, rather than cost-benefit.

The costs associated with the use of a drug can be divided into two types: primary costs, which are related to acquisition, and secondary costs (costs of effects), which are related to costs of therapy failure and side effects.[155] Given that the benefits of newer therapies lie mainly in their efficacy and safety profiles, economic analyses need to include the secondary costs associated with these outcomes. IFIs are often difficult to diagnose, resistant to treatment and associated with high rates of failure, which makes the secondary costs particularly important.[154] Although the economic burden of hospitalisation due to IFIs in Australian hospitals has been reported,[14] studies on the economics of individual antifungals are lacking. In a 2005 review of antifungal treatment,[154, 155] only 15 economic evaluations of systemic antifungal therapy were identified, most of which examined prophylaxis, two examined empirical treatment and two examined the treatment of confirmed infections; none of the papers was from Australia. Nearly all the published pharmacoeconomic studies[155-168] were comparisons of a high-cost antifungal agent versus cheaper conventional amphotericin B and/or azoles (i.e. fluconazole and itraconazole).

Economic evaluations are carried out to identify, measure and value costs and consequences of alternatives, which aid healthcare providers in deciding on the most efficient interventions to use.[169, 170] Four basic economic evaluation models are commonly used. These are cost-effectiveness, cost-minimisation, cost-benefit and cost-utility analyses. A cost-effectiveness analysis presumes similar outcomes (effects) that have different values. This analysis compares the cost per unit of effect (or the effect per unit of cost) among the different alternatives. In cost-minimisation analysis, alternatives have similar effects that have equal value. This type of analysis determines the alternative with the least associated cost. With cost-benefit analysis, alternatives have similar or different outcome effects, which are given monetary values and compared accordingly. In cost-utility analysis, different levels of a health status are assigned different values, upon which, alternatives are compared.[169-171] Regardless of the model used, the number of economic studies is increasing, along with a greater acknowledgment of their usefulness in healthcare decision making.

Table 2-3. Prices of currently used antifungals in Australia

Drug	Price
Conventional amphotericin B	AU$34.65 / 50 mg intravenous vial, AU$12.03 / intravenous vial (10 mg)[172]
Liposomal amphotericin B	AU$295.00 / intravenous vial (50 mg)[173]
Terbinafine	AU$37.36 - 49.93 / 42 tablets (25 mg)[172, 173]
Itraconazole	AU$246.79 / 60 capsules (100 mg)[172]
Fluconazole	AU$26.60 / 28 capsules (50 mg), AU$51.81 (100 mg), AU$72.94 / 28 capsules (200 mg)[173]
Voriconazole	AU$2,484.72 - 2,631.08 / 56 tablets (200mg),[172, 173] AU$190.84 / Intravenous vial (200 mg)[178]
Posaconazole	AU$669.50 - 711.62 / oral suspension (50 mg / mL, 105 mL)[172, 173]
Caspofungin	AU$700.00 / intravenous vial (50 mg), AU$700.00 / intravenous vial (70 mg)[173]
Anidulafungin	AU$695.00 / intravenous vial (100 mg)[a]

[a]Wang J, Pfizer Australia, personal communication, 2010 March 25.

2.9.1 ECONOMIC ANALYSIS

In the general sense, economic analysis compares the outcome of decision options in terms of their monetary value per unit effectiveness. This enable prioritising in the allocation of resources and in deciding among different therapies based on their values as expressed in monetary terms. An economic analysis can be briefly described in six steps.[174-177]

The first step is to identify the problem. This involves breaking the problem down into its components, comprising identification of the alternative courses of action taken by the decision maker; identification of the events that follow the first course of action and its alternatives; and identification of possible outcomes.

The second step is to define the perspective of the study. This determines the costs that should be collected, valued and included in the analysis. The common perspectives of economic evaluations are hospital and social perspectives.

The third step is to describe the full range of events and consequences resulting from the intervention. This is best achieved using a decision analytic model (decision tree) as the conceptual framework for the analysis. Decision analysis is a systemic quantitative approach for assessing the relative value of the different decision options. A decision analytic model is constructed and probability data are collected for the various consequences and outcomes.

Step four is to identify the outcomes that are considered as benefits. For instance, the interest can be to measure the monetary value for success or death prevented.

Step five is based on the analysis of the decision tree, where an estimate of the net benefit of one intervention over another is produced. The net cost difference between one intervention and another is also calculated. Cost-effectiveness is expressed as the ratio of the net cost to the net benefit.

The last step is sensitivity analysis, which is to assess the stability of the conclusion to assumptions made in the analysis, and also to identify reasons behind differences in costs between interventions.

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CHAPTER THREE: EMPIRICAL ANTIFUNGAL THERAPY IN FEBRILE NEUTROPENIA

As discussed in the outline of thesis (**Chapter One)**, this chapter provides an introduction to studies in **Chapters Four**, **Five** and **Six**. It explains febrile neutropenia and the use of empirical antifungal therapy, and reviews the empirical use of the current antifungal agents.

3.1 MANAGEMENT OF FEBRILE NEUTROPENIA

A body temperature that is higher than the normal temperature is an expression of fever. This elevation in temperature is defined as a single oral temperature of ≥ 38.5 °C or an oral temperature of ≥ 38.0 °C for more than four hours, without apparent environmental causes. Neutropenia is defined as an absolute neutrophil count of < 0.5 x 10^9/L, or < 1.0 x 10^9/L, but with an expected reduction to < 0.5 x 10^9/L. A neutrophil count that is < 1.0 x 10^9/L translates into an increased susceptibility to infections, with the occurrence and intensity of infections being conversely related to the neutrophil count.[1] Both the depth and duration of neutropenia are important factors to consider in the anticipation of invasive fungal infections (IFIs). Patients experiencing neutropenia of duration less than seven days seem to be at minimal risk for developing IFI, although IFI can still occur, whereas those with neutropenia persisting beyond 21 days are at significant risk of developing IFI, with one study showing a four-fold increase in the risk of developing aspergillosis with profound neutropenia persisting beyond 21 days.[2]

Because of the impaired immune response in patients with neutropenia, usual symptoms of inflammation will be lacking.[3] Fever with no symptoms of inflammation is the frequent manifestation of infection in patients with febrile neutropenia. In over 50% of patients who have fever with neutropenia, clinical or microbiological substantiation of infections cannot be established. Attempts to establish a correlation between particular organisms and the fever with neutropenia have been made, but have not been encouraging.[4, 5]

Fever of unknown origin is defined as the febrile state that is not supported by a clinical diagnosis when pathogens cannot be isolated, or by confirmed infection and established microbiological evidence.[6]

Empirical therapy has demonstrated usefulness, as clinical studies have established that therapeutic outcomes were considerably better in patients with fever of unknown origin than in patients with clinical and/or microbiological documentation of infection.[7, 8] Currently,

in practice, with the onset of fever of unknown origin, broad-spectrum empirical antibiotic therapy is commenced. If fever is resolved, the antibiotic therapy will be ceased. If fever persists for three to seven days despite the antibiotic therapy, empirical antifungal therapy will be initiated.[9-11] The concept of empiric antifungal therapy seems to be well established as the standard of care for patients with prolonged febrile neutropenia.[12] The rationale behind empirical use of antifungal agents, in which therapy is initiated for patients who are noted to have fever of unknown origin that is resistant to antibiotic therapy without definitive proof of IFI, is that the early definitive diagnosis of IFI is difficult and often insensitive. Moreover, antifungal therapy initiated upon diagnosis of established fungal infection is often ineffective.[13]

Fever is the primary exclusive reason behind commencing empirical antifungal therapy, and its resolution is the primary signal for stopping the antifungal therapy. The notion of initiating empirical antifungal therapy as a strategy is widely debatable, as it is argued that fever is not specific to IFIs. Hence, a pre-emptive approach was introduced, where antifungal therapy is reserved until an early diagnosis of infection, with a view to reducing drug use, toxicity and costs. Pre-emptive therapy was shown to reduce antifungal drug use by 78%.[14, 15] A recent randomised clinical study has shown, however, that pre-emptive antifungal therapy, despite demonstrating general non-inferiority over empirical therapy in terms of survival rate, was associated with increased incidence of IFIs as well as a lower survival rate for patients receiving induction chemotherapy.[14] The pre-emptive strategy of IFI management requires the use of refined accurate and sensitive new diagnostic tools, facilitating early diagnosis of IFI and, hence, enabling the administration of antifungal therapies only to those patients who need them. Whilst the principle is sound, in current clinical practice, however, this strategy is difficult to implement because such accurate and sensitive diagnostic tools are lacking, and therefore, IFI diagnosis remains a major challenge (see **Chapter Two**). With pre-emptive therapy, there is a risk that some patients who show evidences of IFI during febrile neutropenia will not receive antifungal therapy in a timely manner, as the existing diagnostic tools may report a 'false negative', leading to misdiagnosis. Such risk overweighs any possible reductions in costs and toxicities associated with the strategy. More sensitive and accurate IFI diagnostic tools, supported by firm guidelines regarding clinical and radiological IFI diagnostic criteria, should become available before pre-emptive therapy becomes a standard of care.

3.2 EMPIRICAL ANTIFUNGAL THERAPY

From the available antifungal armamentarium, a variety of agents has been employed for empirical use. Ideally, an antifungal agent for empirical use should have demonstrated activity against the most common causative fungi for IFIs; namely, *Aspergillus* and *Candida* species. Conventional amphotericin B, active against both *Aspergillus* and *Candida* infections, has been the drug of choice for many decades; however, it has a very unfavourable safety profile, including severe infusion-related reactions and renal toxicity.[16] This has led to the search for alternatives. Fluconazole is ineffective empirically if the suspected organism is *Aspergillus*, which significantly limits its clinical usefulness.[17] Itraconazole has been shown to be effective as empirical therapy. It is cheap, but has a poorer safety profile than fluconazole. It also has a poor bioavailability profile and some clinically significant drug interactions. As a result, itraconazole has been superseded by newer antifungal agents, and is now not routinely used.[18-22] Liposomal amphotericin B (LAmB), voriconazole and caspofungin have shown similar efficacy and better tolerability than conventional amphotericin B, and they are being used successfully for empirical therapy.[23] Posaconazole is a recently available antifungal agent, which demonstrated high efficacy as well as safety;[24] however, its success as empirical therapy has not been demonstrated, and it is not being used empirically. The mechanisms, safety profiles and dosing regimens of these agents have been previously discussed in **Chapter Two**.

Given the large price differences between the cheap and older antifungals (i.e. conventional amphotericin B and itraconazole) and the recently available antifungal agents (i.e. LAmB, voriconazole and caspofungin), which are significantly more expensive,[25] the net economic impact of the empirical use of these agents is of particular interest.

In an open-label, randomised, comparative trial between LAmB and voriconazole for empirical therapy in neutropenic patients,[26] voriconazole did not achieve statistical non-inferiority according to a composite endpoint. Nevertheless, the researchers concluded that voriconazole is a suitable alternative to amphotericin B preparations. This conclusion was made partly because of fewer breakthrough fungal infections in the voriconazole treated patients (1.9% versus 5.0%); however, to depend on a single outcome of the composite endpoint for this conclusion is contrary to the reported 'Method' section of the same study, which notes that the secondary analysis of individual composite endpoints was an exploratory assessment and was not intended to be a primary determination of outcome superiority. In addition, the analysis of the other components of the composite endpoint favoured LAmB over voriconazole. To confuse the issue further, correspondents from the Food and Drug Administration (FDA) provided data indicating that voriconazole was statistically inferior to

LAmB with respect to overall success rates (23.7% versus 30.1% respectively).[27] As a result, the members of FDA's Antiviral Drugs Advisory Committee voted unanimously against accepting empirical use of voriconazole in neutropenic patients with fever. Thus, whether voriconazole shows equivalence, near equivalence or frank inferiority to LAmB remains unclear. Nevertheless, voriconazole was associated with fewer breakthrough fungal infections, which is an important efficacy parameter with potential economic benefits. Considering voriconazole's safety profile, this may suggest that it is a suitable alternative for empirical use. A potential advantage of voriconazole is the ability to change patients from intravenous administration to the oral formulation. In the same clinical trial,[26] changing to oral voriconazole in 22% of patients in the voriconazole arm reduced the duration of hospitalisation by an average of one day in all patients, and by two days in high-risk patients. Available economic evaluations of voriconazole as empirical therapy are limited, as will be discussed in **Chapter Four** and, hence, its usefulness and cost-effectiveness as empirical treatment remain unresolved, especially in Australia.

A double-blind, randomised, multi-centre clinical trial showed caspofungin to be non-inferior to LAmB as empirical treatment according to a composite endpoint,[28] where overall response rates were similar between the two. Treatment-related toxicity was lower for caspofungin. Successful treatment in the case of baseline fungal infections was higher for caspofungin, and survival after therapy was better. Nonetheless, absence of breakthrough fungal infections and resolution of fever were higher with LAmB compared to caspofungin. The study suggested that caspofungin is a suitable alternative for empirical treatment; however, given that LAmB and caspofungin were non-inferior to each other and that both are high-cost agents,[25] a health economic assessment would provide important additional information on caspofungin as empirical therapy. The economics of caspofungin as empirical therapy have been recently reported.[29-32] These studies, however, are limited, as discussed in **Chapter Five**, and are not from the Australian setting.

Although both voriconazole and caspofungin are being successfully used for empirical therapy, there are no studies in the literature that directly compare the two in the empirical setting, either in terms of efficacy or in terms of cost-effectiveness.

In summary, conclusions about the cost-effective prescribing of high-cost antifungals for empirical antifungal therapy are difficult to make. To date, there is very limited pharmacoeconomic data in the literature, especially from the Australian perspective, that can be used to guide Australian pharmacists and clinicians in the selection of antifungals for empirical treatment of febrile neutropenia. While recent studies on the economics of high-cost empirical therapies have been reported,[29-33] in addition to being limited, they were from other countries and may not be applicable in the Australian healthcare setting. Accordingly, pharmacoeconomic data related to comparisons among the high-cost antifungals (i.e. LAmB,

voriconazole and caspofungin) are urgently needed to assist prescribers in general and Australian prescribers in particular in optimising the selection of these antifungals in an atmosphere of increasing healthcare costs and financial constraints.

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CHAPTER FOUR: COST-EFFECTIVENESS EVALUATION OF VORICONAZOLE VERSUS LIPOSOMAL AMPHOTERICIN B AS EMPIRICAL THERAPY FOR FEBRILE NEUTROPENIA IN AUSTRALIA

As discussed in **Chapter Three**, comparative pharmacoeconomic data among high-cost antifungals for empirical use in febrile neutropenia are lacking. The following work is an economic evaluation of the empirical use of voriconazole versus liposomal amphotericin B in patients with febrile neutropenia in Australia.

The following material is arranged in a manner suitable for publication in the Journal of Antimicrobial Chemotherapy. Headings, figures and tables are renumbered in order to generate a consistent presentation within the thesis.

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DECLARATION FOR THESIS CHAPTER FOUR

In the case of Chapter Four, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Conception and design. Literature search. Data collection. Statistical experience. Analysis and interpretation. Writing the article. Critical revision of the article.	85%

The following co-authors contributed to the work:

Name[a]	Nature of contribution
David CM Kong	Conception and design. Critical revision of the article. Final approval of the article.
Kay Stewart	Conception and design. Critical revision of the article.
Danny Liew	Design. Statistical experience. Critical revision of the article.

[a]None of the co-authors is a student co-author.

Candidate's signature _____ Date _____

DECLARATION BY CO-AUTHORS

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and

(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	Department of Pharmacy Practice - Faculty of Pharmacy and Pharmaceutical Sciences - Monash University, Melbourne, Australia.

David CM Kong	[redacted]	Date	19/11/09
Kay Stewart	[redacted]		19/11/09
Danny Liew	[redacted]		17/11/9

4.1 STUDY TITLE

Cost-effectiveness evaluation of voriconazole versus liposomal amphotericin B as empirical therapy for febrile neutropenia in Australia.

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4.3 ABSTRACT

Objectives: A major randomized clinical trial, evaluating voriconazole versus liposomal amphotericin B (LAMB) as empirical therapy in febrile neutropenia, recommended voriconazole as a suitable alternative to LAMB. The current study sought to investigate the health economic impact of using voriconazole and LAMB for febrile neutropenia in Australia.

Methods: A decision analytic model was constructed to capture downstream consequences of empirical antifungal therapy with each agent. The main outcomes were: success, breakthrough fungal infection, persistent baseline fungal infection, persistent fever, premature discontinuation and death. Underlying transition probabilities and treatment patterns were derived directly from trial data. Resource use was estimated using an expert panel. Cost inputs were obtained from the latest Australian representative published sources. The perspective adopted was that of the Australian hospital. Uncertainty and sensitivity analyses were undertaken via the Monte Carlo simulation.

Results: Compared with voriconazole, LAMB was associated with a net cost saving of AU$1422 (2.9%) per patient. A similar trend was observed with the cost per death prevented and successful treatment. LAMB dominated voriconazole as it resulted in higher efficacy and lower costs when compared with voriconazole. The results were most sensitive to the duration of therapy and the alternative therapy used post discontinuations. In uncertainty analysis, LAMB had 99.8% chance of costing less than voriconazole.

Conclusions: In this study, which used the current standard five component endpoint to assess the impact of empirical antifungal therapy, LAMB was associated with cost savings relative to voriconazole.

Keywords: economics, model, empirical antifungal.

4.4 INTRODUCTION

Empirical antifungal therapy is well established as the standard of care for febrile neutropenic patients,[1] the rationale being that early definitive diagnosis of invasive fungal infection (IFI) is difficult. Diagnostic investigations are often insensitive. Moreover, antifungal therapy initiated in patients with established fungal infection is mostly ineffective.[2]

Liposomal amphotericin B (LAMB) (Ambisome®, Gilead Sciences) and voriconazole (Vfend®, Pfizer) are two antifungals that have been used successfully in empirical therapy.[3] In an open-labelled randomized trial by Walsh *et al*.,[4] which compared LAMB with voriconazole for empirical therapy in neutropenic patients, voriconazole appeared to be inferior in preventing the composite endpoint of survival, breakthrough fungal infections, premature discontinuations, persistence of baseline fungal infections and fever persistence. Nevertheless, the authors concluded that voriconazole is a suitable alternative to amphotericin B preparations. This conclusion was driven by the fewer breakthrough fungal infections observed among voriconazole-treated patients (1.9% versus 5.0%). However, this is controversial, given that all the other endpoints favoured LAMB. Data analysed by the US Food and Drug Administration (FDA) suggest that voriconazole was inferior to LAMB with respect to overall success rates (23.7% versus 30.1%, respectively).[5] As a consequence, the FDA's Antifungal Drugs Advisory Committee voted unanimously against accepting the empirical use of voriconazole in neutropenic patients with fever.

An advantage voriconazole maintains over LAMB, however, is its significantly lower acquisition costs. Indeed, since voriconazole became available, it has been accepted as an

effective alternative to LAMB for use as a first-line empirical therapy in Australian hospitals as well as in many practices worldwide.[6,7] In a recent study by Collins *et al*.,[8] voriconazole was suggested to be more cost-effective than LAMB for empirical use in febrile neutropenia. The study was from the US perspective, and represented practice at the authors' local institution only. Surprisingly, apart from the study by Collins *et al*., there are no pharmacoeconomic data regarding the empirical use of voriconazole versus LAMB. Indeed, from the Australian hospital perspective, no economic evaluations have been performed yet on voriconazole and/or LAMB, and thus, their financial impact as empirical therapy remains unresolved.

Accordingly, the objective of the current study was to investigate the pharmacoeconomics of using voriconazole versus LAMB as first-line empirical antifungal for the treatment of febrile neutropenia in Australia.

4.5 MATERIALS AND METHODS

This pharmacoeconomic modelling study was based on extrapolation of data from the randomized trial, performed by Walsh *et al*.,[4] of voriconazole versus LAMB for the empirical treatment of febrile neutropenia. In this trial, a total of 837 patients were randomly assigned to receive voriconazole or LAMB. The therapy was considered to be successful if the patient did not experience breakthrough fungal infection, survived for 7 days beyond the end of therapy, did not discontinue therapy prematurely, had resolution of fever during the period of neutropenia and was successfully treated for any baseline fungal infection.

4.5.1 PERSPECTIVE

The economic analysis was performed from a hospital perspective. Only direct medical costs for treating fungal infections were included. These included costs of diagnostic and monitoring tests, medical therapy, concomitant medications, hospitalization and duration of therapy. Direct medical costs related to other underlying diseases were not included. Indirect hospital costs (e.g. staff salary) were also not included.

4.5.2 MODEL STRUCTURE

Decision analysis[9] was applied to the comparison of voriconazole and LAMB, the structure of which is illustrated in **Figure 4-1**. At the base case scenario, the model was analysed based on a regular cohort simulation analysis, and did not involve Markov modelling or Monte Carlo simulation.

For each of the antifungals, the model included eight possible treatment outcomes depending on whether the initial treatment was successful, and if not, for what reason. Febrile neutropenic patients treated with either voriconazole or LAMB were initially assigned to one of the two pathways depending on whether patients had baseline fungal infections. Patients without a baseline infection continued therapy until it succeeded, or failed because of: death, breakthrough fungal infections, premature discontinuations or persistent fever. Patients with baseline fungal infections continued therapy until it succeeded, or failed because of death or persistent baseline fungal infections.

Following initial treatment with either of the medications, patients who had failed therapy, for any reason other than death, were switched to any other licensed antifungal therapy. No specifications were made regarding when therapy ended. All patients were followed until death or successful therapy. Success was the result of either initial therapy or alternative therapy.

4.5.3 MODEL INPUTS

The model was populated with data derived primarily from the trial. These included clinical outcomes rates, morbidity and mortality, duration of initial therapy and reasons for treatment failure. The clinical outcomes and their probabilities as per Walsh *et al*.[4] are summarized in **Table 4-1**.

An independent expert panel was convened, comprising four clinicians from Australia with clinical expertise in systemic antifungal therapy and specialist knowledge in oncology, haematology and infectious diseases. The panel advised on additional analyses of the data by Walsh *et al*. where appropriate. The panel also provided information on the economic consequences of the treatment pathway, which was not available from the literature. This included concomitant antibiotics, screening tests for fungal infections, monitoring tests for side effects and intensive care management [intensive care unit (ICU) data related to changing intravenous (iv) tubes and procedures that are not related to IFI were not included in the study].

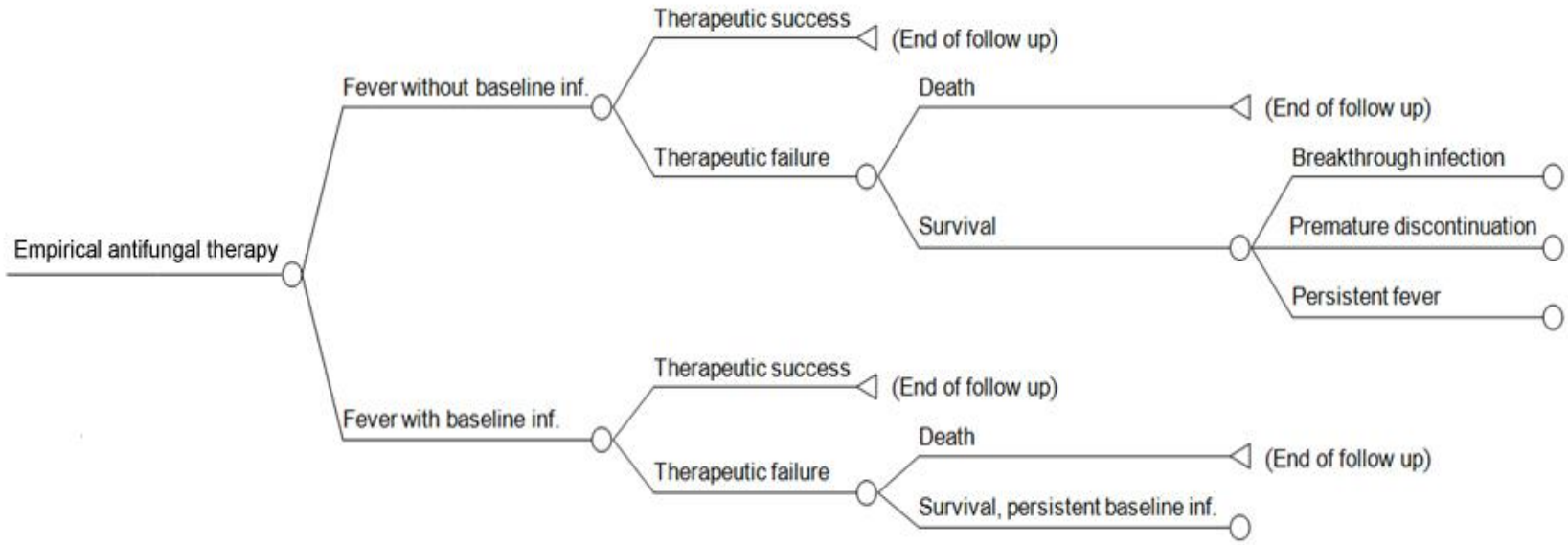

Figure 4-1. Decision analysis model of a typical empirical antifungal (i.e. voriconazole and LAMB) therapy for febrile neutropenia.

In addition, the panel was used to advise on the alternative therapies used after initial therapy discontinuations. These were as per the Australian hospital setting, and included the name, dose and duration of administration of the alternative antifungals. The choice of alternative therapy was dependent on the reason for treatment discontinuation.

Where breakthrough infections and baseline infections resulted in therapy discontinuations, the site of infection and the type of the infection's causative fungi reported by Walsh *et al*.[4] influenced the choice of the alternative antifungal. The expert panel also validated the decision tree model used in this study. An expert panel meeting was used to collect data.

Table 4-1. Outcomes and probabilities of voriconazole and LAMB[4] used in the model

Study clinical outcome	Probability with voriconazole (n = 415)	Probability with LAMB (n = 422)
Fever with no baseline fungal infection	96.87% (n = 402)	98.58% (n = 416)
therapeutic success	25.37% (n = 102)	30.05% (n = 125)
therapeutic failure	74.63% (n = 300)	69.95% (n = 291)
Death	11.00% (n = 33)	8.59% (n = 25)
breakthrough infection	2.67% (n = 8)	7.22% (n = 21)
premature discontinuation	13.67% (n = 41)	9.62% (n = 28)
persistent fever[a]	72.67% (n = 218)	74.57% (n = 217)
Fever with baseline infection	3.13% (n = 13)	1.42% (n = 6)
therapeutic success	46.15% (n = 6)	66.67% (n = 4)
therapeutic failure	53.85% (n = 7)	33.33% (n = 2)

[a]Number of patients with persistent fever = number of patients who failed therapy – number of patients who failed therapy because of other than persistent fever.

Prior to the meeting, the panel members were provided with a list of questions regarding the missing data, and with a copy of the paper by Walsh *et al*.[4] During the meeting, the members were asked to answer each of the questions, and were given the opportunity to discuss their answers until consensus was achieved.

As per Walsh *et al*.,[4] patients on voriconazole received a loading dose of iv 6 mg/kg twice on the first day, followed by daily maintenance iv dose of 3 mg/kg twice a day (or 200 mg tablet taken twice daily). Patients prescribed oral voriconazole received 3 days of iv therapy before commencing oral therapy. LAMB was administered as iv 3 mg/kg/day

throughout the treatment duration. For patients with baseline fungal infections, the maintenance voriconazole regimen was a twice daily iv 4 mg/kg or oral 300 mg, and the LAMB iv dose was 6 mg/kg/day. The oral voriconazole formulation was received by 22% of all patients on voriconazole. A reduction of LAMB dose to 1.5 mg/kg/day was permitted for some patients experiencing side effects.

According to the clinical study, baseline fungal infections are those diagnosed within 24 h after the initiation of therapy. Breakthrough fungal infections were defined as those diagnosed after 24 h of receiving antifungal therapy. For the purpose of the current study, patients with premature discontinuations were further classified as premature discontinuations because of severe side effects (i.e. infusion-related reaction, hepatotoxicity and nephrotoxicity) and premature discontinuation because of lack of efficacy against suspected fungal infection or persistent fever.

4.5.4 DATA PROVIDED BY EXPERT PANEL

On the basis of the median and range provided by Walsh *et al*.,[4] the duration of therapy was estimated to be 10 days for both voriconazole and LAMB. Granulocyte-colony stimulation factors (G-CSF) (i.e. filgrastim), piperacillin/tazobactam and vancomycin were given to patients concurrently. For both voriconazole and LAMB, patient monitoring comprised a daily complete blood count, as well as renal and liver function tests. As for diagnostic tests, a chest X-ray was performed at onset of therapy and then three times a week. All patients received a CT scan 3 days after commencing antifungal therapy and 40% of patients received a second follow-up scan. Blood and non-blood microbiological cultures (i.e. sputum, biopsy, diarrhoea and urine) were performed two to three times a week. The panel estimated that 7.5% of febrile neutropenic patients would spend 5 days in the ICU. In the ICU, patients received one bronchoscopy, an additional CT scan, tests of electrolytes every 3 days and daily monitoring of blood and non-blood microbiological cultures. It was estimated that 1.5% of patients on LAMB received a dose reduction from 3 mg to 1.5 mg/kg/day because of side effects. On the basis of the expert panel, all the 19 patients on voriconazole with premature discontinuation because of side effects, reported by Walsh *et al*.,[4] had severe hepatotoxicity. Out of the 23 patients on LAMB who discontinued prematurely because of side effects,[4] the expert panel estimated that 5 patients had infusion-related reactions, 16 patients had nephrotoxicity and 2 patients had hepatotoxicity. All patients with baseline infections, who failed therapy, survived and had persistent baseline infections. The antifungal alternatives given after the failures of each of the voriconazole and LAMB therapies are as in **Tables 4-2** and **4-3**.

4.5.5 DOCUMENTATION OF COSTS

The respective cost was assigned to each outcome of the decision tree to determine the total cost:

i. In the case of successful treatment, the cost was a result of the duration of hospitalization caused by febrile neutropenia.
ii. In the case of therapeutic failure, two possible results were obtained:
    a. For surviving patients who did not respond to initial treatment, the cost included additional costs resulting from changing treatment procedures and giving alternatives that were associated with prolonged hospitalization and drug administration.
    b. In cases where patients died, as with the successful treatment, the cost was a result of duration of hospitalization caused by febrile neutropenia.

Table 4-2. Alternatives for voriconazole and LAMB after premature discontinuations

Cause of premature discontinuation	Alternative	Details
Voriconazole		
severe infusion-related reactions	LAMB	3 mg/kg/day
severe nephrotoxicity	Caspofungin	Standard[a]
severe hepatotoxicity	LAMB	3 mg/kg/day
lack of efficacy against suspected fungal infection	LAMB	5 mg/kg/day
lack of efficacy against persistent fever	LAMB	3 mg/kg/day
LAMB		
severe infusion-related reactions	Voriconazole	Standard[b]
severe nephrotoxicity	Voriconazole	Standard[b]
severe hepatotoxicity	Caspofungin	Standard[a]
lack of efficacy against suspected fungal infection	Posaconazole	800 mg/day
lack of efficacy against persistent fever	Voriconazole	Standard[b]

[a]70 mg/day (loading dose), 50 mg/day (maintenance dose) .

[b]6 mg/kg twice daily (loading dose), 3 mg/kg twice daily (maintenance dose).

The following assumptions were made with respect to determining costs in the present study:

i. The average patient does not pay for treatment and is covered by Medicare.

ii. Patients are inpatients throughout the study period.

iii. The number of hospitalization days due to febrile neutropenia can be established by the duration of antifungal therapy.

Table 4-3. Alternatives for voriconazole and LAMB after breakthrough fungal infection, non-responding baseline fungal infection and persistent fever

Cause of Therapy Failure	Alternative	Details
Voriconazole (breakthrough fungal infection)		
Aspergillus species	LAMB	5 mg/kg/day
Candida species	Caspofungin	Standard[a]
Zygomycetes	LAMB	5 mg/kg/day
Voriconazole (non-responding baseline fungal infection)		
Aspergillus species	LAMB	5 mg/kg/day
Candida species	Caspofungin	Standard[a]
Zygomycetes	LAMB	5 mg/kg/day
Voriconazole (persistent fever)	LAMB	5 mg/kg/day
LAMB (breakthrough fungal infection)		
Aspergillus species	Posaconazole/LAMB	Combination[b]
Candida species	Caspofungin/Fluconazole	Combination[c]
Dematiaceous mould[s]	Voriconazole/Terbinafine	Combination[e]
LAMB (non-responding baseline fungal infection)		
Aspergillus species	Posaconazole	800 mg/day
Candida species	Caspofungin	Standard[a]
Trichoderma fungemia	Voriconazole	Standard[f]
LAMB (persistent fever)	Voriconazole	Standard[f]

[a]70 mg/day (loading dose), 50 mg/day (maintenance dose).

[b]800 mg/day posaconazole with 3 mg/kg/day LAMB. LAMB will cease when posaconazole steady state is reached.

[c]70 mg/day (loading dose) and 50 mg/day (maintenance dose) caspofungin with 200 mg/day fluconazole.

[d]*Dematiaceous* moulds were of *Alternaria* species and unidentified species.

[e]6 mg/kg twice daily (loading dose) and 3 mg/kg twice daily (maintenance dose) voriconazole with 250 mg/day terbinafine.

[f]6 mg/kg twice daily (loading dose), 3 mg/kg twice daily (maintenance dose).

iv. Antifungal therapy can fail only once. If patients switch therapy after failing the initial therapy, their alternative therapy will be successful.

v. No specifications were made about durations for alternative therapies. Any alternative therapy was assumed to have duration similar to that of the discontinued initial therapy.

All assumptions were validated by the expert panel.

4.5.6 COST CALCULATIONS

The model was used to generate a weighted average cost for patients treated with voriconazole or LAMB. This was calculated as the sum-product of the costs of the eight treatment outcomes and their respective probabilities.

The cost of each failed treatment pathway, except for death, was calculated by adding both the cost of initial antifungal therapy and the cost of alternative therapy to the cost of resources consumed. The cost of the initial therapy was calculated as the cost of a complete course of voriconazole or LAMB according to the number of days of therapy before changing to alternatives. The cost of an alternative therapy was the cost of a complete course of the alternative agent according to the number of days spent on it. The cost per successfully treated or dead patient was calculated as a proportion of both the cost of a complete course of voriconazole or LAMB and the resource used according to the number of days before the therapy ended.

For the purpose of calculations regarding medication doses, all patients were assumed to have an average body weight of 76.05 kg. This is based on the latest available data from the Australian Bureau of Statistics: 2005 National Health Survey.[10] No average patient body weight was reported in the Walsh *et al.*[4] study. With respect to calculating the cost of antifungals, doses for all medications (except of posaconazole) were rounded to the nearest vial size. One or more patients on posaconazole were permitted to share the same posaconazole bottle. These were an attempt to mimic routine hospital practice.

All calculated costs were in Australian dollars for the financial year 2007-08, and no discounts were applied given the short time-frame of the analysis.

The cost inputs used in the modelling analysis are summarized in **Table 4-4**. While the inpatient and ICI hospitalization costs were based on gross (top down) cost estimations, the costing of drugs, and pathology and imaging tests was more micro-costing (bottom up) in nature. Apart from medication and hospitalization costs, all resource costs involved in the

study were obtained from the Australian Medicare Benefits Schedule Book (2007).[11] Medication costs involved in this study were obtained as drug wholesale prices, which are paid by Australian public hospitals, as per Health Purchasing Victoria tender (2007-2009).[12] The cost of hospitalization for febrile neutropenia (Code T62A), excluding the intensive care cost, was obtained from the 2006-07 Australian Refined Diagnosis-related Groups (AR-DRG),[13] and the cost of an ICU bed was as per Rechner and Lipman.[14] Hospitalization costs were adjusted for the financial year 2007-08 as per the 2008 Australian Health Consumer Price Index (CPI).[15]

Table 4-4. Resource costs[11-14]

Item	Unit	Unit cost (AU$)
Voriconazole	200 mg iv vial	190.84
	200 mg oral tablet	45.62
Liposomal AmB	50 mg iv vial	295.00
Caspofungin	50 mg iv vial	700.00
	70 mg iv vial	700.00
Posaconazole	105 mL oral suspension	669.50
Terbinafine	250 mg oral tablet	1.19
Fluconazole	200 mg oral capsule	2.61
Piperacillin/tazobactam	4.5 mg iv vial	24.00
Vancomycin	500 mg iv vial	5.45
Filgrastim	480 μg iv vial	240.70
Chest x-ray	1 test	35.35
CT scan	1 test	295.00
Non-blood culture	≥ 1 tests (1 culture)	34.00
Blood culture	1 test (1 culture)	30.95
Bronchoscopy	1 test	207.70
Complete blood count	1 test	17.20
Renal function test	1 test	139.90
Liver function test	1 test	19.80
Electrolytes test	1 test	24.90
ICU consultant	First day	320.00
	Subsequent day	237.40
Hospitalization	ICU per day	3002.00
	Inpatient per day	1113.00

4.5.7 SENSITIVITY ANALYSIS

One-way sensitivity analysis is the simplest and most commonly performed form of sensitivity analysis. Different scenarios produced by modifications of the values of several key variables and assumptions, in relation to costs and probabilities, were analysed to evaluate the robustness of the study conclusion.

The analysis involved a threshold analysis. For any variable, the highest and lowest values within a reasonable range of values were used as substitutes for the baseline value. Where the highest or lowest substitution changes the study conclusion, more values within the range were used to replace the baseline value. This was repeated until the exact variable value (threshold value) that changes the study conclusion was determined.

As wholesale prices are at the discretion of the pharmaceutical companies and, hence, may change in the future. Thus, the effect of changing the voriconazole and LAMB prices was evaluated. The effect of variations in the hospitalization cost was investigated as well. This is because despite the hospitalisation costs being available, they are known to be imprecise, as they are taken as daily average values. This is especially important in the current study, where precision may have been further compromised by the process of adjustment for inflation made via the use of the CPI. In addition, while drugs, imaging and pathology costs were calculated separately from the hospitalization costs, the use of gross hospitalization costs, as obtained from the AR-DRG, were total costs that included costs associated with pharmacy, imaging and pathology services that were consumed by febrile neutropenia patients, and as such, may introduce double counting. Excluding the costs of these services reduces the total daily hospitalisation costs from AU$1113 to AU$911. Data provided by the expert panel are also associated with some uncertainly, as they vary according to the local epidemiology of diseases and drug use, and also according to clinician behaviour and patient compliance. The sensitivity analysis, therefore, also evaluated the impact of estimations made by the expert panel, investigating and generalisability of results, in addition to their robustness. These included the duration of therapy, duration in ICU, ratio of patients with doses reduced because of side effects, dosage form of LAMB as alternative and dosage form of voriconazole as alternative. Model structure uncertainty concerning controversy about whether particular types of costs or practices should be included in the analysis was also evaluated. Here, the effect of excluding the cost of antibiotics and G-CSF, and the increase in dose with baseline infections, and the effect of the voriconazole dosage form given before discontinuation were also evaluated. The ranges over which key variables were varied are shown in **Table 4-5**.

The degree to which differences in patient distribution, between the voriconazole and LAMB groups, affected the overall cost differences, in isolation from all other input parameters, was of interest, and was evaluated via a scenario analysis, whereby alternative

scenarios were used to replace a base case scenario. The model's sensitivity to the probability of patient distribution in the decision tree was investigated by applying the probability data in the LAMB arm to the voriconazole arm, applying the probability data in the voriconazole arm to the LAMB arm and switching the probability data between the voriconazole and the LAMB arms. Another scenario analysed was the replacement of the probability of patient distribution in the LAMB arm with that reported in another clinical study on the empirical use of LAMB.[16]

Table 4-5. Variation range for variables in sensitivity analysis

		Variation range	
Variable	Base case	low	high
Liposomal amphotericin B (LAMB) cost/vial	AU$295.00	AU$147.50	AU$885.00
Voriconazole iv cost/vial	AU$190.84	AU$0.00	AU$190.84
Voriconazole oral (po) cost/tablet	AU$45.62	AU$0.00	AU$45.62
LAMB administration duration	10 days	5 days	15 days
Voriconazole administration duration	10 days	5 days	15 days
Hospitalization cost per day	AU$1113.00	AU$0.00	AU$2000.00
ICI duration	5 days	1 days	10 days
Voriconazole dosage form given before discontinuation (po: iv)	22:78	0:1	1:0
Voriconazole dosage form given as alternative (po: iv)	0:1	0:1	1:0
Counting for the costs of antibiotics and G-CSF	Yes	No	Yes
Replacement of the 5 mg/kg doses of alternative LAMB with 3 mg/kg doses	No	No	Yes
Increase in the doses of antifungals in the presence of baseline infections	Yes	No	Yes
Reduction in the dose of LAMB in the presence of side effects	Yes	No	Yes

The aforementioned sensitivity analyses are relatively simple to implement, especially as the number of parameters involved is relatively small. These, however, fail to consider the possible correlation or the underlying uncertainty about the inputs of interest, only focusing on a set of arbitrarily chosen values, regardless of the likelihood of each occurring in reality. These limitations can be overcome by what is known as probabilistic sensitivity analysis

(Monte Carlo simulation), which is a procedure where input parameters are considered as random quantities. Using the @Risk-5.0® analysis tool (Palisade Corporation, NY, USA), uncertainty analysis was performed, by means of the Monte Carlo simulation, to investigate the likelihood (probability) of LAMB having an economic advantage over voriconazole. Monte Carlo refers to a method whereby random input values, chosen across a range of a probability distribution of a model input, are simulated and the model is run for each simulated input set.[17] The resulting sample of outputs characterizes the output uncertainty, where obtaining accurate probabilistic sensitivity analysis typically requires 1000 or more model runs.[17] The clinical outcomes that affect the overall drug cost the most were also determined. One-way sensitivity analysis was performed with an assumed uncertainty of 10% for the probabilities of breakthrough fungal infection, premature discontinuation and persistent fever, and of 5% for all other probabilities in the decision tree. The corresponding costs were calculated, and 10 000 iterations were executed to obtain a distribution of the results. The input variables and their uncertainty distributions are shown in **Table 4-6**.

Table 4-6. Input variables and uncertainty distributions used in Monte Carlo simulation

	Uncertainty distribution	
Input variables	voriconazole	LAMB
Fever without baseline infection	Triangular distribution, 92.03%-96.87%-100%	Triangular distribution, 93.65%-98.58%-100%
therapeutic success	Triangular distribution, 24.10%-25.37%-26.64%	Triangular distribution, 28.55%-30.05%-31.55%
therapeutic failure	Triangular distribution, 70.90%-74.63%-78.36%	Triangular distribution, 66.45%-69.95%-73.45%
death	Triangular distribution, 10.45%-11.00%-11.55%	Triangular distribution, 8.16%-8.59%-9.02%
breakthrough infection	Triangular distribution, 2.40%-2.67%-2.94%	Triangular distribution, 6.50%-7.22%-7.94%
premature discontinuation	Triangular distribution, 12.30%-13.67%-15.04%	Triangular distribution, 8.66%-9.62%-10.58%
persistent fever	Triangular distribution, 65.40%-72.67%-79.94%	Triangular distribution, 67.11%-74.57%-82.03%
Fever with baseline infection	Triangular distribution, 2.97%-3.13%-3.29%	Triangular distribution, 1.20%-1.42%-1.49%
therapeutic success	Triangular distribution, 43.84%-46.15%-48.46%	Triangular distribution, 63.34%-66.67%-70.00%
therapeutic failure	Triangular distribution, 51.16%-53.85%-56.54%	Triangular distribution, 31.66%-33.33%-35.00%

4.6 RESULTS

4.6.1 COST OF EMPIRICAL THERAPY

The weighted average cost of empirical therapy per patient for voriconazole (AU$49 237) was higher than that for LAMB (AU$47 815). This represents an economic advantage of LAMB over voriconazole in the order of AU$1422 (2.9%) per patient. The contribution of different components in the overall cost of each of voriconazole and LAMB therapies is illustrated in **Figure 4-2**. For both medications, the persistent fever was the main contributing clinical outcome to the cost of therapy. The proportions and costs per patient for each pathway in the decision tree are shown in **Table 4-7**.

Higher probability of success and lower probability of death were associated with LAMB (30.57% and 5.92%, respectively) when compared with voriconazole (26.02% and 7.95%, respectively). The cost of success and survival per patient with LAMB (AU$156 412 and AU$50 824, respectively) was lower than that with the voriconazole (AU$189 228 and AU$53 489, respectively).

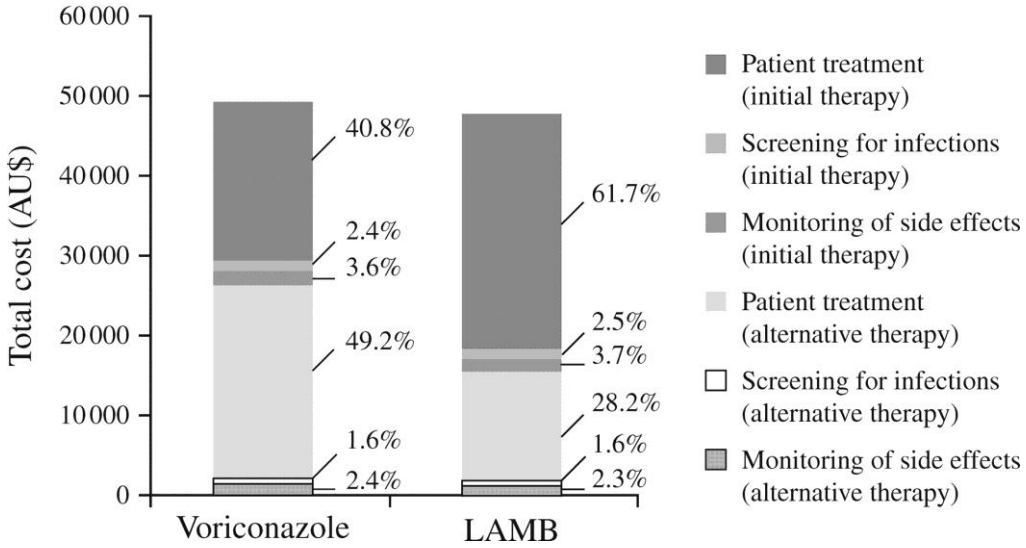

Figure 4-2. Contribution of different cost components in overall therapy.

Table 4-7. The proportional cost of empirical voriconazole and LAMB

	Voriconazole			LAMB		
Therapy outcome	proportion (%)	cost (AU$)[a]/ patient	proportional cost (AU$)[a]	proportion (%)	cost (AU$)[a]/ patient	proportional cost (AU$)[a]
Fever with no baseline infection						
therapeutic success	24.58	23 026	5659	29.62	32 322	9574
death	7.95	23 026	1831	5.92	32 322	1915
breakthrough infection	1.93	60 136	1159	4.98	61 123	3042
premature discontinuation	9.88	56 678	5600	6.64	55 150	3659
persistent fever	52.53	64 286	33 769	51.42	56 089	28 842
Fever with baseline infection						
therapeutic success	1.44	23 393	338	0.95	47 457	450
death	-	-	-	-	-	-
persistent baseline infection	1.69	52 180	880	0.47	70 356	333
Total cost per patient[b]			49 237			47 815

[a]All shown cost values were shortened to the nearest no-decimal digits status.

[b]Calculations involving cost values took in consideration 2 decimal digits (not-shown) associated with each of the cost values.

4.6.2 SENSITIVITY ANALYSIS

Sensitivity analysis indicated that the baseline cost difference (AU$1422) in favour of LAMB was not sensitive to changes in the medications acquisition costs. For voriconazole therapy to have the economic advantage, the price of LAMB had to increase by at least 280% to AU$826.00 per vial. Reducing the price of oral voriconazole to AU$0.00 only reduced the cost savings to AU$1280. Reducing the iv voriconazole price by at least 83% (AU$32.44 per vial) or reducing the price of both oral and iv voriconazole by at least 77% to AU$10.49 and AU$43.89, respectively, was needed for the voriconazole to have an economic advantage. Variations in the hospitalization cost, however, did not affect the study conclusion. Eliminating the daily hospitalization cost reduced the overall costs of voriconazole and LAMB to AU$30 758 and AU$29 616, respectively. This is a reduction in the cost savings to AU$1142. Increasing the daily hospitalization cost by almost 2-fold (AU$2000) increased the overall costs of voriconazole and LAMB to AU$63 964 and AU$62 318, respectively, which is an increase in the overall cost difference to AU$1646.

Regarding the estimations made by the expert panel, the model results were mostly sensitive to the duration of treatment for either of the antifungals. The overall voriconazole therapy had a lower total cost when the LAMB therapy duration increased from 10 days to at least 10.4 days, or when the voriconazole therapy duration was reduced from 10 days to at least 9.6 days. Changing the duration of LAMB therapy by ± 1 day resulted in ± AU$4577 in the value of the total cost saving, and a ± 1 day change in the duration of voriconazole therapy resulted in a ± AU$4710 change in the cost difference. The model was also sensitive to the dose of LAMB when given as an alternative. Replacing the 5 mg/kg/day doses of LAMB, used as alternative therapy after initial treatment failure with voriconazole, with 3 mg/kg/day doses resulted in total cost savings of AU$3560 associated with the use of voriconazole. The sensitivity to the time spent in ICU, tested within a range of 1-10 days, was negligible. A similar outcome was observed with switching all iv doses of the alternative voriconazole to oral doses, as well as with having no patients receiving LAMB dose reduction because of side effects.

The model was not sensitive to the scenario of having no increase in the voriconazole and LAMB doses when administered to patients with baseline fungal infections. It was also not sensitive to the scenario of excluding the costs associated with the use of concurrent antibiotics and G-CSF. However, the model demonstrated some sensitivity to the ratio of patients receiving oral voriconazole as initial therapy. When more than 65% of patients on voriconazole received the oral formulation, the total cost saving was obtained with voriconazole therapy. An overall cost saving of AU$1198 with voriconazole was achieved if all patients received oral voriconazole.

Two-way exchange in probability data between the voriconazole and the LAMB arms in the decision tree resulted in a cost saving of AU$14 associated with voriconazole. The one-way exchange in probability data, however, had no impact on the cost differentials. Even with replacing the LAMB probability data in this study with empirical LAMB data reported elsewhere in the literature,[16] the resulting cost saving (AU$2873) still remained associated with LAMB.

On the basis of the uncertainty analysis, the tornado diagram in **Figure 4-3** demonstrates the ranking of variables as per their impact on the model outcome. Derived from analysing the distribution of expected cost savings, which resulted from the 10 000 iterations of the Monte Carlo simulation, the mean cost saving was AU$28 494 in favour of LAMB per patient. There was 99.8% chance that LAMB would have mean cost saving of more than AU$1 over voriconazole. The maximum expected cost saving with LAMB was AU$60 517, while the maximum expected cost saving with voriconazole was AU$4850. A 'cost saving' probability curve is shown in **Figure 4-4**.

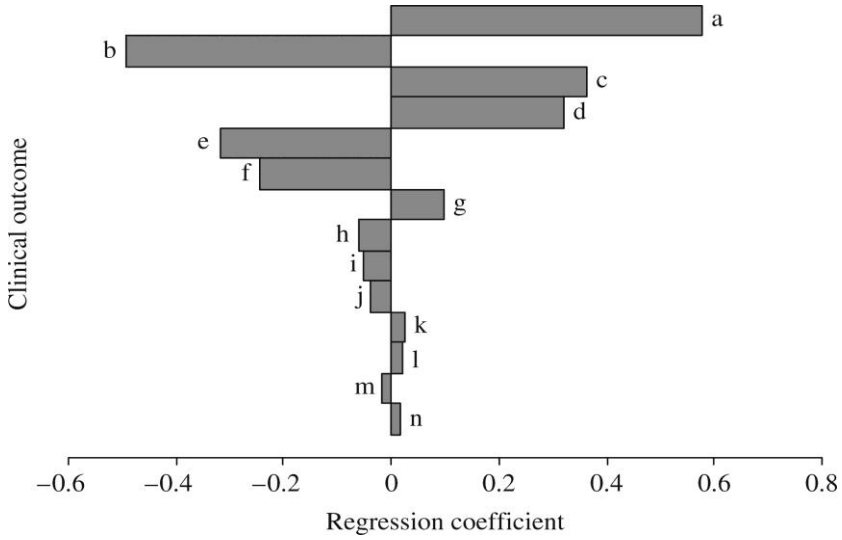

Figure 4-3. A tornado diagram for demonstrating the regression and ranking of variables as per their influence on the model outcome. The influencing variables are persistent fever with voriconazole (a), persistent fever with LAMB (b), therapeutic failure of fever without baseline infections with voriconazole (c), fever without baseline infection with voriconazole (d), therapeutic failure of fever without baseline infections with LAMB (e), fever without baseline infection with LAMB (f), premature discontinuation with voriconazole (g), premature discontinuation with LAMB (h), breakthrough infection with LAMB (i), therapeutic success with LAMB (j), therapeutic success with voriconazole (k), breakthrough infection with voriconazole (l), death with LAMB (m) and death with voriconazole (n).

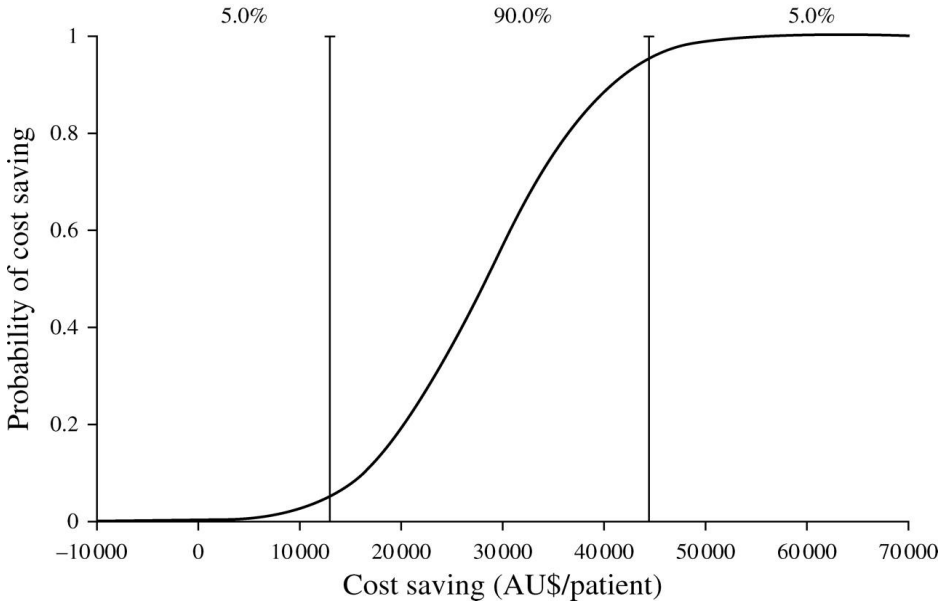

Figure 4-4. 'Cost saving' probability curve.

4.7 DISCUSSION

The present study is the first to investigate the pharmacoeconomics of using voriconazole and LAMB from an Australian perspective. The study compared the cost associated with patients receiving voriconazole versus LAMB as first-line empirical therapies for treating patients with febrile neutropenia. According to the analysis, LAMB demonstrated a total cost saving of AU$1422 per patient (**Table 4-7**). The cost per patient successfully treated with LAMB was AU$32 816 lower than that with the use of voriconaze. The cost of survival was also lower with the use of LAMB (difference of AU$2665). On the basis of the data, LAMB appears to be a dominant empirical medication over voriconazole. It has higher efficacy (i.e. higher success rate and lower death rate) as well as lower total cost.

Life years gained is often the main outcome in pharmacoeconomic investigations.[18] However, for the purpose of the current study, no long-term-survival and quality-of-life data were available. Patients' survival was followed by Walsh *et al*.[4] for up to 7 days only, after median therapy duration of 7 days for both voriconazole and LAMB. Therefore, it was not possible for the present analysis to estimate the life years gained. Even with the application of Markov modelling for simulating long-term use,[19] the outcomes would not be very reliable

due to the inherited limitation of building the model using the short-term data from the Walsh *et al*. study.

The recent cost-effectiveness study by Collins *et al*.[8] has been the only study that directly compared empirical voriconazole with LAMB in febrile neutropenia. The study was from a US perspective, and it concluded that empirical voriconazole was associated with lower overall costs relative to LAMB, and thus, it should be preferred for the management of febrile neutropenia. Owing to the vast differences in modelling and methodology (see below), the conclusion made by Collins *et al*. is not directly comparable to that reported in the current study.

The construction of the decision tree in the current study was based on data collected prospectively by Walsh *et al*.[4] in a randomized double-blind controlled trial. This makes the study findings considerably more reliable than findings based on the model used by Collins *et al*., where data collection is retrospective in nature. A main limitation of the Collins *et al*. study is its retrospective nature that may lead to a selection bias.[20] The model by Collins *et al*.[8] was based on day-to-day clinical practice, and not randomized clinical trials (RCTs). Therefore, it had the advantage of providing a more accurate estimation of care, especially from the local institution's perspective. Nonetheless, Collins *et al*. only evaluated 63 patients in their study. The current study, however, used data from the trial by Walsh *et al*.,[4] involving 837 patients, considerably increasing the precision of data as model inputs.

RCTs are accepted as the most powerful tool for assessing the effectiveness of medications, interventions and procedures. By design, the blind and random assignment of adequate numbers of subjects in studies and the blind assessment of outcomes minimize bias due to observer and confounding factors from known and unknown variables.[21] In the context of economic evaluations, as an ideal, evaluation would be based on the best available clinical evidence, and an RCT would provide the most reliable source of data.[22] Indeed, conducting economic evaluation based on a clinical trial is an efficient way of getting valid and reliable information with minimum assumptions made during data collection.[23] Since 1994, more than 30% of the economic evaluations published on the United Kingdom's NHS Economic Evaluation Database, for instance, have been based on data from a single RCT.[24] However, while randomization minimizes the risk of selection bias, it does not insure the generalizability of results.[24] Thus, for the economic results of the current study to be applicable to the Australian setting, it is important for the results reported by the Walsh *et al*. trial to be generalizable (externally valid) to the Australian setting also. As per the expert panel, the clinical data by Walsh *et al*.[4] are in fact generalizable to Australia. The trial is a multicentre study where patients were recruited from a large number of study sites in several countries and continents. This reflected a variation in healthcare provisions within and among different systems, and increased the efficiency of trial-wide estimates. Also, the criteria for the

inclusion and exclusion of patients were specified in the trial, where the patients included reflected the normal Australian clinical caseload, and the fact that these inclusion criteria were unified for the wide range of study sites has reduced the threat to the trial generalizability. In addition, the administration of both voriconazole and LAMB in the trial is generally similar to that currently recommended in the Australian guidelines. A main indicator of the relevance of the outcomes of the Walsh *et al*. trial to real practice in Australia is the fact that the Walsh *et al*. study is being used as a reference in the current Australian guidelines in relation to the empirical use of voriconazole and LAMB in practice.[6,25]

A strength of the current model is that all patients were followed-up, even after discontinuing the initial treatment and quitting the randomized therapy. The economic model compared the overall cost associated with the group of patients who received voriconazole as initial therapy with that associated with the group of patients who received LAMB as initial therapy. The economic model did not compare between voriconazole and LAMB as initial therapies only. This provides a much more realistic cost and a better understanding of the full impact of using voriconazole and LAMB as first-line therapies. After all, the alternative therapies and, ultimately, their costs are impacted by the type of the initial antifungal used. Furthermore, constructing the current decision model considers all possible clinical patterns reported in the Walsh *et al*. study.[4] This is the first economic study where the structured decision tree fully reflects the standard five component endpoint (i.e. survival, breakthrough infection, persistence of baseline infection, fever persistence and premature discontinuation) currently used in assessing the efficacy of antifungals in empirical therapy.[26] This approach is highly valuable for the accurate representation of the overall cost of treatment. Including some of the treatment pathways while excluding others may result in the analysis overestimating or underestimating. A major limitation in the Collins *et al*.[8] study is that in the model used for the economic comparison, responding and not responding patients were subdivided entirely according to patient's experience with nephrotoxicity. No other key clinical outcomes that are usually associated with empirical therapies were considered. For instance, Collins *et al*. did not investigate the impact of breakthrough infections on cost. They noted, however, that if the breakthrough outcome was included in their analysis, LAMB would be associated with increased cost. The investigators based their assumption on the results reported by Walsh *et al*., where LAMB had a higher rate of breakthrough fungal infections when compared with voriconazole.[4] This argument, however, based on the observations in the current study, is not necessarily accurate. This is because Collins *et al*. did not consider the secondary costs associated with the alternatives given to manage the breakthrough infections. As shown in **Table 4-3**, the alternative to voriconazole is mostly the more expensive LAMB, while the alternative to LAMB can be the cheaper voriconazole and posaconazole. Therefore, LAMB having a higher rate for breakthrough infections does not routinely translate into it having a

higher overall cost. This emphasizes the need to examine each of the treatment pathways that are associated with the use of medications individually and fully.

The expert panel in the present study did not provide any cost data. It provided consensus estimates that focus on the hospital resources used in patient management. These could have been driven directly from available local hospital protocols. For the purpose of this study, however, the expert panel, which represents a wide variety of practices from different hospitals, was used to increase the external validity and generalizability of the results to patients outside the local hospital setting. According to the panel, screening and monitoring tests, ICU management, and antibiotics and G-CSF are not affected by the type of the empirical antifungal agents, and therefore, their frequency and nature were the same during both voriconazole and LAMB therapies. Owing to the absence of literature about the use of empirical antifungals as alternatives, the expert panel was the best available source to provide data regarding alternatives given after discontinuations. Importantly, the current study is rather unique in that the estimation of alternatives considered the site of infections, and the type of the infection's causative fungi (**Table 4-3**), which is not usually seen in other studies. Estimations made by the expert panel were based on their day-to-day clinical experience. This was to reflect the current Australian practice, rather than the theoretical situation reported in the literature. According to the expert panel, none of the patients with baseline infections failed therapy because of death. This was due to the small number of patients with baseline infections who did not respond to therapy (seven and two patients for voriconazole and LAMB, retrospectively). The cost of treating common side effects (e.g. visual disturbances, headache and hypokalaemia), frequently associated with the antifungals, was not included in the current study. This is because it was not possible for the expert panel to provide, with a high degree of reliability, estimations regarding the resources used to manage the side effects. It should be noted, however, that these side effects are usually moderate and do not cause discontinuations in therapy, and therefore, are not expected to affect the total cost.

The sensitivity analysis conducted on the dataset demonstrated that the overall economic conclusion of the study was not sensitive to changes in the acquisition costs of either or both voriconazole and LAMB. This goes against what one may expect as result of the significantly lower acquisition cost of voriconazole when compared with LAMB (approximately AU$332/day versus AU$1475/day, respectively), and is reflective of the role of voriconazole and LAMB as alternative antifungals. LAMB is a common alternative to voriconazole and will increase the total cost of patients treated initially with voriconazole. In contrast, voriconazole is a common alternative to LAMB, which will reduce the total cost associated with patients treated initially with LAMB. This observation highlights the need for clinicians to consider all costs related to treating patients, including both acquisition cost and secondary cost (cost of therapy failure), when making a decision in regard to prescribing a

medication. The hospitalization cost, with a value of AU$1113/day, constitutes a major component in the inpatients' cost of treatment. As one would anticipate, the elimination or the 2-fold increase in the daily cost for hospital stay, as per the sensitivity analysis, considerably affected the overall cost for both voriconazole and LAMB. Nonetheless, the overall economic conclusion made in the study was demonstrated to be insensitive to wide variations in hospitalization cost that covered expected uncertainty. This is to be expected given the similarity in patients' length of stay between the two arms of the study. This same argument also explains the lack of sensitivity to changes made in the ICU duration, whereby, the length of ICU duration is the same between the two study groups.

The sensitivity analysis demonstrated that a primary factor influencing the overall difference in cost was the duration of antifungal therapy, which is expected, as for both antifungals 1 day accounts for almost 10% of the total therapy cost. The difference in total daily cost was low between both antifungals (AU$4577 and AU$4710 for LAMB and voriconazole, respectively). This is also expected given the low 2.9% difference between the overall therapy costs for both agents. The analysis also determined that another primary factor, which influences the economic outcome, is the dose of LAMB when it is given as an alternative. On many occasions in the current study, the expert panel felt that a high 5 mg/kg/day was an appropriate dose of LAMB given as an alternative after failure with initial voriconazole (**Tables 4-2** and **4-3**). Unsurprisingly, this substantially increased the total cost of treating patients who commenced initial therapy with voriconazole. When cost analysis was performed after reducing the LAMB doses from 5 to 3 mg/kg/day, the overall cost saving was significantly shifted in favour of voriconazole as initial therapy. This accentuates the key role played by the current local antifungal-switching practices in influencing the overall cost of empirical therapy. Indeed, voriconazole and LAMB had different numbers of discontinuations, and ultimately, different numbers of resources used. Nevertheless, the difference in the overall therapy costs between voriconazole and LAMB was highly dependent on the antifungals used for the alternative therapy (**Figure 4-2**). In the study by Collins *et al*.,[8] 52% of the patients on LAMB did not respond to therapy, and therefore, their LAMB doses were increased from 3 to 5 mg/kg/day. The increase in dose was for 4 days out of the 7 day LAMB course. This could be one of the main factors that contributed to the higher total cost of LAMB reported by Collins *et al*.[8]

In the study by Walsh *et al*.,[4] dose reduction of LAMB to 1.5 mg/kg/day was permitted with the presence of side effects, which potentially decreases the total cost of LAMB. Nevertheless, applying the scenario where LAMB dose reduction was not allowed did not affect the economic outcome of the current study. This could be because only 1.5% of patients (estimated by the expert panel) receiving LAMB required dose reduction. Importantly, the sensitivity analysis illustrated that prescribing oral voriconazole instead of iv

voriconazole as initial therapy would reduce the total cost associated with voriconazole. However, the use of oral formulations of voriconazole is not always possible, especially in cases where patients have impaired gastrointestinal functions (i.e. mucositis).

The only switch in the overall probability of distribution for variables that affected the study conclusion is the two-way switch made between the two study arms. Nonetheless, the resulting cost saving with voriconazole was only AU$14. It appears that, in the current study, the difference in the overall probability of distribution for variables between both arms is not a key factor behind any wide cost differentials measured between the two antifungals. However, according to the uncertainty analysis (**Figure 4-3**), some individual variables can potentially affect the study outcomes. The individual variables that affected the model the most were persistent fever, therapeutic failure of febrile patients without baseline infections and/or fever without baseline infections. This is expected as these variables have the highest ratios of patient distribution among all variables, which translates into longer overall hospital stay, and ultimately, higher overall cost, especially where the costs of hospitalization is a major component in the cost of patients' treatment. Added to this is the consideration that the treatment of patients under these conditions involves additional costs associated with using alternative antifungals. The economic advantage associated with LAMB increased most sharply if the rate of either or both persistent fever and therapeutic failure in fever without baseline infections associated with voriconazole increased. Conversely, the advantage of LAMB declined fastest if the rate of either or both of persistent fever and therapeutic failure in fever without baseline infections associated with its use increased. Importantly, the Monte Carlo simulation demonstrated a clear economic advantage for LAMB over voriconazole. On the basis of the uncertainty analysis, LAMB empirical therapy has a higher probability of being associated with cost savings when compared to voriconazole. Out of 10 000 simulations, the maximum expected cost savings were associated with LAMB over voriconazole.

The limitations of the present study are mainly related to the assumptions made in the analysis. The fact that the decision tree structure only allowed for a single switch to alternatives is a limitation that may underestimate the cost of patients with multiple discontinuations. However, this assumption was necessary as no available data regarding a second switch to antifungal alternatives were available. In addition, the expert panel was not able to accurately provide the speculative required data. Nevertheless, the fact that therapy discontinuations were more with voriconazole when compared with LAMB (**Table 4-1**) indicates that the additional costs associated with secondary alternatives will be higher for voriconazole as opposed to LAMB, which will further increase the dominance of LAMB. The assumption that any alternative medication had a duration of administration that was similar to that for the discontinued initial medication is another limitation in the study. No data are

available on the duration of empirical therapy in the Australian setting. However, according to the expert panel in this study, the duration appears to be similar for the different empirical antifungal agents, which is consistent with the result from the study by Walsh *et al.*,[4] where both voriconazole and LAMB had a median duration of 7 days. Realizing that the assumptions are limitations in the study, all assumptions were validated by the expert panel before they were applied. The use of an expert panel to estimate data is also recognized as a limitation in the current study. According to the hierarchy of evidence, for evaluating outcome values, expert opinion is the least favourable.[21] Various biases may affect experts' estimates.[21] Nevertheless, expert judgement is often referred to in situations where no other data sources are available,[19,21] which is the case in the present study. The panel opinions were elicited with consensus, where the panel represented a variety of expertise and hospitals to minimize bias and increase generalizability (external validity) of results, as was previously discussed. The possibility of double counting upon measuring the cost of hospitalization, in relation to the costs of pharmacy, imaging and pathology, is another limitation. Nonetheless, as per the previously discussed sensitivity analysis of hospitalization cost, the study conclusion demonstrated to be uninfluenced by the presence or absence of this limitation. An additional limitation is that, ideally, an economic study should be a prospective analysis of a prospective randomized trial. This study, however, was a retrospective analysis of a prospective randomized trial. Indeed, future studies of empirical therapies that prospectively collect economic data will be valuable, and will address the limitations reported in the current available studies. Importantly, future studies should also investigate the long-term costs and quality of life associated with the empirical use of voriconazole and LAMB.

The increasing demand for high-cost antifungals (e.g. voriconazole and LAMB) has resulted in a significant strain on hospital drug budgets.[27,28] Pharmacy managers, clinicians and decision makers are routinely called upon to recommend the appropriate high-cost antifungal.[28] Their decisions are largely based on available clinical efficacy and safety data, and existing guidelines for antifungal use. While these are appropriate from a therapeutic perspective, optimal drug selection should encompass the consideration of economic data as well. The value of the current study extends beyond the reporting of the cost-effectiveness of voriconazole versus LAMB. The current analysis has provided an outline by which one can anticipate costs associated with empirical regimens of voriconazole and LAMB given as per local practices and patterns (e.g. duration of therapy, alternative medications and rates of clinical outcomes).

In conclusion, according to the economic model presented in the current study, first-line therapy of febrile neutropenia with LAMB results in both higher efficacy and lower direct medical costs when compared with voriconazole. From the Australian perspective, LAMB is a dominant empirical medication over voriconazole, which contradicts the current Australian

practices of recommending voriconazole as an effective alternative, with economic advantage, to LAMB for empirical use.

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4.10 TRANSPARENCY DECLARATIONS

None to declare.

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CHAPTER FIVE: ECONOMIC IMPACT OF CASPOFUNGIN AS COMPARED WITH LIPOSOMAL AMPHOTERICIN B FOR EMPIRICAL THERAPY IN FEBRILE NEUTROPENIA IN AUSTRALIA

The work in this chapter investigates the pharmacoeconomics of caspofungin versus liposomal amphotericin B as empirical therapy of febrile neutropenia in Australia.

The following material is arranged in a manner suitable for publication in the Journal of Antimicrobial Chemotherapy. Headings, figures and tables are renumbered in order to generate a consistent presentation within the thesis.

This chapter is a reproduction of the following publication:

Al-Badriyeh D, Liew D, Stewart K *et al*. Economic impact of caspofungin as compared with liposomal amphotericin B for empirical therapy in febrile neutropenia in Australia. *J Antimicrob Chemother* 2009; **63**: 1276-85.

DECLARATION FOR THESIS CHAPTER FIVE

In the case of Chapter Five, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Conception and design. Literature search. Data collection. Statistical experience. Analysis and interpretation. Writing the article. Critical revision of the article.	85%

The following co-authors contributed to the work:

Name[a]	Nature of contribution
David CM Kong	Conception and design. Critical revision of the article. Final approval of the article.
Kay Stewart	Conception and design. Critical revision of the article.
Danny Liew	Design. Statistical experience. Critical revision of the article.

[a]None of the co-authors is a student co-author.

Candidate's signature Date

DECLARATION BY CO-AUTHORS

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;

(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and

(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	Department of Pharmacy Practice - Faculty of Pharmacy and Pharmaceutical Sciences - Monash University, Melbourne, Australia.

David CM Kong	[redacted]	Date 19/11/09
Kay Stewart	[redacted]	19/11/09
Danny Liew	[redacted]	17/11/9

5.1 STUDY TITLE

Economic impact of caspofungin as compared with liposomal amphotericin B for empirical therapy in febrile neutropenia in Australia.

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5.3 ABSTRACT

Background: In a major clinical trial, caspofungin was as efficacious as liposomal amphotericin B (LAmB) for empirical therapy in febrile neutropenia. The current study sought to evaluate the economic impact of caspofungin as compared with LAmB for febrile neutropenia in Australia.

Methods: A decision analytic model was developed to capture the downstream consequences of the empirical antifungal therapy. The main outcomes were success, breakthrough infection, persistent baseline infection, persistent fever, premature discontinuation and death. Underlying transition probabilities and treatment patterns were derived directly from trial data. Resource use was estimated using an expert panel. Cost inputs were obtained from the latest Australian representative sources. The perspective adopted was that of the Australian hospital system. Uncertainty and sensitivity analyses were undertaken via Monte Carlo simulation.

Results: Caspofungin was associated with a net cost saving of AU$7245 (12.6%) per patient over LAmB (AU$50 267 versus AU$57 512). A similar trend was observed with cost per success and death prevented (AU$24 169 and AU$7270, respectively). Caspofungin dominated LAmB as it resulted in higher efficacy and lower costs when compared with LAmB. Persistent fever was the main contributing clinical outcome to the therapeutic costs of both antifungals. The results were most sensitive to therapy duration. Monte Carlo simulation suggested a 99.8% chance for LAmB to cost more than caspofungin.

Conclusion: This is the first economic study to evaluate the place of caspofungin as empirical therapy in Australia. Caspofungin is more cost-beneficial than LAmB, which contradicts the current Australian guidelines of recommending LAmB as the first choice for empirical therapy.

Keywords: model, LAmB, costs.

5.4 INTRODUCTION

The concept of empirical use of antifungal agents is recognized as the standard of care for patients with febrile neutropenia.[1] A variety of agents have been employed for empirical use. Ideally, an antifungal for empirical use should have demonstrated activity against the most common causative fungi for infections, namely *Candida* and *Aspergillus* species.[2]

Caspofungin (Cancidas®, Merck) and liposomal amphotericin B (LAmB) (AmBisome®, Gilead Sciences) are two antifungal agents that have been approved by the US Food and Drug Administration for use as empirical therapy.[3,4]

In a double-blind, randomized, multicentre clinical trial by Walsh *et al*.,[5] comparing caspofungin with LAmB for empirical therapy in febrile neutropenic patients, caspofungin was shown to be non-inferior to LAmB. The authors concluded that caspofungin is a suitable alternative to LAmB for empirical treatment. However, given the differential costs of these agents, related health economic data would be critical to establish the role of caspofungin as the latest addition to the empirical antifungal armamentarium. No overall economic evaluation has been performed yet on empirical caspofungin.

The objective of the current study was to investigate the pharmacoeconomics of caspofungin as compared with standard care (i.e. LAmB)[6,7] for empirical antifungal therapy of febrile neutropenia in Australia.

5.5 MATERIALS AND METHODS

The modelling in the current study was based on data extrapolated from the randomized trial by Walsh *et al*.[5] on empirical therapy in febrile neutropenia. In the trial, 1095 patients were randomly assigned to receive either caspofungin or LAmB. Successful therapy was determined by a five composite endpoint, comprising absence of breakthrough fungal infection, survival for 7 days beyond the therapy completion, no premature discontinuation of therapy because of related side effects or lack of efficacy, resolution of fever during the period of neutropenia and successful treatment for any baseline fungal infection.

5.5.1 PERSPECTIVE

The economic analysis was undertaken from the perspective of the Australian hospital system. The analysis included direct medical costs related to febrile neutropenia. These included costs of diagnostic and monitoring tests, medical therapy, concomitant medications, hospitalization and duration of therapy. Direct medical costs related to other underlying diseases were not included.

5.5.2 MODEL STRUCTURE

A decision analytic model[8] was constructed to capture the downstream consequences of empirical antifungal therapy with each agent (**Figure 5-1**). The running of this model at the base case scenario was based on a regular cohort simulation analysis, and did not involve any Markov modelling or Monte Carlo simulation.

The model included eight possible treatment pathways depending on whether the initial treatment was successful, and on the reasons for failures. Patients with febrile neutropenia were initially assigned to one of two pathways depending on whether they had baseline fungal infections. Patients without baseline infection continued therapy until success, or failure because of death, breakthrough fungal infections, premature discontinuations or persistent fever. Patients with baseline infection continued therapy until success, or failure because of death or persistent baseline infection.

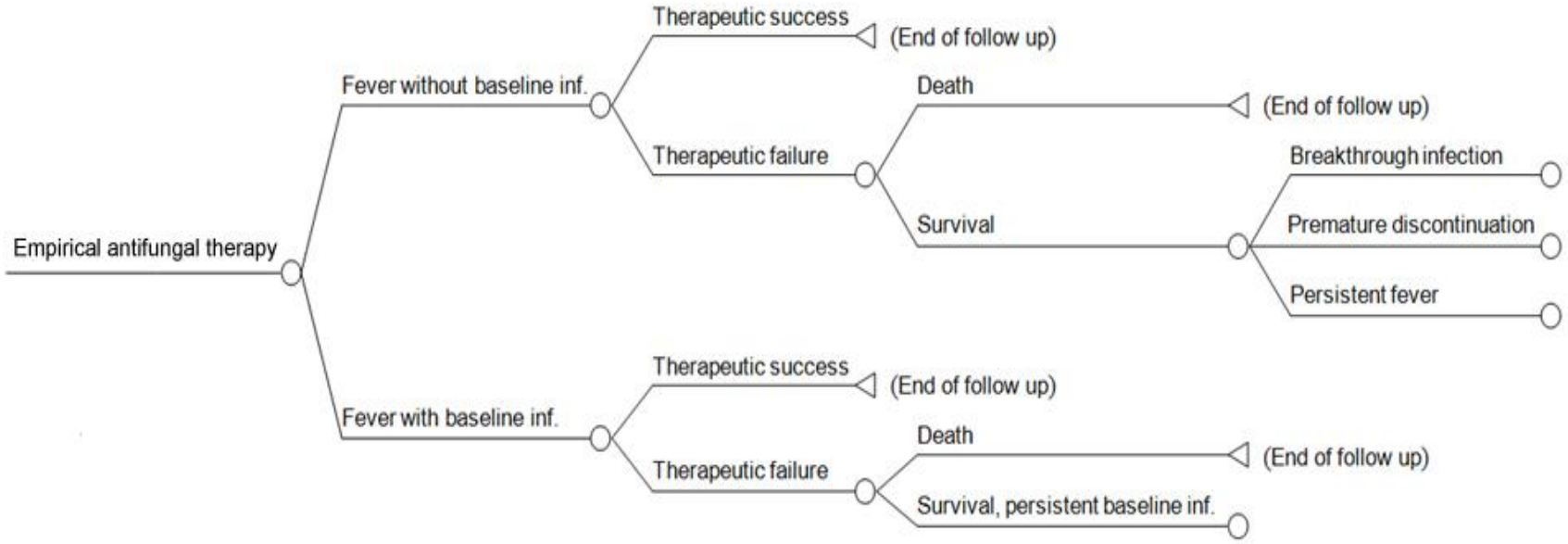

Figure 5-1. Decision analytic model of a typical empirical antifungal (i.e. caspofungin and LAmB) therapy for febrile neutropenia.

Patients who failed to respond to initial therapy for reasons other than death were switched to any licensed antifungal therapy. No specifications were made regarding when therapy ended. All patients were followed until death or successful therapy. Success was the result of either initial therapy or alternative therapy.

5.5.3 MODEL INPUTS

Input data derived from the trial[5] included clinical outcome rate, morbidity and mortality, duration of initial therapy and cause of treatment failure. Clinical outcomes and their probabilities are summarized in **Table 5-1**.

Table 5-1. Outcomes and probabilities of caspofungin and LAmB[5] used in the model

Study clinical outcome	Probability with caspofungin, % (*n* = 556)	Probability with LAmB, % (*n* = 539)
Fever with no baseline fungal infection	95.14% (*n* = 529)	94.99% (*n* = 512)
therapeutic success	33.27% (*n* = 176)	33.98% (*n* = 174)
therapeutic failure	66.73% (*n* = 353)	66.02% (*n* = 338)
death	11.61% (*n* = 41)	17.16% (*n* = 58)
breakthrough infection	8.22% (*n* = 29)	7.10% (*n* = 24)
premature discontinuation	16.15% (*n* = 57)	23.08% (*n* = 78)
persistent fever[a]	64.02% (*n* = 226)	52.66% (*n* = 178)
Fever with baseline infection	4.86% (*n* = 27)	5.01% (*n* = 27)
therapeutic success	51.85% (*n* = 14)	25.93% (*n* = 7)
therapeutic failure	48.15% (*n* = 13)	74.07% (*n* = 20)

[a]Number of patients with persistent fever = number of patients who failed therapy – number of patients who failed therapy because of other than persistent fever.

An independent expert panel was convened comprising four clinicians from Australia with clinical expertise in systemic fungal therapy and specialist knowledge in oncology, haematology and infectious diseases. The panel provided a consensus view on required data that were not available from the literature. These included concomitant antibiotics, screening and monitoring tests and intensive care unit (ICU) management that relates to fungal infections. A single meeting among all panel members was used to collect data. Before the

meeting, members of the panel were provided with a list of questions related to the missing data to be provided. They were also provided with a copy of the paper by Walsh *et al*.[5] During the meeting, the members were asked to respond to each of the questions. The members were then given the time and opportunity to discuss their answers until consensus was achieved.

The panel also advised on alternative antifungal therapies used after initial therapy discontinuation. The choice of alternative therapy was dependent on the reason for treatment discontinuation,[5] which included, where breakthrough infections and baseline infections occurred, the site of infection and the type of causative fungi. The expert panel validated the decision tree in the current model.

Based on the trial, patients on caspofungin received 70 mg on day 1, followed by a daily dose of 50 mg. LAmB was administered intravenously at 3 mg/kg/day throughout the treatment duration. The mean duration of caspofungin administration was 13 days. For LAmB, the mean duration of therapy was 12.5 days. Baseline fungal infections were those present within 48 h of therapy initiation. Breakthrough fungal infections were those diagnosed after 48 h of therapy. For the purpose of this study, patients with premature discontinuations were further classified according to premature discontinuations because of severe toxicity (i.e. infusion-related reaction, hepatotoxicity and nephrotoxicity) and those due to lack of efficacy against suspected fungal infection or persistent fever.

5.5.4 DATA PROVIDED BY EXPERT PANEL

Filgrastim [granulocyte-colony stimulating factor (G-CSF)], piperacillin/tazobactam and vancomycin were concomitantly given to patients. Patient monitoring tests comprised a daily complete blood count, as well as renal and liver function tests. For diagnostic tests, a chest X-ray was done at onset of therapy and then three times weekly. Patients received a computed tomography (CT) scan 3 days after commencing antifungal therapy, with 40% of patients receiving a second follow-up scan. Blood and non-blood microbiological cultures (i.e. sputum, biopsy, diarrhoea and urine) were performed two to three times a week. Based on the panel's advice, it was assumed that 7.5% of patients spent 5 days in the ICU, where patients received a bronchoscopy, an additional CT scan, thrice-daily tests of electrolytes and daily monitoring of blood and non-blood microbiological cultures. Antibiotics and G-CSF, screening and monitoring tests and ICU management were not affected by the type of empirical antifungal agent and, therefore, their frequency and nature were the same during both therapies. As reported by Walsh *et al*.,[5] 27 patients receiving caspofungin prematurely ceased treatment because of side effects. The expert panel felt that 21 of these

discontinuations would be due to infusion-related reactions. Three patients had nephrotoxicity and three had hepatotoxicity. Out of the 44 patients who discontinued LAmB prematurely because of side effects,[5] 9 had infusion-related reactions, 31 had nephrotoxicity and four had hepatotoxicity. Patients who had baseline infections and failed therapy survived with persistent baseline infections. The antifungal alternatives given after the failures of each of the therapies were as shown in **Table 5-2**.

Table 5-2. Alternatives after failure of caspofungin and LAmB

Cause of therapy failure	Alternative	Details
Caspofungin, with premature discontinuations		
severe infusion-related reactions	voriconazole (iv)	standard[a]
severe nephrotoxicity	voriconazole (iv)	standard[a]
severe hepatotoxicity	LAmB	3 mg/kg/day
lack of efficacy against suspected fungal infection	voriconazole (iv)	standard[a]
lack of efficacy against persistent fever	voriconazole (iv)	standard[a]
Caspofungin, with breakthrough fungal infection		
Aspergillus species	voriconazole (iv)	standard[a]
Candida species	LAmB	3 mg/kg/day
Zygomycetes	LAmB	5 mg/kg/day
Fusarium species	voriconazole (iv)	standard[a]
Trichosporon species	voriconazole (iv)	standard[a]
Caspofungin, with non-responding baseline fungal infection		
Aspergillus species	voriconazole (iv)	standard[a]
Candida species	LAmB	3 mg/kg/day
Dipodascus capitatus	voriconazole (po)	standard[b]
Zygomycetes	LAmB	5 mg/kg/day
Caspofungin, with persistent fever	voriconazole (iv)	standard[a]
LAmB, with premature discontinuations		
severe infusion-related reactions	voriconazole (iv)	standard[a]
severe nephrotoxicity	voriconazole (iv)	standard[a]
severe hepatotoxicity	caspofungin	standard[c]
lack of efficacy against suspected fungal infection	posaconazole	800 mg/day
lack of efficacy against persistent fever	voriconazole (iv)	standard[a]
LAmB, with breakthrough fungal infection		
Aspergillus species	posaconazole/LAmB	combination[d]
Candida species	caspofungin/fluconazole	combination[e]

Table 5-2 *Continued*

Cause of therapy failure	Alternative	Details
mould, not further identified[f]	posaconazole/LAmB	combination[d]
LAmB, with non-responding baseline fungal infection		
Aspergillus species	posaconazole	800 mg/day
Candida species	caspofungin	standard[c]
Fusarium species	voriconazole (iv)	standard[a]
mould, not further identified[f]	posaconazole/LAmB	combination[d]
LAmB, with persistent fever	voriconazole (iv)	standard[a]

iv, intravenous; po, oral.

[a]6 mg/kg twice daily (loading dose), 3 mg/kg twice daily (maintenance dose).

[b]6 mg/kg twice daily (loading dose), 200 mg twice daily (maintenance dose).

[c]70 mg/day (loading dose), 50 mg/day (maintenance dose).

[d]800 mg/day posaconazole with 3 mg/kg/day LAmB. LAmB will cease when posaconazole steady state is reached.

[e]70 mg/day (loading dose) and 50 mg/day (maintenance dose) caspofungin with 200 mg/day fluconazole.

[f]The infections included disseminated fungal infections and pneumonia.

5.5.5 OTHER STUDY ASSUMPTIONS

The assumptions made with respect to determining costs in the present study were as follows:

i. Patients did not incur any out-of-pocket costs, and were covered by Medicare (Australia's public health insurance scheme).
ii. If patients switched initial therapy after initial failure, the subsequent alternative therapy was successful.
iii. Any alternative therapy was assumed to have a duration similar to that of the discontinued initial therapy.

All assumptions were validated by the expert panel.

5.5.6 COST CALCULATIONS

This model was used to generate a weighted average cost per patient. This was the sum-product of the eight-treatment-outcome costs and their respective probabilities.

The cost of the initial therapy was the cost of a complete course of caspofungin or LAmB before changing to alternatives. The cost of the alternative therapy was the cost of a complete course of the alternative agent. The cost of each failure pathway, except for death, was the cost of initial and alternative therapies added to the cost of resources consumed. The cost per successfully treated or deceased patient was calculated as a proportion of both the cost of a complete course of caspofungin or LAmB and the cost of resources used.

Regarding medication doses, all patients were assumed to have an average body weight of 76.05 kg, based on the latest available data from the Australian Bureau of Statistics.[9] No average patient body weight was reported in the Walsh *et al*.[5] study. Doses for all medications (except posaconazole) were rounded to the nearest vial size. Patients on posaconazole were permitted to share the same posaconazole bottle, as is routine hospital practice in Australia.

Costs were calculated in Australian dollars (AU$) for the financial year 2008-09, and no discounting was applied given the short time-frame of analysis.

Hospitalization costs in the current model were based on gross (top down) cost estimations. However, the costs of drugs used, and pathology and imaging tests were based on micro-costing (bottom up costing). Medication costs used were the drug wholesale prices paid by Australian public hospitals, as per Health Purchasing Victoria tender (2007-09).[10] Hospitalization costs were obtained from published records associated with the 2006-07 Australian Refined Diagnosis-Related Groups (AR-DRG).[11] Hospitalization costs used were the average total costs associated with febrile neutropenia (Code T62A), and included the cost of intensive care management. Hospitalization costs were adjusted for the financial year 2008-09 as per the Australian Health Consumer Price Index (2008).[12] All other resource costs involved in the study were obtained from the Australian Medicare Benefits Schedule Book (2009).[13] The cost inputs used in the model are summarized in **Table 5-3**.

5.5.7 SENSITIVITY ANALYSES

Deterministic and probabilistic sensitivity tests were produced by modifications of the baseline values of several key variables and assumptions, in relation to costs and probabilities, to evaluate the robustness of the study conclusion.

In the deterministic sensitivity analysis, threshold analysis was performed, whereby, baseline values were substituted by the highest and lowest values within a reasonable range of values. Where a substitution changes the study conclusion, more values within the range replaced the baseline value. This was repeated until the threshold value that changes the study outcome was identified.

Cost and duration of hospitalization were obtained as daily average values and, hence, are not exact. The uncertainty of hospitalization costs may have increased because of the adjustment for inflation made via the use of the CPI. Furthermore, costs of drugs, imaging and pathology in the model were calculated separately from the hospitalization cost; nonetheless, gross hospitalization costs, as obtained from the AR-DRG, were total cost that already included costs that were associated with used pharmacy, imaging and pathology services in febrile neutropenia. This may introduce double counting. All these suggest uncertainly and, therefore, the effects of variations in the duration and cost of hospital stay were investigated.

Table 5-3. Resource costs[10,11,13]

Item	Unit	Unit cost (AU$)
Caspofungin	70 mg iv vial	700.00
	50 mg iv vial	700.00
LAmB	50 mg iv vial	295.00
Voriconazole	200 mg iv vial	190.84
	200 mg oral tablet	45.62
Posaconazole	105 mL oral suspension	669.50
Fluconazole	200 mg oral capsule	2.61
Piperacillin/tazobactam	4.5 mg iv vial	24.00
Vancomycin	500 mg iv vial	5.45
Filgrastim	480 µg iv vial	240.70
Chest x-ray	1 test	35.35
CT scan	1 test	295.00
Non-blood culture	≥ 1 tests (1 culture)	34.00
Blood culture	1 test (1 culture)	30.95
Bronchoscopy	1 test	217.15
Complete blood count	1 test	17.20
Renal function test	1 test	146.30
Liver function test	1 test	17.80
Electrolytes test	1 test	24.90
ICU consultant	first day	334.55
	subsequent day	248.20
Hospitalization	inpatient per day	1111.00

i.v, intravenous.

Because future changes in medications prices are possible and, as a result, associated with uncertainty, the caspofungin and LAmB prices were investigated as well. Estimations made by the expert panel can vary according to local practices and experiences, and are doubtful. The estimations, therefore, were also evaluated. These were related to alternative medications used, ICU duration, antibiotic and G-CSF use and screening and monitoring tests. Key variables, and the ranges over which they were varied, are shown in **Table 5-4**.

The model's sensitivity to the probability of patient distribution in the decision tree was investigated via scenario analyses, which involved switching the probability data between the caspofungin and LAmB arms, and applying the probability data in the LAmB arm to the caspofungin arm and vice versa. Another scenario analysed was replacing the probability of patient distribution in the LAmB arm with that reported in a similar study comparing empirical LAmB with empirical voriconazole.[14]

Uncertainty analysis, by means of Monte Carlo simulation, was performed via the @Risk-5.0® analysis tool (Palisade Corporation, NY, USA) to investigate the likelihood of an antifungal's economic advantage. Monte Carlo is a method whereby simulated input values, chosen randomly across a range of probability distributions of a model input, are added into the model.[15] The model is run for each simulated input, resulting in a range of outputs characterizing the output uncertainty. An accurate probabilistic sensitivity analysis typically requires 1000 or more model runs.[15] The clinical outcomes that affected the overall drug cost the most were also determined. One-way sensitivity analysis was performed with an assumed uncertainty of 10% for the probabilities of breakthrough fungal infection, premature discontinuation and persistent fever. A 5% uncertainty range was applied for all other probabilities in the model. Corresponding costs were calculated, and a distribution of 'cost saving' was obtained by executing 10 000 iterations of the Monte Carlo simulation. The input variables and their uncertainty distributions are shown in **Table 5-5**.

5.6 RESULTS

5.6.1 COST OF EMPIRICAL THERAPY

Caspofungin had an economic advantage over LAmB in the order of AU$7245 (12.6%). The proportions and costs for each pathway in the decision tree are shown in **Table 5-6**. For both antifungals, persistent fever was the main contributing clinical outcome to therapeutic costs. Main components, and their contribution, in the overall costs of caspofungin and LAmB are demonstrated in **Figure 5-2**.

Table 5-4. Variation range for variables in sensitivity analysis

Variable	Base case	Variation range	
		low	high
LAmB cost/vial	AU$295.00	AU$118.00	AU$300.00
Caspofungin cost/70 mg vial	AU$700.00	AU$60.00	AU$1500.00
Caspofungin cost/50 mg vial	AU$700.00	AU$0.00	AU$1500.00
Caspofungin cost/both 50 mg and 70 mg vials	AU$700.00	AU$0.00	AU$1500.00
Hospitalization cost per day	AU$1111.00	AU$0.00	AU$2222.00
ICU cost per day	AU$1111.00	AU$1111.00	AU$2996.00
LAmB administration duration	12.5 days	7 days	17 days
Caspofungin administration duration	13 days	7 days	17 days
ICU duration	5 days	1 days	10 days
Dosage form of voriconazole given as alternative (po:iv)	1:1	0:1	1:0
Counting for the costs of antibiotics and G-CSF	Yes	No	Yes
Replacement of the 3 mg/kg doses of alternative LAmB with 5 mg/kg doses	No	No	Yes
Counting for the cost of screening and monitoring tests	Yes	No	Yes

iv, intravenous; po, oral.

Table 5-5. Input variables and uncertainty distributions used in Monte Carlo simulation

	Uncertainty distribution	
Input variables	caspofungin	LAmB
Fever without baseline infection	triangular distribution, 90.38-95.14-99.9%	triangular distribution, 90.24-94.99-99.74%
therapeutic success	triangular distribution, 31.61-33.27-34.93%	triangular distribution, 32.28-33.98-35.67%
therapeutic failure	triangular distribution, 63.39-66.73-70.07%	triangular distribution, 62.72-66.02-69.32%
death	triangular distribution, 11.03-11.61-12.19%	triangular distribution, 16.30-17.16-18.02%
breakthrough infection	triangular distribution, 7.4-8.22-9.04%	triangular distribution, 6.39-7.1-7.81%
premature discontinuation	triangular distribution, 14.54-16.15-17.77%	triangular distribution, 20.77-23.08-25.39%
persistent fever	triangular distribution, 57.62-64.02-70.42%	triangular distribution, 47.39-52.66-57.93%
Fever with baseline infection	triangular distribution, 4.62-4.86-5.1%	triangular distribution, 4.76-5.01-5.26%
therapeutic success	triangular distribution, 49.26-51.85-54.44%	triangular distribution, 24.63-25.93-27.23%
therapeutic failure	triangular distribution, 45.74-48.15-50.56%	triangular distribution, 70.34-74.07-77.77%

Higher probability of success and lower probability of death were associated with caspofungin (34.17% and 7.37%, respectively) versus LAmB (33.58% and 10.76%, respectively) (**Table 5-1**). The costs of success and survival per patient with caspofungin (AU$147 097 and AU$50 304, respectively) were lower than those with LAmB (AU$171 266 and AU$57 574, respectively).

Table 5-6. Proportional cost of empirical caspofungin and LAmB

	Caspofungin			LAmB		
Therapy outcome	proportion (%)	cost (AU$)[a]/ patient	proportional cost (AU$)[a]	proportion (%)	cost (AU$)[a]/ patient	proportional cost (AU$)[a]
Fever with no baseline infection						
therapeutic success	31.65	31 828	10 075	32.28	40 327	13 018
death	7.37	31 828	2347	10.76	40 327	4339
breakthrough infection	5.22	69 959	3649	4.45	73 138	3257
premature discontinuation	10.25	62 486	6406	14.47	69 017	9988
persistent fever	40.65	62 381	25 356	33.02	72 300	23 876
Fever with baseline infection						
therapeutic success	2.52	32 232	812	1.30	40 714	529
death	-	-	-	-	-	-
persistent baseline infection	2.34	69 365	1622	3.71	67 514	2505
Total cost per patient[b]			50 267			57 512

[a]All shown cost values were shortened to the nearest no-decimal digits status.

[b]Calculations involving cost values took in consideration 2 decimal digits (not-shown) associated with each of the cost values.

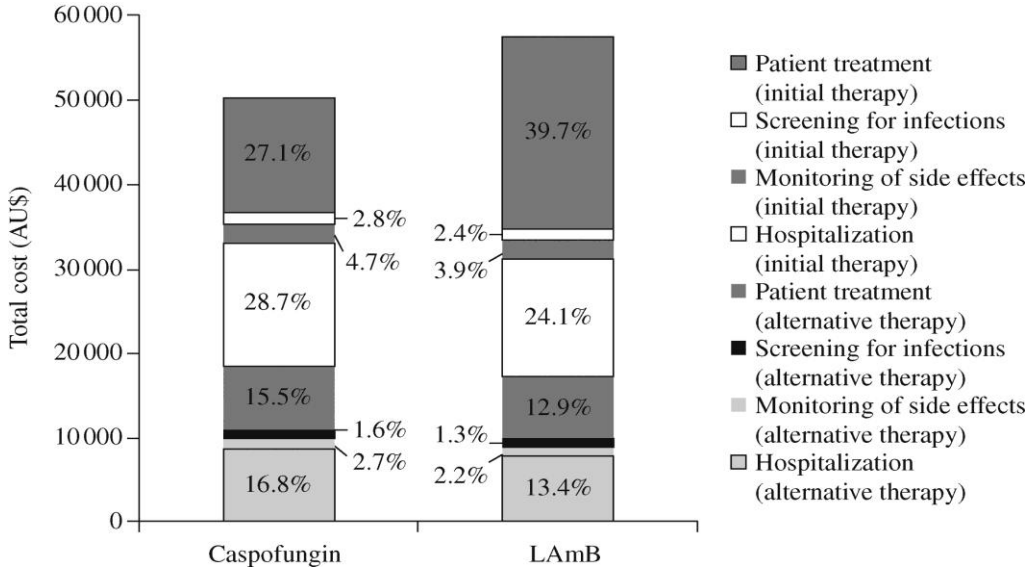

Figure 5-2. Contribution of different cost components in overall therapy.

5.6.2 SENSITIVITY ANALYSES

Sensitivity analyses demonstrated that the baseline cost difference was most sensitive to the duration of either of the antifungals. LAmB had a lower overall cost when the duration of caspofungin therapy increased from 13 to > 14.9 days, or when the LAmB therapy was reduced in duration from 12.5 to < 10.9 days. The cost per day was higher with LAmB (AU$4377 versus AU$3742).

The model was insensitive to changes in drug acquisition costs. LAmB had the economic advantage when its price decreased from AU$295.00 to AU$174.40 per vial. A 2-fold increase in the 70 mg caspofungin price did not affect the cost savings. Increasing the price of 50 mg caspofungin alone or the price of both 70 and 50 mg caspofungin from AU$700 to AU$1330 per vial was needed for LAmB to have an economic advantage. The main study result was also insensitive to variations in hospitalization costs, including those attributable to ICU care. The elimination and two-fold increase in hospitalization cost per day resulted in a ± AU$20 000 difference in the total cost of each antifungal. However, changes in the overall cost difference were negligible. The model was not sensitive to the cost of hospitalization in ICU. While an almost three-fold increase in the cost of ICU stay significantly increased the total cost of caspofungin and LAmB (AU$65,193 and AU$72,175, respectively), it had no effect on the overall cost difference between the two medications.

Baseline cost difference was also not sensitive to the estimations made by the expert panel. It was not sensitive to the dose of LAmB when given as an alternative, or to the LAmB

given in combination with posaconazole as an alternative. Replacing 3 mg/kg/day doses with 5 mg/kg/day doses for alternative LAmB did not affect the cost advantage of caspofungin. The sensitivity to the time spent in the ICU, tested within a range of 1-10 days, was negligible. A similar outcome was observed with excluding the use of concurrent antibiotics and G-CSF, and the costs of screening and monitoring tests, as well as with switching all intravenous doses of the alternative voriconazole to oral voriconazole and vice versa.

One- and two-way exchanges in probability data, between the caspofungin and LAmB arms in the decision tree, did not impact the cost differential. A similar outcome resulted when the LAmB probability data were replaced with empirical LAmB data reported elsewhere in the literature.[14]

According to the uncertainty analysis, main clinical variables, as per the ranking of their impact on the model outcome, are demonstrated in **Figure 5-3**.

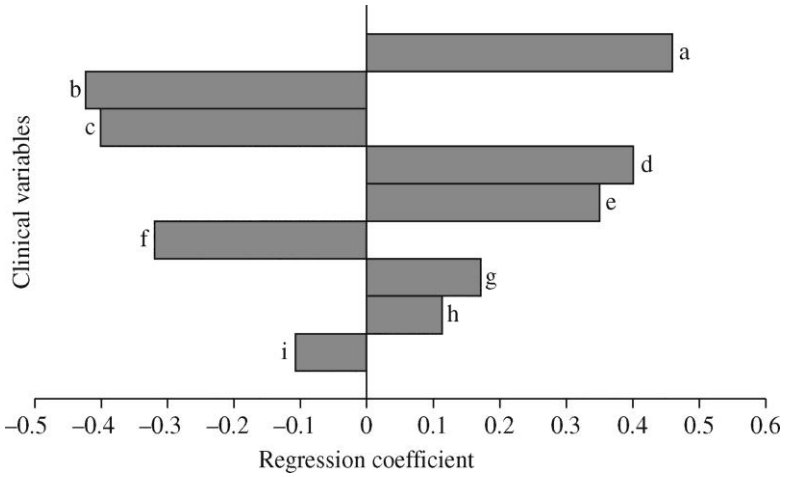

Figure 5-3. A tornado diagram of the regression of variables as per their influence on the model outcome. The influencing variables are fever without baseline infections with LAmB (a), persistent fever with caspofungin (b), fever without baseline infections with caspofungin (c), persistent fever with LAmB (d), therapeutic failure of fever without baseline infections with LAMB (e), therapeutic failure of fever without baseline infections with caspofungin (f), premature discontinuation with LAmB (g), therapeutic success with LAMB (h) and premature discontinuation with caspofungin (i).

Based on the 'cost saving' probability distribution, resulting from the Monte Carlo simulation, the mean cost saving was AU$7247 per patient in favour of caspofungin. There was a 99.8% chance that caspofungin would be associated with a cost saving over LAmB. The maximum

expected cost saving with caspofungin was AU$16 354, while the maximum expected cost saving with LAmB was AU$1583. A 'cost saving' probability curve is shown in **Figure 5-4**.

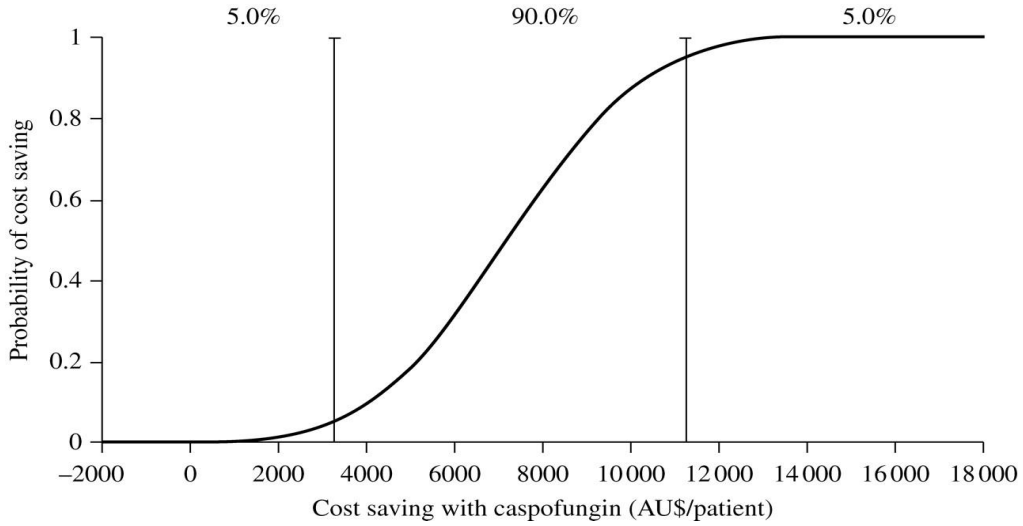

Figure 5-4. 'Cost saving' probability curve of caspofungin.

5.7 DISCUSSION

This economic investigation is the first to focus on the role of caspofungin as empirical therapy from an Australian perspective. Caspofungin was evaluated in comparison with LAmB, the standard empirical antifungal therapy as per the current Australian guidelines.[6,7] Caspofungin demonstrated a cost saving over LAmB (AU$7245 difference, **Table 5-6**). Importantly, because caspofungin was associated with a higher efficacy (i.e. higher success rate and lower death rate) as well as lower cost per success and death prevented (in the order of AU$24 169 and AU$7270, respectively), it appears to be a dominant empirical antifungal treatment over LAmB.

As there were no long-term-survival and quality-of-life data available from Walsh *et al.*,[5] it was not possible for the present analysis to estimate the life years gained[16] as well as to apply the Markov modelling.[17] Moreover, long-term data are more relevant to studies adopting a healthcare system or societal perspective, while the hospital perspective is more appropriate for acute diseases such as febrile neutropenia.

An ideal economic evaluation would be based on the best available clinical evidence, whereby a double-blinded randomized clinical trial would be the most valid and reliable source of data.[18-20] Importantly, the economic results of the current study are applicable to the

Australian setting, as the results from the trial by Walsh *et al*.[5] are generalizable to the Australian healthcare setting. The trial was an international multicentre study, the patients reflected the normal Australian clinical caseload and the administration of both caspofungin and LAmB is similarly recommended in current Australian guidelines.[6,7]

A major strength of the current model is that all patients were followed up, even after discontinuing randomized therapy. In addition, the decision model considered all possible clinical patterns reported in the Walsh *et al*. study.[5] In a recent Germany-based economic evaluation,[21] caspofungin was demonstrated to be at least cost-neutral compared with LAmB for empirical use. Nonetheless, as per the study objective and design, costs presented were based on the nephrotoxicity outcome alone, and thus, were not directly comparable to the current study. Two recent studies, one from Italy[22] and the other from the UK,[23] aimed to compare the overall costs (combined acquisition and secondary costs) of caspofungin and LAmB for neutropenia with fever. Both evaluations, based on the same model, extracted data from the Walsh *et al*.[5] trial, and revealed a lower cost associated with caspofungin. These studies, however, did not consider the cost consequences associated with lack of efficacy, persistence of fever and breakthrough fungal infections. This is the only caspofungin economic study in which measured costs fully reflected the standard five component endpoint currently used in assessing the efficacy of empirical antifungal therapy.[24] This approach is critical for the accurate depiction of the overall cost of treatment. Including some treatment pathways while excluding others may lead to inaccurate estimation of costs. Importantly, the Italy- and UK-based studies assumed that patients who discontinued caspofungin were switched to LAmB only, and that patients who discontinued LAmB were switched to caspofungin only. These are impractical, given the availability of cheaper and effective antifungals (i.e. voriconazole and posaconazole) in actual practice, and will lead to unrealistic secondary costs and, ultimately, actual overall medications costs. The current evaluation, on the other hand, is unique as the estimation of alternatives considered the site of infections as well as the type of causative fungi. The estimations by the expert panel were based on day-to-day clinical experience, which reflected current Australian practice and provided more realistic cost estimates. A better understanding of the full impact of therapies was also enabled. According to the expert panel, no patients with baseline infections failed therapy because of death. This was due to the small number of patients with baseline infections who did not respond to therapy (13 and 20 patients for caspofungin and LAmB, respectively).[5]

The current model compared the overall cost associated with the group of patients who received voriconazole as initial therapy with that associated with the group of patients who received LAMB as initial therapy. While caspofungin had lower treatment-related toxicity, better success with patients with baseline fungal infections and a higher rate of survival after the end of therapy, LAmB was associated with fewer breakthrough fungal

infections and higher rate of resolution of fever. However, the total monetary values of these outcomes (i.e. secondary/alternatives costs) were similar between the two medications (**Figure 5-2**), mainly because the overall failure rates were similar between the antifungals (**Table 5-1**), and the alternatives given after failures comprised similarly cheaper voriconazole or posaconazole (**Table 5-2**). The cost associated with the use of LAmB as an alternative to caspofungin was more than that associated with the caspofungin use as an alternative to LAmB, and hence, LAmB was associated with the lower cost of the alternative therapy, but only slightly (AU$7730 versus AU$8442) (**Figure 5-2**). Therefore, the observed net cost difference was almost totally due to the difference in the initial antifungal treatment costs; the lower acquisition cost of caspofungin (AU$13 622) relative to LAmB (AU$22 804) (**Figure 5-2**). These observations highlight the need for decision-makers to consider both acquisition costs and secondary costs (cost of therapy failure), when deciding on the prescribing of a medication. The current model did not compare the economics between voriconazole and LAMB as initial therapies only.

The cost of treating common side effects (e.g. chills and rash) was not included in the current study. It was not possible for the expert panel to provide reliable estimations for the resources used to manage such side effects. However, these side effects are usually moderate and do not cause discontinuations of therapy; in addition, they are not likely to affect cost estimations.

The sensitivity analyses conducted on the dataset demonstrated that the overall difference in cost was only sensitive to the duration of antifungal therapy. This is expected as, for both antifungals, 1 day accounts for almost 8% of the total therapy cost. LAmB had the economic advantage when the mean duration of its administration was < 10.9 days. This is important given that two previous studies[14,25] on empirical LAmB, which also used the five component endpoint to assess outcomes, reported LAmB treatment durations of 10.8 days (mean) and 7 days (median), respectively.

The cost advantage of caspofungin was robust enough that it was not sensitive to realistic variations in antifungal prices or hospitalization costs. Regarding the ICU cost per day, from the Australian perspective, no exclusive cost per bed was available, and thus, the average total hospitalization cost per day was used instead. In any case, when cost per day during the ICU stay was replaced with a total ICU daily cost (AU$2996) reported in the literature for a local hospital,[26] the net difference in cost did not change. As expected, the three-fold increase in ICU hospitalization cost per day considerably affected the total cost for each of the antifungals. Nonetheless, the reason the net cost difference did not change is that the ICU was the same in terms of both duration and cost in both arms of the study. Importantly, the main result was not sensitive to the estimations by the expert panel. Similarly, the difference in the overall probability of distribution for variables between both

arms of the study appears not to be a key factor behind any cost differentials measured between the two antifungals, as the switches made in the overall probability of distribution did not affect the study conclusion.

According to the uncertainty analysis, the variables that affected the model most were fever without baseline infections, persistent fever and therapeutic failure of fever without baseline infections (**Figure 5-3**). This is expected, as these variables have the highest ratios of patient distribution among all variables, which translates into longer overall hospital stay and, ultimately, higher overall cost. Importantly, the Monte Carlo simulation demonstrated a clear economic advantage with using caspofungin. The probability of caspofungin generating cost savings over LAmB was very high. Out of 10 000 simulations, the mean net saving was associated with caspofungin. The maximum expected cost saving was higher with caspofungin than with LAmB (**Figure 5-4**).

The use of an expert panel to estimate data is recognized as a limitation in the current study. Hospital resources used in patient management could have been driven from local hospital protocols. For the purpose of this study however, the expert panel, representing a wide variety of hospital practices, was used to increase the generalizability of results to patients outside the local hospital setting. As no literature regarding the use of empirical antifungals as alternatives is available, the expert panel provided data regarding alternatives given after discontinuations. Expert judgement is often referred to as the best available source in situations where no other data sources are available.[27] The number of panel members involved was in accordance with the literature.[28-30]

Another limitation is that related to the possibility of double counting upon measuring the cost of hospitalization, in relation to the costs of pharmacy, imaging and pathology. As per discussed sensitivity analysis of hospitalization cost, however, this limitation does not influence the study conclusion.

It is a limitation that the decision tree structure only allowed for a single switch to alternatives after failures. There, however, were no available data in the literature to guide the modelling of a second switch to antifungal alternatives, and also, it was not possible for the expert panel to provide accurate anticipations on this matter. Nevertheless, the two model arms were similar in terms of failure ratio (**Table 5-1**) and in the most commonly used alternative (**Table 5-2**). The assumption that the duration of subsequent alternative medication was similar to that of the discontinued initial medication is another limitation. No data are available regarding the duration of empirical therapy in Australia. However, according to the expert panel, the duration appears to be similar for different antifungal empirical agents if used in similar settings, which is consistent with the results in the literature on empirical antifungals.[5,14,25] All assumptions were validated by the panel before they were applied. Future

investigations that prospectively collect economic data of empirical therapies will be valuable, and will address the limitations in the current study.

The decision regarding the best antifungal for empirical use is mostly based on available efficacy and safety data. However, cost considerations remain critically important, especially since increasing demand for high-cost antifungals (e.g. LAmB, caspofungin and voriconazole) is exerting a significant strain on limited hospital budgets.[31,32] A recent Australia-based economic evaluation has established the role of voriconazole as compared with the antifungal of choice (i.e. LAmB) for empirical use in Australia.[28] This work helps to establish the role of caspofungin in the same setting. Importantly, the value of the current study extends beyond the reporting of economics. The analysis has provided an outline to anticipate costs associated with empirical regimens of caspofungin and LAmB as per local practices and patterns (e.g. therapy duration and alternative medications).

In conclusion, caspofungin appears to be a more cost-beneficial empirical therapy than LAmB in febrile neutropenia, as it displayed higher efficacy and was associated with lower direct medical costs. The findings of the present study suggest that current Australian guidelines may need to be reviewed, as these recommend LAmB as the first choice for empirical therapy.

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5.10 TRANSPARENCY DECLARATIONS

None to declare.

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CHAPTER SIX: PHARMACOECONOMIC ANALYSIS OF VORICONAZOLE VERSUS CASPOFUNGIN IN THE EMPIRICAL ANTIFUNGAL THERAPY OF FEBRILE NEUTROPENIA

This chapter is an economic evaluation of voriconazole versus caspofungin as empirical therapy in febrile neutropenia in Australia.

The following material is arranged in a manner suitable for publication in the journal Value in Health. Headings, figures and tables are renumbered in order to generate a consistent presentation within the thesis.

This chapter is a reproduction of the following publication:

Al-Badriyeh D, Liew D, Stewart K *et al*. Pharmacoeconomic analysis of voriconazole versus caspofungin in the empirical antifungal therapy of febrile neutropenia. *Value in Health* 2010, in review.

DECLARATION FOR THESIS CHAPTER SIX

In the case of Chapter Six, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Conception and design. Literature search. Data collection. Statistical experience. Analysis and interpretation. Writing the article. Critical revision of the article.	85%

The following co-authors contributed to the work:

Name[a]	Nature of contribution
David CM Kong	Conception and design. Critical revision of the article. Final approval of the article.
Kay Stewart	Conception and design. Critical revision of the article.
Danny Liew	Design. Statistical experience. Critical revision of the article.

[a]None of the co-authors is a student co-author.

Candidate's signature Date

DECLARATION BY CO-AUTHORS

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;

(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and

(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	Department of Pharmacy Practice - Faculty of Pharmacy and Pharmaceutical Sciences - Monash University, Melbourne, Australia.

David CM Kong	[redacted]	Date 19/11/09
Kay Stewart	[redacted]	19/11/09
Danny Liew	[redacted]	17/11/9

6.1 STUDY TITLE

Pharmacoeconomic analysis of voriconazole versus caspofungin in the empirical antifungal therapy of febrile neutropenia in Australia.

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6.4 ABSTRACT

Background: Voriconazole and caspofungin are recommended alternatives to liposomal amphotericin B for empirical use in febrile neutropenia. This study investigated the health economic impact of using voriconazole versus caspofungin in patients with febrile neutropenia.

Methods: A decision analytic model was developed to measure downstream consequences of empirical antifungal therapy. Clinical outcomes measured were success, breakthrough infection, persistent baseline infection, persistent fever, premature discontinuation and death. Treatment transition probabilities and patterns were directly derived from data in two relevant randomized controlled trials. Resource use was estimated using an expert clinical panel. Cost inputs were obtained from latest Australian sources. The analysis adopted the perspective of the Australian hospital system. Sensitivity and uncertainty analyses were undertaken via Monte Carlo simulation.

Results: The use of caspofungin led to a lower expected mean cost per patient than voriconazole (AU$40,558 versus AU$41,356), with a net cost saving of AU$798 (1.9%) per patient. The cost differences per death prevented and per successful therapy had a similar trend and were AU$801 and AU$40,804, respectively. Failure due to persistent fever was the main driver of cost for either medication. Results were most sensitive to the duration of therapy and the alternative therapy used post-discontinuation. In uncertainty analysis, the cost associated with caspofungin is less than that with voriconazole in 65.5% of cases.

Conclusion: This is the first economic evaluation of voriconazole versus caspofungin for empirical therapy. Caspofungin appears to be a more cost-beneficial option than voriconazole in empiric treatment of febrile neutropenia.

Keywords: Economic, model, empirical, voriconazole, caspofungin.

6.5 INTRODUCTION

Invasive fungal infection (IFI) is a significant cause of morbidity and mortality in patients with neutropenia, with the predominant infections being disseminated candidiasis and pulmonary aspergillosis [1,2]. A definitive diagnosis of IFI is difficult, given the lack of sensitivity with the available diagnostic measures [3]. In addition, once an IFI has been established, commencing antifungal therapy is often ineffective [3]. Therefore, empirical antifungal therapy, initiated when patients are noted to have fever of unknown origin without definitive proof of IFI, is well established as the standard of care for patients with febrile neutropenia [4].

Only few systemic antifungal agents have demonstrated significant activity against both *Candida* and *Aspergillus* species, required for successful empirical use [5]. Of these,

voriconazole and caspofungin were the latest to be introduced [6,7], in 2003 and 2005, respectively. Voriconazole (Vfend®, Pfizer) is a third generation 'azole' that is available in intravenous (i.v.) and oral (p.o.) dosage forms, while caspofungin (Cancidas®, MSD) is a member of new class of antifungals called echinocandins, and is only available in an i.v. preparation [8]. These antifungals were investigated recently in two major recent multi-center randomized clinical trials by Walsh et al. [9,10], where voriconazole and caspofungin were separately compared with liposomal amphotericin B (LAmB) for empirical therapy in patients with febrile neutropenia. The authors concluded that voriconazole and caspofungin were effective with favorable safety profiles and, hence, suitable for empirical use. However, no direct comparative studies have been undertaken of voriconazole versus caspofungin for empirical use. Therefore, the superiority of either agent over the other in febrile neutropenia remains unknown. An important advantage that voriconazole maintains over caspofungin is a significantly lower acquisition cost. From the Australian perspective, both medications are recommended for empirical use in current guidelines [11,12]. Associated health economic data of these latest additions to the empirical antifungal armamentarium would further inform decision-making in this clinical scenario.

This study sought to determine the cost-benefit of using voriconazole versus caspofungin as first-line antifungals for empirical use in patients with febrile neutropenia in an Australian hospital setting.

6.6 METHODS

This modeling study was based on data extrapolated from two randomized trials by Walsh et al. of voriconazole versus LAmB [9] and caspofungin versus LAmB [10] as empirical therapy for febrile neutropenia. In the voriconazole versus LAmB study, a total of 837 patients were randomly assigned to receive voriconazole or LAmB. In the caspofungin versus LAmB study, 1095 patients were randomly assigned to receive either caspofungin or LAmB. In both trials, patients had received chemotherapy for cancer, undergone transplantation of hematopoietic stem cells, had fever (above 38ºC), had neutropenia (a neutrophil count below 500 per cubic millimeter) and received parenteral antibacterial therapy for at least 96 hours. Also in both trials, successful therapy was determined by a five-part composite endpoint for assessing empirical antifungal therapy; these being absence of breakthrough fungal infection, survival for seven days beyond the end of therapy, no premature discontinuation of therapy because of related side effects or lack of efficacy, resolution of fever during the period of neutropenia, and successful treatment of any baseline fungal infection.

6.6.1 PERSPECTIVE

The perspective adopted for the economic analysis was that of the Australian hospital system. The analysis included direct medical costs related to fungal infections, concerning costs of diagnostic and monitoring tests, associated medical therapy, concomitant medications, and hospitalization. Direct medical costs related to other underlying diseases were not included.

6.6.2 MODEL STRUCTURE

Decision analysis [13] was developed to capture downstream consequences of empirical antifungal therapy, as shown in **Fig.6-1**. A range of uncertainly was associated with hospitalization cost at the baseline level (discussed below), with the baseline model in the current study ran via Monte Carlo simulation (5,000 iterations), using @Risk-5.5® (Palisade Corporation, NY, USA).

The model included eight possible treatment pathways depending on whether the initial treatment was successful, and on the causes of failures, if appropriate. Patients with febrile neutropenia were initially assigned to one of two pathways depending on whether or not they had baseline fungal infection. Patients without baseline infection continued therapy until therapy was successful, or failed because of death, breakthrough fungal infection, premature discontinuation, or persistence of fever. Patients with baseline infection continued therapy until success, or failure because of death or persistent baseline infection.

Patients who failed to respond to initial therapy, for reasons other than death, were switched to any other licensed antifungal therapy. No specifications were made regarding when therapy ended. All patients were followed until deceased or successfully treated. Success resulted with either initial or alternative therapy.

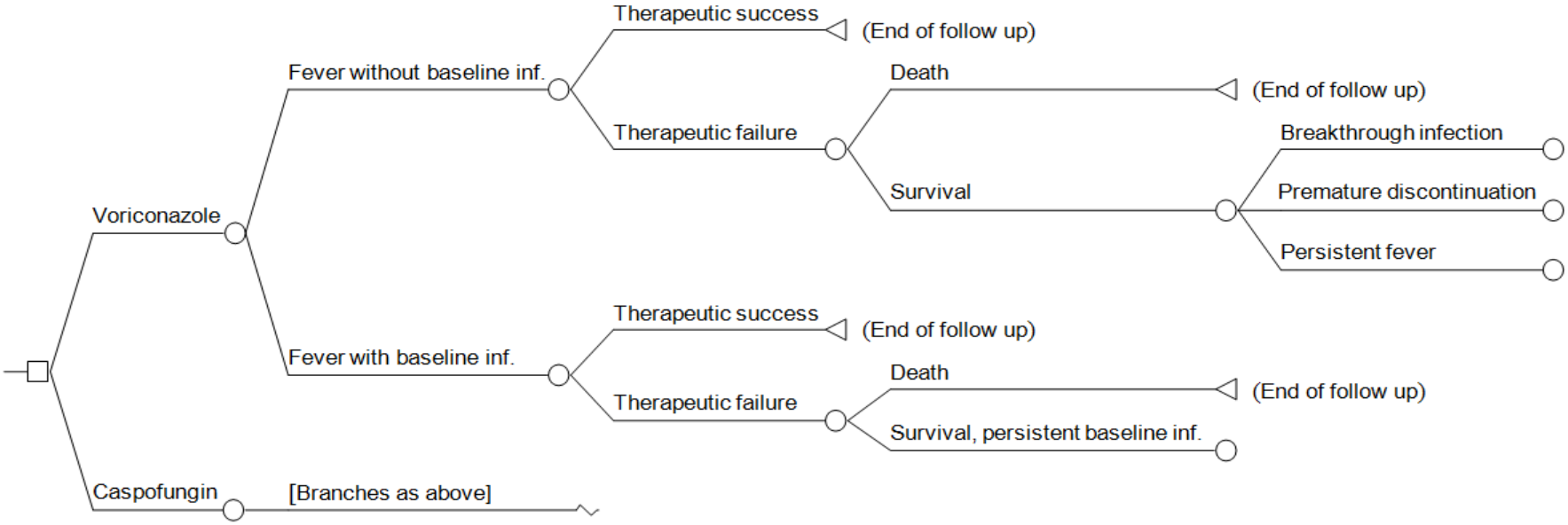

Figure 6-1 Decision tree model of a typical empirical antifungal (i.e., voriconazole and caspofungin) therapy for febrile neutropenia.

6.6.3 MODEL INPUTS

Input data were derived primarily from the trials, and included the incidence of clinical outcomes, duration of initial therapy, and cause of treatment failure. Data inputs for the model regarding clinical outcomes and their probabilities were derived from the two Walsh studies [9,10]. Baseline clinical and probability inputs are summarized in **Table 6-1**.

Table 6-1 Outcomes and probabilities of voriconazole [9] and caspofungin [10] used in the model

Study clinical outcome	Probability with voriconazole (n = 415)	Probability with caspofungin (n = 556)
Fever with no baseline fungal infection	96.87% (n = 402)	95.14% (n = 529)
Therapeutic success	25.37% (n = 102)	33.27% (n = 176)
Therapeutic failure	74.63% (n = 300)	66.73% (n = 353)
Death	11.00% (n = 33)	11.61% (n = 41)
Breakthrough infection	2.67% (n = 8)	8.22% (n = 29)
Premature discontinuation	13.67% (n = 41)	16.15% (n = 57)
Persistent fever*	72.67% (n = 218)	64.02% (n = 226)
Fever with baseline infection	3.13% (n = 13)	4.86% (n = 27)
Therapeutic success	46.15% (n = 6)	51.85% (n = 14)
Therapeutic failure	53.85% (n = 7)	48.15% (n = 13)

*Number of patients with persistent fever = number of patients who failed therapy - number of patients who failed therapy because of other than persistent fever.

An independent expert panel was convened comprising four clinicians, from different major Australian hospitals, with clinical expertise in systemic fungal therapy and specialist knowledge in oncology, hematology, and infectious diseases. All panel decisions were taken at a single meeting in June 2008. Before the meeting, members of the panel were provided with a list of questions regarding missing data to be estimated, and provided with copies of the papers by Walsh *et al*. During the meeting, the members were asked to answer each of the questions, and were given the time and opportunity to discuss their answers until consensus was achieved. The panel provided a consensus view on data required for the model that were otherwise not available, including from literature. These included concomitant antibiotics,

screening and monitoring tests, and intensive care unit (ICU) management. The panel also advised on alternative antifungal therapies commonly used after initial therapy discontinuation. The choice of these was as per the Australian hospital setting, and was dependent on the reason for treatment discontinuation, which included, where breakthrough and baseline infections occurred, the site of infection and the type of infection-causative fungi. The expert panel validated the decision tree in the model.

Based on the trials [9,10], voriconazole was received as a loading dose of i.v. 6 mg/kg twice on the Day 1, followed by twice-daily i.v. dose of 3 mg/kg (or twice-daily 200-mg tablet). Patients on p.o. voriconazole received three days of i.v. therapy before initiating p.o. therapy. For patients with baseline fungal infections, the maintenance voriconazole dose increased to twice-daily i.v. 4 mg/kg or 300-mg tablet. The p.o. voriconazole was received by 22% of all patients on voriconazole. Patients on caspofungin received 70 mg on Day 1, followed by 50-mg daily. The median duration of voriconazole administration was 7 days with a range of 1-113 days [9]. For caspofungin, the mean duration of administration was 13 days [10].

Baseline fungal infections were those diagnosed up to 48 hours after therapy initiation. Fungal infections diagnosed after the baseline infections were categorized as breakthrough infections. For the purpose of this study, patients with premature discontinuation were further classified according to premature discontinuation because of severe toxicity (i.e., infusion-related reaction, hepatotoxicity, and nephrotoxicity) and premature discontinuation due to lack of efficacy against suspected fungal infection or persistent fever.

6.6.4 DATA PROVIDED BY THE EXPERT PANEL

Based on the median and range provided by Walsh et al. [9], the duration of voriconazole therapy was estimated to be 10 days. Filgrastim [granulocyte-colony stimulating factor (G-CSF)], piperacillin/tazobactam, and vancomycin were given to patients concomitantly. Details of diagnostic and monitoring tests given were as described in Appendix (**Section 6.11**). The opinion of the panel was that all 19 patients [9] in the voriconazole arm who experienced premature discontinuation because of side effects would have had severe hepatotoxicity. In the caspofungin arm, 21 of the 27 patients who experienced premature discontinuation because of side effects [10] had infusion-related reactions. Of the remaining six patients in the caspofungin arm, three patients had nephrotoxicity and three had hepatotoxicity. Patients who had baseline infections and failed to respond to therapy, survived with persistent baseline

infections. Alternative antifungal agents given after failures of each of the therapies are shown in **Table 6-A-1** (Appendix, **Section 6.11**).

6.6.5 OTHER STUDY ASSUMPTIONS

The assumptions made with respect to determining costs in the model were as follows:

i. Patients did not incur any out-of-pocket costs. They were covered by Medicare (Australia's public health insurance scheme).
ii. If patients switched initial therapy because of failure, their alternative therapy was successful.
iii. Any alternative therapy was assumed to have duration similar to that of the discontinued initial therapy.

All assumptions were validated by the expert panel.

6.6.6 COST CALCULATIONS

Cost calculations in the current model are defined in Appendix (**Section 6.11**).

Regarding medication doses, patients were assumed to have an average body weight of 76.05 kg, based on the latest available data from the Australian Bureau of Statistics [14]. No average patient body weight was reported in the Walsh et al. studies. Doses for all medications (except posaconazole) were rounded to the nearest vial size. Patients on posaconazole were permitted to share the same posaconazole bottle, as is routine hospital practice in Australia.

Costs were calculated in Australian dollars (AU$) for the financial year 2008/2009. No discounts were applied given the short time-frame of analysis.

Gross (top down) costing was used to measure hospitalization costs in the current study; however, the costing of drugs used, and pathology and imaging tests was more based on micro-costing (bottom up costing). Medication costs used were the drug wholesale prices paid by Australian public hospitals, as per the Health Purchasing Victoria tender (2007-2009) [15]. Hospitalization costs were obtained from published records regarding the 2006/2007 Australian-Refined Diagnosis-Related Groups (AR-DRG) (Code T62A) [16]. Hospitalization costs used were the average direct costs associated with febrile neutropenia, and included the cost of intensive care management. To reduce double counting, the hospitalization costs used

excluded pharmacy, pathology, and imaging costs, as reported in the AR-DRG. In the baseline scenario, hospitalization costs were analyzed with a ± 25% uncertainty. These were adjusted for the financial year 2008/2009 as per the Australian Health Consumer Price Index (2008) [17]. Any other resource costs involved in the study were obtained from the Australian Medicare Benefits Schedule (2009) [18]. Cost inputs used in the model are summarized in **Table 6-2**.

Table 6-2 Resource costs [15,16,18]

Item	Unit	Unit cost (AU$)
Voriconazole	200 mg i.v. vial	190.84
	200 mg p.o. tablet	45.62
Caspofungin	70 mg i.v. vial	700.00
	50 mg i.v. vial	700.00
LAmB	50 mg i.v. vial	295.00
Posaconazole	105 mL p.o. suspension	669.50
Fluconazole	200 mg p.o. capsule	2.61
Piperacillin/tazobactam	4.5 mg i.v. vial	24.00
Vancomycin	500 mg i.v. vial	5.45
Filgrastim	480 µg i.v. vial	240.70
Chest x-ray	1 test	35.35
CT scan	1 test	295.00
Non-blood culture	≥ 1 tests (1 culture)	34.00
Blood culture	1 test (1 culture)	30.95
Bronchoscopy	1 test	217.15
Complete blood count	1 test	17.20
Renal function test	1 test	146.30
Liver function test	1 test	17.80
Electrolytes test	1 test	24.90
ICU consultant	First day	334.55
	Subsequent day	248.20
Hospitalization	Inpatient per day	639.00

i.v., intravenous; p.o., oral.

6.6.7 SENSITIVITY ANALYSIS

Different scenarios produced by modification of the values of several key variables and assumptions in relation to costs and probabilities, were analyzed to evaluate the robustness of the study conclusion.

Alternative scenario. The two Walsh trials were of the same design, including having identical inclusion and exclusion criteria and outcomes. However, the population recruited into the caspofungin versus LAmB trial appeared sicker than that of the voriconazole versus LAmB trial. This is because the mortality rate associated with patients on LAmB in the voriconazole versus LAmB study was 4.92% [9], while the mortality rate associated with patients on LAmB in the caspofungin versus LAmB study was 10.76% [10]. To account for this, sensitivity analyses down-adjusted the probabilities of the outcomes in the caspofungin trial the same proportional amount as observed in the respective LAmB groups. For example, regarding the probability of premature discontinuation, the rate of premature discontinuation of LAmB, as in the caspofungin versus LAmB study [10], was 14.47%, while the rate of premature discontinuation of LAmB, as in the voriconazole versus LAmB study [9], was 6.64%. This constitutes a relative reduction of 54.11% in the rate of premature discontinuation of LAmB. This reduction ratio was used to down-adjust, in a liner fashion, the probability of premature discontinuation of caspofungin; whereby, the 10.25% probability of premature discontinuation, associated with caspofungin [**Table 6-A-2**, Appendix (**Section 6.11)**], was reduced by 54.11% (absolute reduction of 5.55%) to produce an adjusted value of 4.70%. The sensitivity analyses also tested adjusted duration of caspofungin therapy according to voriconazole therapy.

One-way sensitivity analyses. The sensitivity of the results to other key input variables was also evaluated.

The analyses included a threshold analysis, in which, for an input variable, the highest and lowest values within a reasonable range of values were used as substitutes for the baseline value. If the study conclusion did not change, the range of substitution was further increased in the direction that minimized the "leading drug's" economic advantage. Where the highest or lowest substitution changed the study conclusion, more values within the range were used to replace the baseline value. This was repeated until the threshold value that changed the study conclusion was determined. The inputs included variations in price of the antifungals, duration of hospitalization, omission of the increase in voriconazole dose with baseline infections, and voriconazole dosage form given before discontinuation. These were important due to that medication prices can easily vary, and that the average daily hospitalization costs and durations are known to be not precise. Similarly, data provided by the expert panel may be influenced by the clinicians' local circumstances, practices and experiences. The effects of

estimations made by the expert panel were investigated as a result. These included ICU duration, use of antibiotic and G-CSF, screening and monitoring tests, and dose of alternative LAmB. Key variables and the ranges of their variations are shown in **Table 6-A-3** (Appendix, **Section 6.11**).

Probabilistic sensitivity analyses. Uncertainty analyses were performed via Monte Carlo simulation (5,000 iterations), using @Risk-5.5® (Palisade Corporation, NY, USA). A description of the Monte Carlo method is provided in Appendix (**Section 6.11**). One-way sensitivity analysis was performed with an assumed uncertainty of 10% for the probabilities of breakthrough infection, premature discontinuation, and persistent fever. A 5% uncertainty range was used for all other probabilities in the model. Corresponding costs were calculated, and a distribution of "cost saving" was obtained. Input variables and their uncertainty distributions are shown in **Table 6-A-4** (Appendix, **Section 6.11**).

6.7 RESULTS

6.7.1 COST OF EMPIRICAL THERAPY

In the base-case analysis, use of caspofungin led to a lower weighted average cost of empirical therapy compared to voriconazole, an economic advantage in the order of AU$798 (1.9%) (**Table 6-3**). Persistent fever was the main contributing clinical outcome to therapeutic costs for both medications. The proportion and cost for each model outcome are shown in **Table 6-A-2** (Appendix, **Section 6.11**). Main components, and their contribution, in total costs are illustrated in **Fig. 6-2**.

Higher probability of success and lower probability of death were associated with caspofungin (**Table 6-3**). The costs of success and survival with caspofungin were lower than that with voriconazole.

6.7.2 SENSITIVITY ANALYSES

Alternative scenario. Down-adjustment of the caspofungin outcomes further increased the economic advantage of caspofungin to AU$5,681 (CI, 2,640; 8,810).

Table 6-3 Results from the model of empirical therapy

	Caspofungin (AU$) mean (p2.5; p97.5)*	Voriconazole (AU$) mean (p2.5; p97.5)*	Incremental cost (AU$) mean (p2.5; p97.5)*
Total cost /patient	40,558 (36,870; 44,290)	41,356 (37,760; 45,270)	798 (-3,370; 4,840)
Probability of success	34.22 (32.50; 36.00)	25.96 (24.65; 27.25)	
Total cost /successful case	118,516 (108,360; 129,100)	159,320 (145,450; 174,270)	40,804 (27,240; 54,950)
Probability of survival	92.63 (92.12; 93.13)	92.07 (91.53; 92.58)	
Total cost /life saved	40,588 (36,900; 44;330)	41,389 (37,790; 45,300)	801 (-3,370; 4,840)

*Uncertainty range (2.5th percentile and 97.5th percentile of simulated uncertainty distribution).

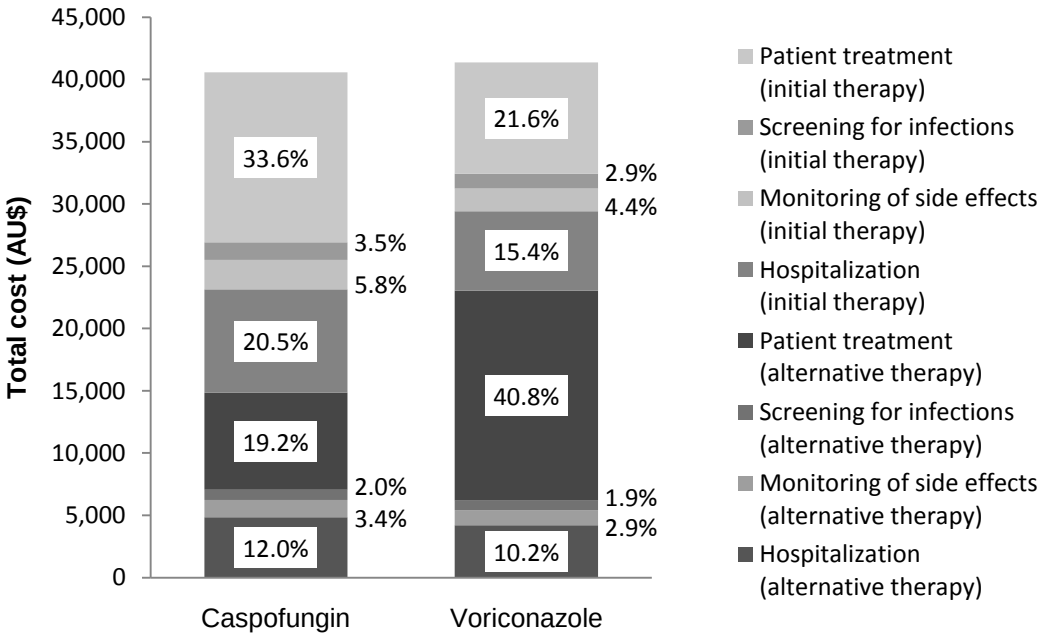

Figure 6-2 Cost components and their contributions in overall therapy.

One-way sensitivity analyses. The model was not sensitive to changes in the voriconazole acquisition prices. Voriconazole had the economic advantage when the price of its i.v. vial was reduced from AU$190.84 to AU$41.98, and when the prices of its i.v. vial and p.o. tablet were reduced by 69% to AU$59.16 and AU$14.14, respectively. Reducing the price of the tablet alone from AU$45.62 to AU$0.00 did not change the study conclusion. The model was faintly sensitive to the price of caspofungin. Increasing the price of 50-mg caspofungin from

AU$700.00 to AU$766.50, the price of 70-mg caspofungin from AU$700.00 to AU$1,463, or the prices of both 50- and 70-mg caspofungin to AU$763.00 was needed for voriconazole to have a lower total cost. Nonetheless, the model was sensitive to the acquisition price of LAmB. A AU$18.00 reduction in the price of LAmB (to AU$277.00) caused the economic advantage to be with voriconazole. The study was also sensitive to the duration of therapy. Voriconazole had a cost saving over caspofungin when its duration was less than 9.8 days, or when the caspofungin duration was more than 13.3 days. The study result was insensitive to the cost of hospitalization. Elimination of the daily hospitalization cost resulted in more than AU$10,000 reduction in the total cost of either antifungal, but the overall cost difference (AU$3,381) was still in favor of caspofungin. The model was not sensitive to the daily cost of ICU stay. A more than four-fold increase (to AU$2,996) in the cost of ICU stay raised the total cost of each of voriconazole and caspofungin by about AU$20,000. This had no effect on the cost savings with caspofungin (a AU$5,558 difference).

The sensitivity of the model outcome to the scenario of having no increase in the voriconazole dose, when given to patients with baseline fungal infections, was negligible. However, the model showed some sensitivity to the ratio of patients receiving p.o. voriconazole as initial therapy. When the p.o. formulation of voriconazole was given to more than 48% of patients on voriconazole, cost savings were with voriconazole. When all patients in the voriconazole arm received the p.o. formulation only, an overall cost saving of AU$1,816 was associated with voriconazole over caspofungin.

Baseline cost difference was not sensitive to the time spent in ICU, tested within a range of 1-10 days, where change in outcome was negligible. Similarly, the study outcome was insensitive to excluding the use of concurrent antibiotics and G-CSF, or the screening and monitoring tests. Excluding either of these variables increased the cost advantage of caspofungin to about AU$2,060. The study outcomes, however, were sensitive to the dose of LAmB prescribed as alternative therapy. Replacing the 5-mg/kg/day doses of alternative LAmB by 3-mg/kg/day doses, led to a cost difference of AU$4,859 in favor of voriconazole.

Probabilistic sensitivity analyses. As per uncertainty analysis, via Monte Carlo simulation, the mean expected cost saving was AU$733 per patient in favor of caspofungin. The analysis demonstrated that caspofungin has a 65.5% chance of having an economic advantage over voriconazole. Caspofungin had a maximum expected cost advantage of AU$6,418, while the maximum expected cost saving with voriconazole was AU$5,684. A "cost saving" probability curve is shown in **Fig. 6-3**, which illustrates the likelihood of any of caspofungin and voriconazole to have an overall economic advantage over the other. The ranking of main clinical variables, based on their impact on the model outcome as resulted from the Monte Carlo simulation, is shown in **Fig. 6-4**.

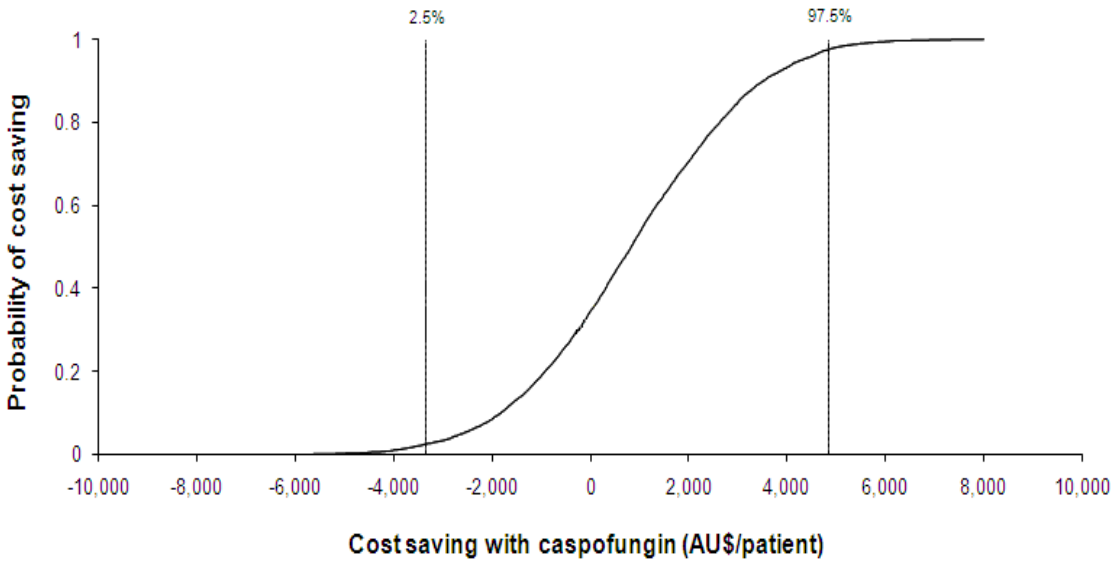

Figure 6-3 "Cost saving" probability curve of caspofungin.

6.8 DISCUSSION

This is the first comparative investigation of voriconazole versus caspofungin for the empirical use in febrile neutropenia. With a mean expected cost difference of AU$798 per patient, caspofungin was associated with a cost saving over voriconazole (**Table 6-3**). In addition, from therapy success and deaths prevented standpoints, caspofungin demonstrated higher success and survival rates, as per the Walsh et al. trials [9,10], as well as lower costs of success and survival (AU$40,804 and AU$801 difference, respectively). It appears that caspofungin is a dominant empirical medication over voriconazole.

Despite similar trial design and population demographics, the caspofungin versus LAmB study appeared to have recruited a sicker population than that in the voriconazole versus LAmB trial. In spite of this, however, caspofungin demonstrated dominance over voriconazole in the current investigation. Thus, it was not surprising that down-adjusting the caspofungin outcomes to align with those observed in the voriconazole trial increased the caspofungin advantage further.

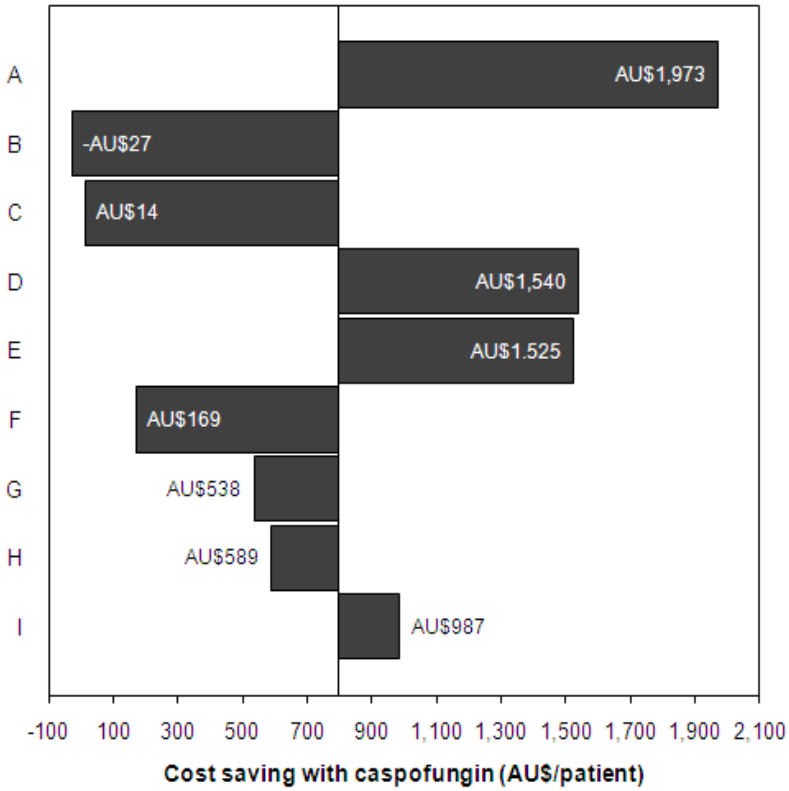

Figure 6-4. A tornado diagram of the regression of variables as per their influence on the model outcome. The influencing variables are persistent fever with voriconazole (A), persistent fever with caspofungin (B), fever without baseline infections with caspofungin (C), fever without baseline infections with voriconazole (D), therapeutic failure of fever without baseline infections with voriconazole (E), therapeutic failure of fever without baseline infections with caspofungin (F), premature discontinuation with caspofungin (G), premature discontinuation with voriconazole (H), and therapeutic success of fever without baseline infections with caspofungin (I).

As no long-term-survival and quality-of-life data were available from the Walsh et al. studies [9,10], it was not possible for the current analysis to estimate the life years gained [20] as well as to apply the Markov modeling [21] with high degree of reliability, given inherent limitations with basing these on short-term data. Furthermore, long-term data are of more relevance to studies with a healthcare system or societal perspective, whereas the adoption of the hospital system perspective in this study is more appropriate for acute diseases such as febrile neutropenia.

An ideal economic evaluation would be based on a randomized clinical trial, which is the best available clinical source to provide the most valid and reliable evidence of data [22-24]. Importantly, the economic results reported in this study are applicable to the Australian

setting, as the results from the trials by Walsh et al. are generalizable to the Australian healthcare setting, since both trials were international multi-center studies, patients reflected the Australian clinical caseload, and both voriconazole and caspofungin were administered similarly to what is recommended in current Australian guidelines [11,12].

A strength of the current model is the follow up of all patients after the discontinuation of randomized therapies in the trials, whereby, the model evaluated the overall cost associated with the group of patients who received voriconazole as initial therapy with that associated with the group of patients who received LAMB as initial therapy. This facilitates the estimation of realistic costs, and provides a better understanding of the full impact of medications as first-line therapies. The model did not compare between voriconazole and LAMB as initial therapies only. Furthermore, the decision model fully depicted the standard five-component endpoint (i.e., survival, breakthrough infection, persistence of baseline infection, fever persistence, and premature discontinuation) currently used in assessing the efficacy of antifungals in empirical therapy [25]. This would result in the measured costs fully reflecting all possible clinical patterns and pathways reported, and will be highly valuable for the accurate representation of the overall cost of empirical therapies. The current evaluation is also unique in that the breakthrough and baseline infections were given a monetary value through measuring the costs associated with alternative antifungals used for treating them [**Table 6-A-1**, Appendix (**Section 6.11**)]; these were decided on after consideration of the site of infection as well as the type of infection-causative fungi (e.g. aspergillosis, candidiasis, zygomycosis). These estimations were based on day-to-day clinical experience of the expert panel, which reflected current Australian practice, as well as providing practical secondary-costs estimates. A better understanding of prescribing habits was also enabled.

Caspofungin was associated with a higher rate of overall therapy success over voriconazole. While voriconazole had lower rates of breakthrough fungal infections and persistent baseline infections, caspofungin was associated with lower rates for all other causes of failure (i.e., death, premature discontinuation, and persistent fever). Importantly, the total monetary value of the model's outcomes was lower with caspofungin. This may have not been expected given the relatively lower acquisition costs associated with voriconazole as compared with caspofungin (AU$8,931 versus AU$13,629, **Fig. 6-2**). This is important as it reflects the role of the alternative medications, given that overall medication cost is the sum of both acquisition and secondary costs. While alternatives given after voriconazole discontinuation were mostly of the high-cost LAmB, alternatives to caspofungin mainly comprised the significantly cheaper voriconazole. This is especially important in relation to the outcome of persistent fever, where the difference in alternatives given, after each of caspofungin and voriconazole, resulted in AU$8,407 in favor of caspofungin (**Table 6-A-2**).

Indeed, the caspofungin cost advantage regarding secondary costs (AU$7,772 versus AU$16,864) was higher than the voriconazole advantage in relation to the acquisition costs to the extent that the study conclusion was not sensitive to realistic variations in the voriconazole and caspofungin prices. The model, however, was sensitive to the LAmB price, which further emphasizes the role of alternative medications. More than AU$18.00 reduction in the cost of alternative LAmB resulted in the secondary cost for voriconazole being lower than that for caspofungin and, ultimately, the overall costs as well. These observations highlight the need for decision makers to consider both acquisition costs and secondary costs (cost of therapy failure), when making decisions on medication prescribing. On more occasions with voriconazole than with caspofungin, the expert panel felt that the higher 5-mg/kg/day dose was appropriate for the alternative LAmB [**Table 6-A-1**, Appendix (**Section 6.11**)]. The sensitivity analysis of the scenario of replacing the 5-mg/kg/day doses with 3-mg/kg/day doses, resulted in the overall cost saving significantly shifting to favor voriconazole. This highlights the influence of clinicians' antifungal-switching practices on therapy costs.

In addition to the sensitivity to alternative therapies, the model outcome was also highly sensitive to the duration of antifungal therapy. This is expected given that the daily costs associated with the use of either antifungals account for more than 7% of the total therapy. Daily costs of caspofungin and voriconazole were AU$2,995 and AU$3,921, respectively.

Further to the sensitivity analyses, the model demonstrated sensitivity to the initial voriconazole dosage form used. If more of the p.o. form relative to the i.v. form of voriconazole was prescribed, the total cost of voriconazole was decreased. Nonetheless, prescribing voriconazole orally may not be always possible, given the frequent cases of impaired gastrointestinal function (i.e., mucositis) in patients receiving chemotherapy.

As expected, eliminating the hospitalization cost considerably reduced the total cost associated with both antifungals. Nevertheless, the study conclusion was not affected. In relation to the cost of ICU stay, for the Australian setting, there is no available exclusive ICU cost per bed and, hence, the average hospitalization cost per day was used instead. In any case, when cost per day during the ICU stay was replaced with a total ICU daily cost (AU$2,996), reported in literature for a local hospital [26], the net study outcome did not change.

The baseline cost difference was also not sensitive to the scenario of not having a voriconazole dose increase in patients with baseline infections. The model outcome was also not sensitive to estimations made by the expert panel regarding ICU duration of stay, concurrent antibiotics and G-CSF, and screening and monitoring tests.

According to the uncertainty analysis, the variables that affected the model most were persistent fever, fever without baseline infection, and therapeutic failure of fever without

baseline infection (**Fig. 6-4**). This was anticipated, as these variables have the highest ratios of patient distribution among all variables, which translates into longer overall hospital stay and, ultimately, higher overall cost. The economic advantage of caspofungin declined the sharpest, if the rate of persistent fever and/or fever without baseline infection decreased with voriconazole and/or increased with caspofungin. Importantly, the Monte Carlo simulation demonstrated a clear economic advantage with using caspofungin. The likelihood of caspofungin generating cost savings over voriconazole was above 60%. The mean expected net saving, generated from 5,000 simulations, was associated with caspofungin. The maximum expected cost saving was higher with caspofungin than with voriconazole (**Fig. 6-3**).

Estimating data based on expert panel opinion is also a limitation of this study. Hospital resources could have been obtained from local hospital protocols. An expert panel, representing a wide variety of hospital practices, was used however, to increase the study's generalizability to patients outside the local hospital setting. Because no literature in relation to alternatives to empirical antifungals is available, the expert panel provided required data on alternatives usually given in the case of treatment failure. Expert judgment is considered the best available source in situations where no other data sources are available [27]. The number of panel members involved was in accordance with the literature [28-31].

The cost of treating common side effects (e.g., visual disturbances, headache, and chills) was not accounted for in this study. It was not possible for the expert panel to provide reliable estimations for the resources used to manage such side effects. However, these are usually moderate and do not cause therapy discontinuations, nor are they likely to significantly impact cost estimations. Furthermore, caspofungin has fewer reported side effects than voriconazole [32]; therefore, accounting for all side effects associated with the two antifungals would most likely increase the caspofungin economic advantage further. Based on the expert panel, no patients with baseline infections would have failed therapy because of death. This was due to the small number of patients with baseline infections who did not respond to therapy (7 and 13 patients for voriconazole and caspofungin arms, respectively) [9,10].

Given that no head-to-head comparisons had been performed of voriconazole versus caspofungin for empirical therapy, for the purpose of this study, the voriconazole and caspofungin data were derived from different sources, albeit with similar trial design and population demographics. This is a limitation, as medications can perform differently in different settings. Nonetheless, the current results favored caspofungin over voriconazole, and down-adjusting caspofungin outcomes according to voriconazole outcomes only increased its advantage further.

It is a limitation that the decision model only allowed for a single switch to alternatives after discontinuations. This assumption was made because no data regarding a second switch to antifungal alternatives were available. In addition, it was not possible for the expert panel to reliably provide the speculative required data. Nevertheless, given that the total discontinuation probability was higher with voriconazole (66.03 versus 58.46, **Table A-1**), allowing for secondary therapy switches will mostly advantage caspofungin. The assumption that subsequent alternative medication had a similar duration to that of the initial medication is another limitation. There is no data available about the duration of empirical antifungal therapy in Australia. Given that the voriconazole and caspofungin data were driven from different settings, their duration of therapy was different (10 and 13 days, respectively). However, despite longer duration of therapy for caspofungin and its alternatives, caspofungin had a lower total cost than voriconazole. Accordingly, as part of the sensitivity analyses, adjusting either antifungal's duration of therapy according to the other will only increase the advantage of caspofungin further.

Indeed, prospectively collected economic data from head-to-head studies involving voriconazole and caspofungin in empiric therapy will be valuable, and will address the limitations in the current study.

Due to an increasing demand for the high-cost antifungals (e.g., voriconazole and caspofungin) which exerts a considerable strain on limited hospital budgets [1,2], it is extremely important that decisions regarding the choice of empirical antifungals should be based on cost considerations, in addition to efficacy and safety data. The value of this study extends beyond the reporting of comparative economic data. This study provides an outline to anticipate costs associated with the different empirical regimens as per local practices and patterns (e.g., therapy duration and dose, and type of alternative medications).

In conclusion, given the data, assumptions, limitations, and perspective used, caspofungin appears to be a more cost-beneficial option than voriconazole for empirical therapy in neutropenia with fever. Caspofungin was associated with lower overall medical costs.

6.9 ACKNOWLEDGMENTS

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6.11 APPENDIX

6.11.1 DATA PROVIDED BY THE EXPERT PANEL

Patient monitoring tests were a daily complete blood count, as well as renal and liver function tests. For diagnostic tests, a chest X-ray was done at onset of therapy and then thrice weekly. Patients received a Computed Topography (CT) scan three days after commencing antifungal therapy, with 40% of patients receiving a second follow-up scan. Blood and non-blood

microbiological cultures (i.e., sputum, biopsy, feces, and urine) were performed twice to thrice weekly. Based on panel's estimation, 7.5% of patients spent five days in ICU, where patients received a bronchoscopy, an additional CT scan, thrice-daily tests of electrolytes, and daily monitoring of blood and non-blood microbiological cultures. Antibiotics and G-CSF, screening and monitoring tests, and ICU management were not affected by the type of empirical antifungal agent, and therefore, their frequency and nature were the same during both therapies.

6.11.2 COST CALCULATIONS

The model was used to generate a weighted average cost per patient treated with either voriconazole or caspofungin. This was the sum-product of the eight treatment pathways costs and their respective probabilities.

The cost per successfully-treated or deceased patient was calculated as a proportion of both the cost of a complete course of initial therapy and the cost of resources consumed. The cost of any failure, except death, was the cost of both initial and alternative therapies added to the cost of resources used. The cost of initial therapy was the cost of a complete course of voriconazole or caspofungin before switching to alternatives. The cost of an alternative therapy was the cost of a complete course of the alternative agent.

6.11.3 MONTE CARLO SIMULATION

Monte Carlo refers to a method whereby simulated input values, chosen from ranges defined by probability distributions, are run in the model [19]. The simulated inputs result in a range of outcomes that portrays the outcomes' uncertainty. An accurate probabilistic sensitivity analysis typically requires 1000 or more model runs [19]. Uncertainly analysis was applied to investigate the likelihood of cost saving. Clinical outcomes that most affected the overall drug cost were also determined.

Table 6-A-1 Alternatives after voriconazole and caspofungin failure

Cause of therapy failure	Alternative	Details
Voriconazole, with premature discontinuations		
Severe infusion-related reactions	LAmB	3 mg/kg/day

Table 6-A-1 *Continued*

Cause of therapy failure	Alternative	Details
Severe nephrotoxicity	Caspofungin	Standard*
Severe hepatotoxicity	LAmB	3 mg/kg/day
Lack of efficacy against suspected fungal inf.	LAmB	5 mg/kg/day
Lack of efficacy against persistent fever	LAmB	3 mg/kg/day
Voriconazole, with breakthrough fungal infection		
Aspergillus species	LAmB	5 mg/kg/day
Candida species	Caspofungin	Standard*
Zygomycetes	LAmB	5 mg/kg/day
Voriconazole, with non-responding baseline fungal infection		
Aspergillus species	LAmB	5 mg/kg/day
Candida species	Caspofungin	Standard*
Zygomycetes	LAmB	5 mg/kg/day
Voriconazole, with persistent fever	LAmB	5 mg/kg/day
Caspofungin, with premature discontinuations		
Severe infusion-related reactions	Voriconazole (i.v.)	Standard†
Severe nephrotoxicity	Voriconazole (i.v.)	Standard†
Severe hepatotoxicity	LAmB	3 mg/kg/day
Lack of efficacy against suspected fungal inf.	Voriconazole (i.v.)	Standard†
Lack of efficacy against persistent fever	Voriconazole (i.v.)	Standard†
Caspofungin, with breakthrough fungal infection		
Aspergillus species	Voriconazole (i.v.)	Standard†
Candida species	LAmB	3 mg/kg/day
Zygomycetes	LAmB	5 mg/kg/day
Fusarium species	Voriconazole (i.v.)	Standard†
Trichosporon species	Voriconazole (i.v.)	Standard†
Caspofungin, with non-responding baseline fungal infection		
Aspergillus species	Voriconazole (i.v.)	Standard†
Candida species	LAmB	3 mg/kg/day
Dipodascus capitatus	Voriconazole (p.o.)	Standard‡
Zygomycetes	LAmB	5 mg/kg/day
Caspofungin, with persistent fever	Voriconazole (i.v.)	Standard†

i.v., intravenous; p.o., oral.

*70 mg/day (loading dose), 50 mg/day (maintenance dose).

†6 mg/kg twice daily (loading dose), 3 mg/kg twice daily (maintenance dose).

‡6 mg/kg twice daily (loading dose), 200 mg twice daily (maintenance dose).

Table 6-A-2 Weighted cost of empirical voriconazole and caspofungin

	Voriconazole			Caspofungin		
Therapy outcome	Proportion (%)	Cost (AU$)* /patient	Proportional cost (AU$)* (p2.5; p97.5)‡	Proportion (%)	Cost (AU$)* /patient	Proportional cost (AU$)* (p2.5; p97.5)‡
Fever with no baseline infection						
Therapeutic success	24.51	18,338	4,495 (4,114; 4,899)	31.65	25.692	8,132 (7,467; 8,847)
Death	7.95	18,338	1,455 (1,321; 1,602)	7.37	25.692	1,894 (1,719; 2,076)
Breakthrough infection	1.93	50,761	977 (874; 1,084)	5.22	57,687	3,010 (2,678; 3,367)
Premature discontinuation	9.86	47,295	4,662 (4,173; 5,191)	10.25	50,214	5,149 (4,552; 5,774)
Persistent fever	52.40	54,911	28,774 (25,840; 31,940)	40.65	50,109	20,367 (17,990; 22,820)
Fever with baseline infection						
Therapeutic success	1.44	18,719	270 (248; 295)	2.57	26,096	670 (615; 728)
Death	-	-	-	-	-	-
Persistent baseline infection	1.69	42,832	722 (665; 782)	2.34	57,093	1,336 (1,231; 1,447)
Total cost per patient†			41,356 (37,760; 45,270)			40,558 (36,870; 44,290)

*All shown cost values were shortened to the nearest no-decimal digits status.

†Calculations involving cost values took in consideration 2 decimal digits (not-shown) associated with each of the cost values.

‡Uncertainty range (2.5th percentile and 97.5th percentile of simulated uncertainty distribution).

Table 6-A-3 Key variables and ranges over which they varied in one-way sensitivity analysis

Variable	Base case	Variation range	
		Low	High
Voriconazole cost/i.v. vial	AU$190.84	AU$00.00	AU$200.00
Voriconazole cost/p.o. tablet	AU$45.62	AU$00.00	AU$50.00
Caspofungin cost/70 mg vial	AU$700.00	AU$650.00	AU$1,600.00
Caspofungin cost/50 mg vial	AU$700.00	AU$650.00	AU$1,600.00
LAmB cost/vial	AU$295.00	AU$200.00	AU$350.00
Voriconazole administration duration	10 days	5 days	10 days
Caspofungin administration duration	13 days	13 days	18 days
Counting for the hospitalization cost	Yes	No	Yes
ICU cost per day	AU$639.00	AU$639.00	AU$2,996.00
Increase in the voriconazole dose in the presence of baseline infections	Yes	No	Yes
Dosage form of initial voriconazole (p.o.:i.v.)	1:1	0:1	1:0
ICU duration	5 days	1 days	10 days
Counting for the costs of antibiotics and G-CSF	Yes	No	Yes
Counting for the cost of screening and monitoring tests	Yes	No	Yes
Replacement of the 5 mg/kg doses of alternative LAmB with 3 mg/kg doses	No	No	Yes

i.v., intravenous; p.o., oral.

Table 6-A-4 Input variables and uncertainty distributions used in Monte Carlo simulation

	Uncertainty distribution*	
Input variables	Voriconazole	Caspofungin
Fever without baseline infection	Triangular distribution, 92.03%-96.87%-100%	Triangular distribution, 90.38%-95.14%-99.90%
Therapeutic success	Triangular distribution, 24.10%-25.37%-26.64%	Triangular distribution, 31.61%-33.27%-34.93%
Therapeutic failure	Triangular distribution, 70.90%-74.63%-78.36%	Triangular distribution, 63.39%-66.73%-70.07%
Death	Triangular distribution, 10.45%-11.00%-11.55%	Triangular distribution, 11.03%-11.61%-12.19%
Breakthrough infection	Triangular distribution, 2.40%-2.67%-2.94%	Triangular distribution, 7.40%-8.22%-9.04%
Premature discontinuation	Triangular distribution, 12.30%-13.67%-15.04%	Triangular distribution, 14.54%-16.15%-17.77%
Persistent fever	Triangular distribution, 65.40%-72.67%-79.94%	Triangular distribution, 57.62%-64.02%-70.42%
Fever with baseline infection	Triangular distribution, 2.97%-3.13%-3.29%	Triangular distribution, 4.62%-4.86%-5.10%
Therapeutic success	Triangular distribution, 43.84%-46.15%-48.46%	Triangular distribution, 49.26%-51.85%-54.44%
Therapeutic failure	Triangular distribution, 51.16%-53.85%-56.54%	Triangular distribution, 45.74%-48.15%-50.56%

*The type of distribution, and the minimum - most likely - maximum values in the uncertainty ranges, used in the Monte Carlo simulation.

CHAPTER SEVEN: ANTIFUNGAL PROPHYLAXIS IN ACUTE MYELOID LEUKAEMIA

The preceding studies in **Chapters Four** to **Six** of this thesis focussed on the use of high-cost antifungals in the empirical setting. It is important to note that high-cost antifungals are also used prophylactically to prevent invasive fungal infections (IFIs), especially in patients with high risk for infections, for example, in the setting of acute myeloid leukaemia. This chapter provides an introduction to the economic evaluation reported in **Chapter Eight**. It describes the antifungal prophylaxis, followed by a review of voriconazole and posaconazole as current prophylactic antifungal agents.

7.1 ACUTE MYELOID LEUKAEMIA

Acute leukaemia is a major risk factor for IFI, second only to hematopoietic stem-cell transplant.[1, 2] Until about 150 years ago, it was diagnosed as infection, anaemia, dropsy, or other conditions with variable aetiologies. Leukaemia is believed to be the result of an abnormal process of differentiation of the hematopoietic stem-cell (HSC) into the different types of normal blood cells, a process called hematopoiesis.[3-6] A low count of red blood cells leads to anaemia and general weakness, while low neutrophil and monocyte counts lead to slow recovery and severe infections.[7] Leukaemia is primarily classified into chronic or acute. In the chronic leukaemia, leukaemia cells develop from abnormal mature cells, which grow and progress slowly. The acute leukaemia cells develop from young cells called blasts. These divide frequently and progress rapidly. Acute leukaemia is classified as myeloid or lymphoid, according to the type of differentiation shown by the affected cells.[8, 9] These are called acute myeloid leukaemia (AML) and acute lymphoid leukaemia (ALL), respectively. Standardised classification of AML and ALL was first introduced in the 1970s by the French/American/British (FAB) classification, which was founded on differences in cell morphology descriptions.[10] While FAB classified ALL into L1, L2 and L3 according to size and morphology, AML was classified into eight subtypes, M0 to M7. M1, M2 and M4 subtypes are involved in 17%, 30% and 25% of all AML episodes, respectively. M3 and M5 are responsible for about 10% of reported AML episodes, and M0, M6 and M7 are linked to less than 5% of AML episodes.[11] In 2001, the World Health Organisation (WHO) updated the classification of AML and ALL into one that is not solely based on morphological data, but

also clinical, phenotypic and genetic data.[12] FAB, however, is one of the well recognised classification systems for acute leukaemia, and is still being used to date.[10]

Patients with AML are particularly at higher risk of IFI. This is mainly because of the prolonged and severe neutropenia associated with the potent myelosuppressive cytotoxic regimens that are administered to these patients during the initial induction phase of the treatment and again after relapse.[13, 14]

In patients with AML, the administration of prophylactic antifungal agents has been associated with a reduction in IFIs. This was especially notable with regard to yeast infections, reflected by the fact that in most published studies on the prophylactic use in this population, patients received fluconazole as the prophylactic agent.[15, 16]

7.2 ANTIFUNGAL PROPHYLAXIS IN AML

Antifungal prophylaxis, where antifungal agents are administered to patients who are at high risk of developing IFIs, is increasingly being used in haematology and oncology settings, where the prophylactic antifungal agent is initiated with the commencement of chemotherapy. The clinical rationale for adopting this approach is based on the poor diagnostic techniques available, the ineffectiveness and high cost of treating established and suspected fungal infections,[17-19] the high rates of recurrent fungal infection if the patient requires and receives further immunosuppressive therapy, and the fact that environmental control (e.g. by air filtration) is only partially successful in reducing the incidence of invasive aspergillosis.[20, 21]

Characteristics of antifungal drugs that should be used prophylactically against IFIs would include broad spectrum of activity (e.g. against *Candida* species, *Aspergillus* species and other moulds), proven effectiveness in the prophylactic setting, availability as an oral formulation with high systemic bioavailability, availability in parenteral form (especially if low compliance or oral bioavailability is expected with oral administration), acceptable safety profile, few clinically significant drug interactions and low cost.

Prophylaxis with fluconazole has been shown to result in excellent clinical outcomes against *Candida* species, resulting in reduced colonisation, rate of IFIs and rate of mortality;[22] however, its use is limited by narrow spectrum of activity (i.e. it is inactive against *Aspergillus*).[23] Itraconazole has an extended spectrum of activity, and in a randomised clinical trial, it was shown to be more effective than fluconazole for prophylaxis; however, mainly because of poor oral bioavailability, it was superseded by newer safer and more effective antifungal agents.[24] Conventional amphotericin B-based prophylaxis was associated with success and reduced the risks of IFIs; however, its use is limited by the lack of oral

formulations and severe infusion-related toxicity.[14] Nebulised amphotericin B was shown to significantly reduce the nephrotoxicity associated with conventional amphotericin B; however, it is ineffective in preventing aspergillosis.[25] Liposomal amphotericin B (LAmB) usage is limited by a considerably high cost. Thus, it is being used intermittently as a means of reducing cost.[26] LAmB, however, is limited by its intravenous (IV) administration and the lack of clinical data in the prophylaxis setting. Voriconazole and posaconazole have demonstrated success as prophylaxis,[27, 28] and are discussed in detail below.

7.2.1 VORICONAZOLE VERSUS POSACONAZOLE

Of the 'newer' triazole antifungals (i.e. voriconazole, posaconazole, ravucinazole and albaconazole),[29, 30] voriconazole and posaconazole are the only agents currently available in clinical practice in Australia. Both voriconazole and posaconazole have broad spectra of activity against most fungi. Voriconazole has been available since 2002 and has been a primary therapy for IFIs.[31] It is available in oral tablets and IV formulations, and is administered twice daily.[32] Posaconazole became commercially available in Australia and Europe early in 2006, and was later approved in the United States. It is only available as an oral suspension, and optimal oral bioavailability is obtained when administered with food, as four-daily doses for targeted therapy,[33] and three-daily doses for prophylaxis.[28] Key characteristics of voriconazole and posaconazole are compared in **Table 7-1**.

The availability of both IV and well-absorbed oral formulations is a distinct advantage for voriconazole;[32] however, drug interactions are a major drawback for its use. In contrast, posaconazole has fewer drug interactions. Posaconazole is fungistatic against most fungi and prolonged treatment may be needed.[34] It is only available in oral formulation and its administration can be problematic in patients who cannot tolerate oral treatment.[33]

Voriconazole has a favourable toxicity profile. Visual disturbances are the most common side effects associated with voriconazole (21%), but they are reversible and rarely lead to discontinuation.[32] Hepatotoxicity has been reported with voriconazole in 10% of patients and, although reversible, it can be severe and lead to treatment discontinuation. Dermatological reactions (e.g. rash) were reported in 7% of patients on voriconazole, but they rarely result in discontinuation of therapy.[32] Posaconazole appears to have fewer side effects than voriconazole and they are usually mild. Side effects were observed in 38% of patients, most commonly nausea (8%), vomiting (6%), headache (5%), abdominal pain (4%) and diarrhoea (4%). Hepatotoxicity was observed in 3% of patients.[35]

Table 7-1. Characteristics of voriconazole and posaconazole[32, 33]

Characteristic	Voriconazole	Posaconazole
Derivative	Fluconazole	Itraconazole
Formulation	Oral and intravenous	Oral
Oral bioavailability	Decreases with fatty meals	Increases with food
Protein binding	58%	98%
Bioavailability	> 90%	8-47
Pharmacokinetics	Non-linear in adults; linear in children	Linear
Metabolism	Hepatic, primarily via N-oxidation. Also through several CYP isoenzymes.	Hepatic, inhibits CYP3A4 isoenzyme only
Steady-state concentration	5-6 days	7-10 days
Half-life	6-12 hours	15-35 hours
Dose adjustment	In patients with hepatotoxicity	Neither liver not renal impairment require adjustment
Daily dose	200 mg[a] or 3-6 mg/kg, twice daily	800 mg[b] in divided doses

[a]Tablets or intravenous infusion.

[b]Oral suspension.

In a large international randomised clinical trial, voriconazole was compared with conventional amphotericin B in 277 patients with definite or probable aspergillosis.[36] After 12 weeks of treatment, successful outcomes were achieved in 53% of patients in the voriconazole arm and in 31.6% of participants randomised to the conventional amphotericin B treatment arm. The survival rate was 70.8% in the voriconazole arm and 57.9% in the amphotericin B arm. Voriconazole was shown to be the drug of choice against *Aspergillus* species. Posaconazole has not been evaluated in prospective controlled trials for the treatment of aspergillosis. Its effect against aspergillosis has only been investigated as a salvage therapy in patients who failed to respond or could not tolerate standard antifungal therapies, mostly conventional amphotericin B. In this circumstance, posaconazole was shown to be more efficacious, with a 42% response rate versus 26% for the other antifungal agents.[37]

Voriconazole has a broad spectrum of activity against all *Candida* species. A large multi-centre clinical study compared the efficacy of voriconazole alone versus conventional amphotericin B followed by fluconazole, involving 370 patients with candidemia.[38] At the end of treatment, the primary success rate was identical for both treatment arms (41%). With regard to posaconazole, no randomised clinical trials have explored its use in invasive

candidiasis or candidemia. A randomised clinical trial of posaconazole versus fluconazole, for treating AIDS-associated oropharyngeal candidiasis, showed equivalent efficacy between the two arms, with successful therapy in up to 87% of the posaconazole arm and 89% in the fluconazole arm.[39]

Voriconazole and posaconazole have both been used successfully for refractory fungal infections caused by *Scedosporium*, *Fusarium* and other invasive fungal species.[37, 40, 41] A major difference between voriconazole and posaconazole is that posaconazole is the only antifungal agent, besides amphotericin B, with an acceptable activity against zygomycosis. In two separate studies using posaconazole as salvage therapy against zygomycosis in patients, who failed to tolerate conventional amphotericin B, posaconazole had a success rate of 60-70%.[37, 42]

With respect to prophylactic use, a recent randomised clinical trial compared posaconazole with fluconazole or itraconazole for prophylaxis in patients who had acute leukaemia or myelodysplastic syndrome and who were neutropenic.[28] Posaconazole was shown to be superior, with 64% versus 54% clinical success rate. Importantly, posaconazole demonstrated a lower mortality rate than fluconazole or itraconazole (16% versus 22%). Data on the prophylactic use of voriconazole in haematology disorders are lacking. In a retrospective evaluation of 56 lung transplant recipient who received prophylactic voriconazole or itraconazole, it was concluded that voriconazole is effective as prophylaxis in lung transplantation, where it was associated with declined airway colonisation with *Aspergillus* and *Candida* species.[27] A large randomised clinical study comparing voriconazole versus fluconazole for prophylaxis in the bone marrow transplant population is currently in progress in the USA. This study should help define the benefits and risks of prophylactic use of voriconazole.

At the Royal Melbourne Hospital (RMH) (Melbourne, Australia), systemic antifungals are used as prophylaxis in patients with leukaemia. Voriconazole became the first-line antifungal agent for prophylaxis in AML at the RMH in 2002. Since June 2006, posaconazole has replaced voriconazole as the drug of choice in the same setting. This was because of posaconazole's potent activity against zygomycosis and, mainly, because of the recent clinical evidence that demonstrated reduction in mortality with posaconazole compared to itraconazole and fluconazole.[28, 37, 42]

Although posaconazole was demonstrated to be more effective than either fluconazole or itraconazole when used prophylactically,[28] the superiority of either of voriconazole or posaconazole for prophylactic use is still to be demonstrated. No head-to-head studies have compared the two. In such circumstances, decision making at administrative level on the choice of medications often focuses on differences in the cost of use. Data on the hospital costs associated with voriconazole and posaconazole prophylaxis and, hence, the

success or otherwise of the changeover at the RMH, are not available. In addition, it is difficult to generalise conclusions about outcomes and cost-effectiveness of prophylactic strategies, as these depend on local epidemiology and risk factors.

A pharmacoeconomic analysis of posaconazole and voriconazole for prophylaxis is therefore needed, especially as both are high-cost antifungals with similar acquisition costs, when voriconazole is given orally.[43]

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CHAPTER EIGHT: PHARMACOECONOMIC EVALUATION OF VORICONAZOLE VERSUS POSACONAZOLE FOR ANTIFUNGAL PROPHYLAXIS IN ACUTE MYELOID LEUKAEMIA

As discussed in the previous chapter (**Chapter Seven**), an economic evaluation of posaconazole versus voriconazole in the prophylactic setting is needed. The following study investigates the pharmacoeconomics of posaconazole and voriconazole as antifungal prophylaxis in patients with acute myeloid leukaemia in Australia.

The following material is arranged in a manner suitable for publication in the Journal of Antimicrobial Chemotherapy. Headings, figures and tables are renumbered in order to generate a consistent presentation within the thesis.

This chapter is a reproduction of the following publication:

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DECLARATION FOR THESIS CHAPTER EIGHT

In the case of Chapter Eight, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Conception and design. Literature search. Data collection. Statistical experience. Analysis and interpretation. Writing the article. Critical revision of the article.	60%

The following co-authors contributed to the work:

Name[a]	Nature of contribution
David CM Kong	Conception and design. Critical revision of the article. Final approval of the article.
Kay Stewart	Conception and design. Critical revision of the article.
Monica Slavin	Provision of materials, patients, or resources. Critical revision of the article. Final approval of the article.
Danny Liew	Design. Statistical experience. Critical revision of the article.
Karin Thursky	Design. Critical revision of the article.
Maria Downey	Data collection.
Andrew Grigg	Provision of patients. Critical revision of the article. Final approval of the article.
Ashish Bajel	Data collection.

[a]None of the co-authors is a student co-author.

Candidate's signature _____ Date _____

DECLARATION BY CO-AUTHORS

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.

(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;

(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;

(4) there are no other authors of the publication according to these criteria;

(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and

(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	Victorian Infectious Diseases Services - Royal Melbourne Hospital, Melbourne, Australia.

David CM Kong	[redacted]	Date 19/11/09
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Karin Thursky	[redacted]	16/11/09.
Maria Downey	[redacted]	20/11/09
Andrew Grigg	[redacted]	17/11/09
Ashish Bajel	[redacted]	19/11/2009.

8.1 STUDY TITLE

Pharmacoeconomic evaluation of voriconazole versus posaconazole for antifungal prophylaxis in acute myeloid leukaemia.

8.2 AUTHORS

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8.3 ABSTRACT

Background: Voriconazole and posaconazole are used prophylactically against invasive fungal infection (IFI) in patients with acute myeloid leukaemia (AML). The current study attempted to evaluate the economics of voriconazole versus posaconazole for prophylaxis in AML.

Methods: A decision analytic model was developed to depict options and consequences involved in the antifungal prophylaxis, from the perspective of the hospital system. Patients

were followed up through the induction stage of chemotherapy. Model outcomes included success, survival, possible and proven IFIs, and discontinuations due to intolerance. Outcome probabilities and prescribing patterns were derived from a six-year (2003-2009) review of AML patients at a major Australian tertiary hospital. Cost inputs were obtained from latest Australian representative sources.

Results: Fifty-six and 38 patients were evaluated in the voriconazole and posaconazole groups, respectively. Baseline demographic characteristics were not significantly different between the study cohorts. Posaconazole was associated with an overall cost saving of AU$17 458 (29%) per patient over voriconazole. The posaconazole group was associated with lower rate of death, as well as lower probability of discontinuation because of possible infections and intolerance to oral administration. The voriconazole group was associated with less proven infections. As per sensitivity analyses, results were highly robust over variations in all costs and probabilities in the model. Monte Carlo simulation suggested a 91.6% chance for posaconazole to cost less than voriconazole.

Conclusion: This is the first economic evaluation of voriconazole versus posaconazole; where posaconazole appears to be more cost-beneficial than voriconazole as antifungal prophylaxis in AML.

Keywords: Cost-benefit, model, prophylaxis, voriconazole, posaconazole.

8.4 INTRODUCTION

In the absence of preventive therapy, the risk of developing invasive fungal infection (IFI) can be up to 50% in some groups of patients with haematological malignancies, particularly among patients with acute myeloid leukaemia (AML).[1,2] Once established, IFIs are associated with a mortality rate of 30-90%.[3] Antifungal prophylaxis is often administered to patients who are at risk of IFIs;[4] the rationale being, the lack of sensitive and specific tools for the early diagnosis of infections, as well as poorly effective and costly curative therapies.[5]

A variety of antifungal agents are commonly available for the prophylactic use. These include voriconazole, posaconazole, liposomal amphotericin B (LAmB), itraconazole and fluconazole. In Australia, for patients with intermediate to high risk for IFIs, including AML patients, the prophylactic use of voriconazole, posaconazole, intermitted LAmB, itraconazole and fluconazole is suggested as per guidelines.[6,7]

Voriconazole (Vfend®, Pfizer) and posaconazole (Noxafil®, Schering-Plough) are two high-cost, new-generation triazole antifungals that are currently prescribed for prophylactic antifungal therapy.[8] A major difference between voriconazole and posaconazole is that posaconazole is the only non-amphotericin B antifungal with an acceptable activity against zygomycosis.[9] In addition, in a recent clinical trial, posaconazole was shown to be superior over fluconazole or itraconazole, with higher clinical success rate and lower mortality rate.[10] Clinical trials that help define the benefits and risks of prophylactic use of voriconazole are yet to be performed. Voriconazole has been available since 2002, and is available in oral and intravenous (iv) forms, administered twice daily.[11,12] Posaconazole was launched in 2006, and is only available as a suspension. For prophylaxis, it is best administered with three-daily doses.[10,13] Although the potential clinical advantages and disadvantages of these azoles are recognised,[12,13] there have been no head-to-head studies directly comparing these two agents. Hence, the superiority of one antifungal agent over the other for prophylactic use is still to be demonstrated. Likewise, little is known about the pharmacoeconomics of using these agents prophylactically. Data from cost-effectiveness studies comparing these two azoles will guide their use.

The current study sought to undertake a cost-benefit analysis of voriconazole versus posaconazole for prophylaxis in AML patients.

8.5 MATERIALS AND METHODS

8.5.1 PERSPECTIVE

The economic modelling adopted the perspective of the Australian hospital system. The analysis included direct medical costs only. Direct medical costs related to other underlying diseases were not included because the interest here revolved around the costs of prophylactic antifungals only.

8.5.2 MODEL STRUCTURE

A decision analytic model was constructed to capture downstream consequences of prophylaxis in patients with AML (**Figure 8-1**).

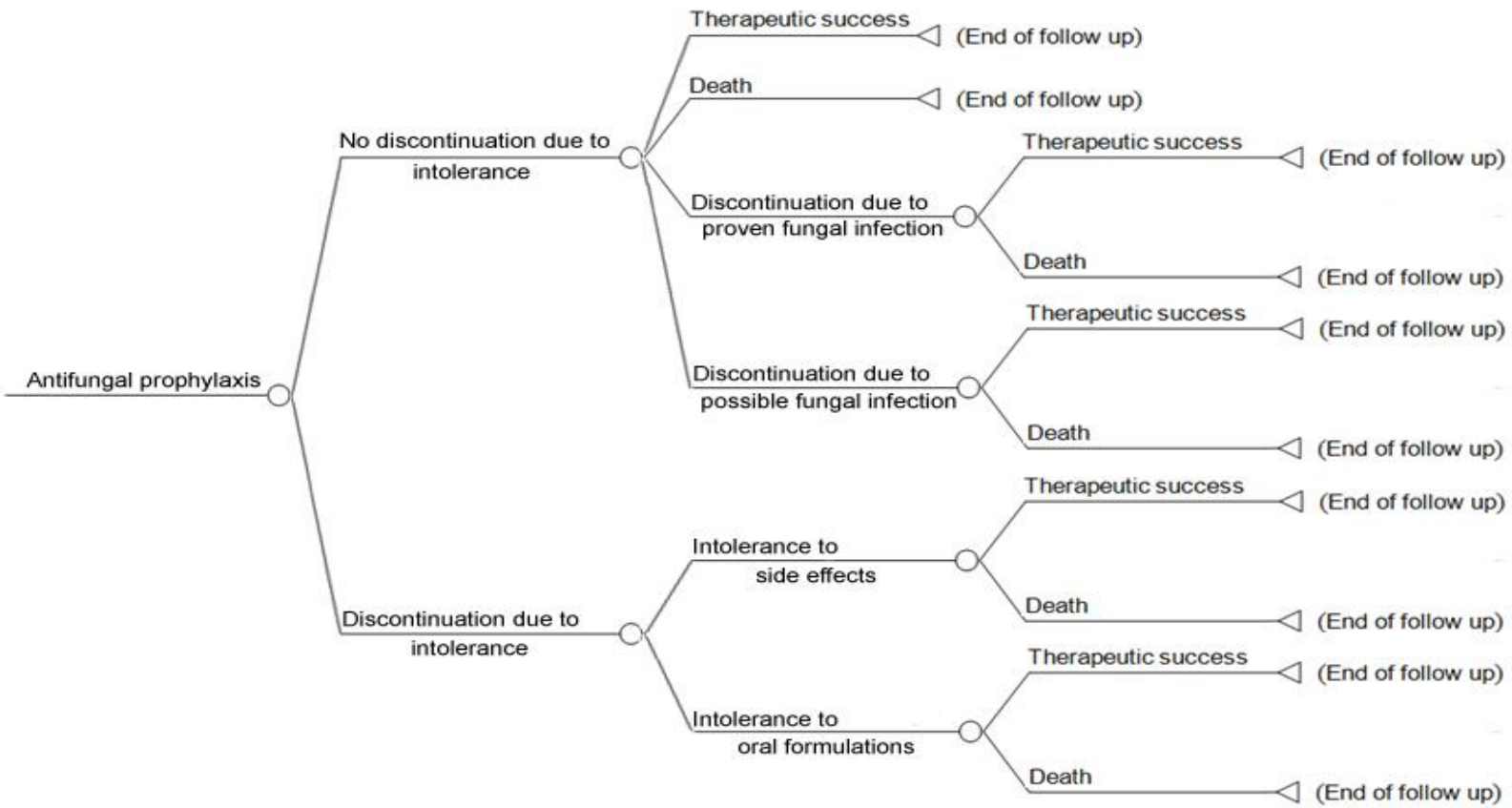

Figure 8-1. Decision analytic model of antifungal prophylactic therapy in AML.

The analysis of the baseline model in the current study was a regular cohort simulation analysis, and did not involve Markov modelling or Monte Carlo simulations.

Discontinuation due to intolerance was ascribed to either side effects or inability to consume oral medications. Patients were switched to any other licensed antifungal prophylactic agents, and were followed until the end of the induction chemotherapy stage. After such discontinuation, patients who switched to empirical therapy (because of possible infection) or targeted therapy (because of proven infection) were analysed as part of the intolerance pathway, and were followed until success or death. Patients, who had possible or proven infections after the induction stage finished, were not considered.

Patients who did not switch prophylaxis because of intolerance encountered the possibilities of therapeutic success, death, a switch to empirical therapy (because of possible infection), or a switch to targeted therapy (because of proven infection). The patients who switched to empirical or targeted therapies were then followed until success or death.

For initial prophylaxis, success was defined as the absence of initial antifungal discontinuation for the duration of the induction stage.

For patients who received alternative antifungals, success was defined as the absence of IFI with alternative prophylaxis, resolution of fever with empirical therapy, or eradication of fungal infections with targeted therapy. Death was that reported before the initial or alternative antifungal therapies were deemed successful. Switching to alternative medications may lead to extension of the duration of the induction stage and delay in subsequent chemotherapy.

8.5.3 MODEL INPUTS

The modelling was based on data extracted from a six-year (June 2003-June 2009) review of hospital medical records of all AML patients at the Royal Melbourne Hospital (RMH), a major tertiary hospital in Victoria, Australia. At the RMH, AML patients are defined and classified according to the standardised international French/American/British classification of acute leukaemia.[14] The study was approved by the human research ethics committee of RMH and Monash University. Informed consents were not required from the study subjects.

At RMH, voriconazole was the first-line antifungal prophylactic agent in AML patients from June 2003 until June 2006, when posaconazole replaced voriconazole as the drug of choice for the same setting. Patients were eligible for inclusion if they had newly diagnosed AML, underwent chemotherapy, and received voriconazole or posaconazole as the

primary antifungal prophylactic agent. Patients were excluded from analysis if they had any underlying haematological disease other than newly diagnosed AML, use of systemic antifungals within seven days prior to commencing voriconazole or posaconazole, renal impairment [creatinine level ≥ 2 times the upper limit of normal (ULN)], liver impairment (any liver enzyme level ≥ 2 times the ULN), or current or previous history of proven or probable IFI. Comparison of baseline characteristics between the voriconazole and posaconazole patient groups was made with Student's *t* test or Fisher's Exact Test using SPSS 17.0 (SPSS Inc., Illinois, USA).

8.5.4 COST CALCULATIONS

Costs were calculated in Australian dollars (AU$) for the financial year 2008-09, and no discounting was performed.

The cost of initial prophylaxis was the cost of a complete course of voriconazole or posaconazole until success or death, or until switching to alternative therapy. The cost of alternative therapy was the cost of a complete course of the alternative agent until success or death. The cost of each treatment outcome was the cost of initial and alternative therapies added to the cost of resources consumed. Regardless of outcome, patients were analysed according to the group that they were initially assigned to.

Medication costs used were the drug wholesale prices paid by Australian public hospitals, as per the Health Purchasing Victoria tender (2007-2009).[15] Doses for all medications (except posaconazole) were rounded to the nearest vial size. Patients on posaconazole were considered to share the same posaconazole bottle, as is routine hospital practice in Australia.

The hospitalization costs were measured via gross (top down) costing. The micro-costing (bottom up costing) was used to estimate the costs for the drugs used, and the pathology and imaging tests performed. Hospitalization costs were obtained from published data for the 2006-07 Australian Refined Diagnosis-Related Groups (AR-DRG) (Code R60A).[16] Hospitalization costs used were the average direct costs associated with acute leukaemia [including both acute lymphoid leukaemia (ALL) and AML], and included the cost of intensive care management. No hospitalisation costs that relate only to AML patients are available. To avoid double counting, hospitalization costs used excluded pharmacy, pathology and imaging costs, as reported in the AR-DRG. Hospitalization costs were inflated to 2008-09 values as per the Australian Health Consumer Price Index (2009).[17]

All other resource costs involved in the study were obtained from the Australian Medicare Benefits Schedule Book (2009).[18] The cost inputs used in the model are summarised in **Table 8-1**.

Table 8-1. Resource costs[15,16,18]

Item	Unit	Unit cost (AU$)
Voriconazole	200 mg iv vial	190.84
	200 mg oral tablet	45.62
Posaconazole	105 mL oral suspension	669.50
LAmB	50 mg iv vial	295.00
Caspofungin	50 mg iv vial	700.00
Fluconazole	200 mg oral capsule	2.61
	200 mg iv vial	19.90
Vancomycin	500 mg iv vial	5.45
Terbinafine	250 mg oral tablet	1.19
Chest X-ray scan	1 test	35.35
CT scan	1 test	295.00
Ultrasound scan	1 test	111.30
MRI scan	1 test	358.40
Non-blood culture	≥ 1 tests (1 culture)	34.00
Blood culture	1 test (1 culture)	30.95
Bronchoscopy	1 test	207.70
PCR	1 test	30.00
Mc&s	1 test	49.00
Histology	1 test	72.00
Complete blood count	1 test	17.20
Renal function test	1 test	146.30
Liver function test	1 test	17.80
Hospitalization	inpatient per day	610.00

iv, intravenous.

8.5.5 SENSITIVITY ANALYSES

Variations in the values of key variables and assumptions, related to deterministic and probabilistic data, were analysed to assess the robustness of the study conclusion.

Alternative scenario. Throughout the study duration, the way that any particular medication was administered did not change. However, posaconazole was only marketed in Australia for use in June 2006 and, therefore, it was not available as an alternative option after the discontinuation of the initial prophylactic antifungal (i.e. voriconazole) during the period of June 2003 to June 2006. To account for this, sensitivity analyses investigated the scenario of posaconazole being available as alternative to voriconazole, whereby, in cases where initial voriconazole was discontinued because of side effects, patients were switched to posaconazole as an alternative. The alternative posaconazole was assumed to be successful and was given for the remainder of the chemotherapy induction stage.

In addition, because data on the use of each of voriconazole and posaconazole were based on different chronological periods, another alternative scenario analysed was the matching of posaconazole patients with patients receiving voriconazole according to potential confounding factors, which were determined using the expert opinion of two clinicians with clinical expertise in systemic fungal therapy and specialist knowledge in oncology, haematology and infectious diseases.

One-way sensitivity analyses. The potential impact of any variations in costs on the study outcome was investigated. A threshold analysis was performed and included prices of antifungals, cost of hospital stay and the use of screening and monitoring tests. The effects of the voriconazole dosage form as alternative therapy as well as the duration of hospitalization were also evaluated. Key variables, and the ranges over which they were varied, are shown in **Table 8-2**.

Probabilistic sensitivity analyses. Uncertainty analysis, by means of Monte Carlo simulation, was performed via @Risk-5.5® (Palisade Corporation, NY, USA). Monte Carlo refers to a method, whereby, multiple model simulations are run, each time sampling from pre-defined uncertainty ranges of input values. The current probabilistic sensitivity analysis, defined by a triangular type of distribution, was performed with an assumed uncertainty range of 0-100% associated with the probability of prophylaxis discontinuation due to possible infection, and with an uncertainly of ± 5% for all other outcome probabilities in the model. The current uncertainty analysis was based on 10 000 model simulation. Corresponding costs were calculated, and a distribution of "cost savings" was obtained. The clinical outcomes that affected the overall therapeutic cost the most were also determined.

Table 8-2. Variation range for variables in sensitivity analysis

		Variation range	
Variable	Base case	low	high
Voriconazole cost/vial	AU$190.64	AU$0.00	AU$381.68
Voriconazole cost/tablet	AU$45.62	AU$0.00	AU$91.24
Posaconazole cost/vial	AU$669.50	AU$0.00	AU$1339.00
LAmB cost/vials	AU$295.00	AU$0.00	AU$590.00
Caspofungin cost/vial	AU$700.00	AU$0.00	AU$1400.00
Fluconazole cost/tablet	AU$2.61	AU$0.00	AU$5.20
Fluconazole cost/vial	AU$19.9	AU$0.00	AU$39.80
Terbinafine cost/tablet	AU$1.19	AU$0.00	AU$4.00
Hospitalization cost/day	AU$610.00	AU$0.00	AU$1220
Duration of therapy in voriconazole group	46 days	31 days	46 days
Duration of therapy in posaconazole group	45 days	45 days	66 days
Dosage form of voriconazole given as alternative (oral:iv)	1:1	0:1	1:0
Counting for the costs of monitoring, pathology and imaging tests	Yes	No	Yes

iv, intravenous.

8.6 RESULTS

8.6.1 CLINICAL OUTCOMES

A total of 94 patients met eligibility criteria, 38 of whom were initially given posaconazole and 56 were initially given voriconazole. At baseline, the voriconazole and posaconazole groups were only significantly different in terms of the AML grade 'M3'. All other baseline demographic characteristics were not significantly different between the two groups (**Table 8-3**).

The duration of initial prophylaxis was almost similar in both groups; the mean duration was 18 days [median, 19 (range, 1 to 47)] with voriconazole and 19 days [median, 20 (range, 1 to 42)] with posaconazole. The mean duration on alternative medications was also about similar in the two groups; 28 days [median, 9 (range, 1 to 172)] with voriconazole and 26 days [median, 12 (range, 2 to 48)] with posaconazole.

The group of patients starting with posaconazole was associated with more possible IFIs and intolerance to side effects and oral consumption of medications, while the voriconazole group was associated with less proven IFIs. The clinical outcomes and their probabilities are summarised in **Table 8-4**.

Table 8-3. Baseline patient demographics

Characteristic	Voriconazole (*n* = 56)	Posaconazole (*n* = 38)	p-Value
Age (year) (mean ± SD)	51.2 ± 17.7	50.3 ± 16.7	0.814
< 60 years old [no. (%)]	35 (63)	26 (68)	
≥ 60 years old [no. (%)]	21 (38)	12 (32)	
Gender [no. (%)]			0.833
Male	26 (46)	22 (58)	
Female	30 (54)	16 (42)	
Weight (Kg) (mean ± SD)	77.6 ± 17.2	79.1 ± 15.5	0.666
HIV/AIDS [no. (%)]	0 (0.0%)	0 (0.0%)	> 0.999
Smoking status [no. (%)]			
Current	8 (14)	8 (21)	0.282
Previous	17 (30)	9 (24)	0.639
Never	31 (56)	21 (55)	> 0.999
Intermediate- or high-dose cytarabine / idarubicin chemotherapy [no. (%)]	32 (57)	15 (40)	0.141
AML grade [no. (%)]			
M0	4 (7)	2 (5)	> 0.999
M1	10 (18)	3 (8)	0.229
M2	16 (28)	5 (13)	0.129
M3	1 (2)	6 (16)	0.016
M4	9 (16)	8 (21)	0.591
M5	7 (13)	5 (13)	> 0.999
M6	4 (7)	3 (8)	> 0.999
Not graded	5 (9)	6 (16)	0.342

IFIs were only experienced by patients in the posaconazole group (*n* = 2). In addition, the only IFI-related death in the study was reported for a patient in the posaconazole group. For the patients who experienced proven IFIs in the posaconazole group; one patient, who did not discontinue therapy because of intolerance, was diagnosed with a mixed infection with *Scedosporium apiospermum* and *Aspergillus* species, not further identified, that resulted in death on the day of diagnosis; and a second patient was diagnosed, after discontinuation because of intolerance to oral administration, with *Aspergillus* species, not further identified, that was treated successfully after 30 days of LAmB therapy and 28 days of oral voriconazole.

The administration of posaconazole was based on three-daily oral 200 mg doses in all patients. Voriconazole was administered as twice-daily oral/iv 200 mg doses, whereby, 53 patients received the oral initial voriconazole prophylaxis and three patients received the iv

initial voriconazole prophylaxis. Where initial antifungal therapies were discontinued, the alternative therapies included twice-daily oral/iv 200 mg voriconazole, trice-daily oral 200 mg posaconazole, daily iv 50 mg caspofungin, daily oral/iv 200 mg fluconazole and/or daily oral 250 mg terbinafine, as well as a range of 50-400 mg doses of iv LAmB, administered as daily as targeted or empiric therapy, or intermittently for prophylaxis.

Table 8-4. Outcomes and probabilities as per the medical records review

Study clinical outcome	Probability in voriconazole arm (n = 56)	Probability in posaconazole arm (n = 38)
No discontinuations due to intolerance	64.29% (n = 36)	71.05% (n = 27)
therapeutic success	69.44% (n = 25)	88.89% (n = 24)
death	8.33% (n = 3)	0.00% (n = 0)
discontinuation due to proven fungal inf.	0.00% (n = 0)	3.70% (n = 1)
therapeutic success	0.00% (n = 0)	0.00% (n = 0)
death	0.00% (n = 0)	100.00% (n = 1)
discontinuation due to possible fungal inf.	22.22% (n = 8)	7.41% (n = 2)
therapeutic success	62.50% (n = 5)	100.00% (n = 2)
death	37.50% (n = 3)	0.00% (n = 0)
Discontinuation due to intolerance	35.71% (n = 20)	28.95% (n = 11)
intolerance to side effects	15.00% (n = 3)	0.00% (n = 0)
therapeutic success	100.00% (n = 3)	0.00% (n = 0)
death	0.00% (n = 0)	0.00% (n = 0)
intolerance to oral administration	85.00% (n = 17)	100.00% (n = 11)
therapeutic success	100.00% (n = 17)	100.00% (n = 11)
death	0.00% (n = 0)	0.00% (n = 0)

8.6.2 COST OF PROPHYLAXIS

Compared to voriconazole, posaconazole had an economic advantage in the order of AU$17 458 per patient (29% difference). The total daily cost of posaconazole was AU$952 per patient, while for voriconazole it was AU$1320 per patient. While, for voriconazole, discontinuation because of intolerance to oral dosage form was the major clinical outcome that most influenced the therapeutic cost, for posaconazole, it was the rate of success among patients who did not discontinue because of intolerance that most influenced the therapy cost.

The weighted probability and costs for therapy outcomes are given in **Table 8-5**. Cost components, and their proportional contribution to the overall costs of therapies with voriconazole and posaconazole are shown in **Figure 8-2**. The cost per patient associated with voriconazole and posaconazole as initial medications was higher for voriconazole (AU$7045 versus AU$2306, **Figure 8-2**). A similar trend was observed with the total cost of alternative therapies (AU$29 728 versus AU$10 203, **Figure 8-2**). Similar costs, however, were observed in relation to monitoring, pathology and imaging tests (AU$3689, AU$481 and AU$628, respectively, for voriconazole, and AU$4673, AU$708 and AU$542, respectively, for posaconazole). For hospitalization costs, those associated with posaconazole were higher than those associated with voriconazole (AU$24 191 versus AU$18 708, respectively, per patient).

Higher probability of successful completion of follow up (i.e. lower probability of death) was associated with the posaconazole group (97.37% versus 89.29%, **Table 8-5**). The cost of successful completion of follow up per patient in the posaconazole group (AU$44 074) was lower than that for voriconazole (AU$67 617).

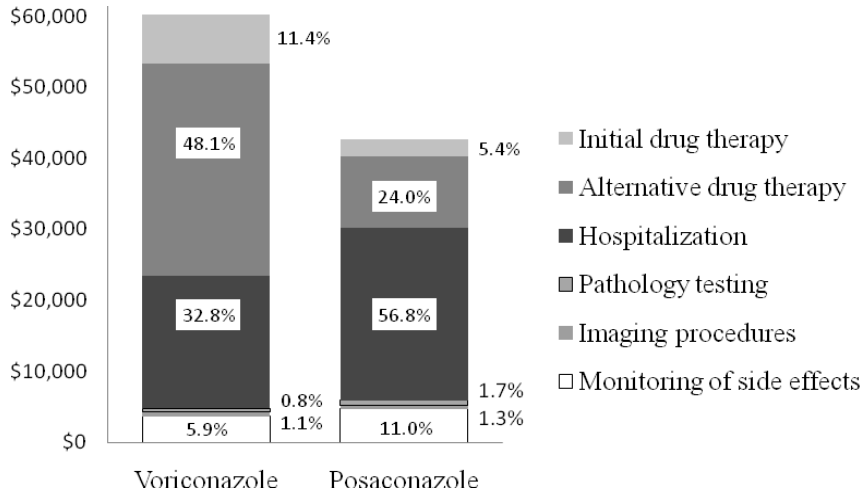

Figure 8-2. Contribution of different cost components in overall therapy.

Table 8-5. The proportional cost of prophylactic voriconazole and posaconazole

	Voriconazole			Posaconazole		
Therapy outcome	proportion (%)	cost (AU$) /patient	proportional cost (AU$)	proportion (%)	cost (AU$) /patient	proportional cost (AU$)
No discontinuations due to intolerance						
therapeutic success	44.64	33 919	15 142	63.16	33 067	20 885
death	5.36	18 161	973	_	_	_
discontinuation due to proven fungal inf.						
therapeutic success	_	_	_	_	_	_
death	_	_	_	2.63	44 677	1176
discontinuation due to possible fungal inf.						
therapeutic success	8.93	70 315	6278	5.26	52 369	2756
death	5.36	54 077	2897	_	_	_
Discontinuation due to intolerance						
intolerance to side effects						
therapeutic success	5.36	39 824	2133	_	_	_
death	_	_	_	_	_	_
intolerance to oral administration						
therapeutic success	30.36	108 437	32 949	28.95	62 521	18 098
death	_	_	_	_	_	_
Total cost per patient[a]			60 373			42 915

[a]Individual costs may not add up to total costs because of rounding.

8.6.3 SENSITIVITY ANALYSES

Alternative scenario. The scenario of providing an alternative course of posaconazole to patients with intolerance to voriconazole-related side effects, resulted in a negligible reduction in the overall cost difference (AU$16 654 in favour of posaconazole).

It is worth mentioning, however, that this scenario resulted in a 37.7% reduction (from AU$39 824 to AU$24 812) in costs associated with discontinuation due to intolerance to side effects with voriconazole.

Regarding the scenario of matching posaconazole patients with voriconazole patients, matching was only undertaken on the basis of age (< 60 and ≥ 60 years), especially as, given the small sample size of the cohort analysed, matching according to a variety of demographic characteristics was not possible. Matching resulted in 18 'excess' patients in the voriconazole group to be discarded, leaving a total sample of 78 patients. The scenario significantly reduced the cost difference between the two antifungal agents to AU$6369, but still to the advantage of posaconazole.

One-way sensitivity analyses. The model was insensitive to changes in the acquisition costs of the initial antifungals. The economic advantage of posaconazole changed by a maximum of ± AU$3000 when posaconazole or oral voriconazole varied between AU$0.00 and two-fold increase in price. A similar range of variation in the iv voriconazole price resulted in about ± AU$7000 in the posaconazole cost advantage. Similar variation in the acquisition costs of alternative LAmB, caspofungin and fluconazole did not affect the overall cost advantage of posaconazole.

The study outcome was also not sensitive to variations in the cost of hospital stay. A daily hospitalization cost of AU$0.00 increased the cost advantage of posaconazole to AU$23 105. Two-fold increase in the hospitalization cost reduced the posaconazole advantage to AU$15 484. A similar outcome was observed with excluding the use of monitoring and screening tests, as well as with switching all iv doses of the initial and/or alternative voriconazole to oral doses. It must be noted, however, that with switching iv doses of initial voriconazole to oral doses, although the overall economic advantage of posaconazole was only reduced to AU$12 210, the cost of initial voriconazole prophylaxis was significantly reduced from AU$7054 to AU$1806.

The result, however, was more sensitive to the duration of therapy. With daily costs of AU$1320 and AU$952 associated with voriconazole and posaconazole, respectively, voriconazole had a cost saving over posaconazole when the total average therapy duration associated with voriconazole decreased from 46 to 31 days, or when the duration of therapy associated with posaconazole increased from 45 to 66 days.

Probabilistic sensitivity analyses. Main clinical variables, as per the ranking of their impact on the model outcome in the Monte Carlo simulation, are given in **Figure 8-3**.

According to the Monte Carlo simulation, the mean cost difference was AU$17 159 per patient in favour of posaconazole. Posaconazole had a 91.6% probability of having an economic advantage over voriconazole, with expected cost savings ranging between AU$19 313 with voriconazole and AU$55 324 with posaconazole. A "cost saving" probability curve is shown in **Figure 8-4**.

8.7 DISCUSSION

This is the first study to investigate the pharmacoeconomics of voriconazole versus posaconazole as antifungal prophylaxis. The aim was to assess the direct economic impact of relevant discontinuations that are associated with each drug as primary prophylaxis in patients with AML. Therefore, patients were followed up for the period of the induction stage of the chemotherapy for AML, which is about one month. The induction stage is the stage most likely to give an accurate reflection on the effectiveness of these agents, as confounding would be at a minimum. Due to limited diagnostic tools, it is hard to attribute the onset of IFIs occurring during subsequent chemotherapy episodes. IFIs that are detected after the induction stage could actually have been present earlier.

The patient demographics were not significantly different between the voriconazole and posaconazole groups for all baseline characteristics, except for the M3 subtype of AML. Nonetheless, this significant difference in the proportion of M3 class is not expected to be of influence on the outcomes of the study, because the classification of AML is based on the FAB classification, which is, unlike with the more recent World Health Organisation classification of AML, based solely on differences in morphology descriptions, but not phynotypic and genetic descriptions, which are important in determining prognosis.[14,19]

From a clinical standpoint, initial therapy with posaconazole demonstrated lower overall rate of treatment discontinuation and lower mortality. From an economic perspective, initial treatment with posaconazole resulted in a lower cost per success and death prevented.

Death as an endpoint in the current study included both IFI-related and -unrelated mortality. This is a recommended outcome to compare between drugs in clinical studies, and is important to at least ensure that a drug is not associated with worse mortality outcome.[20]

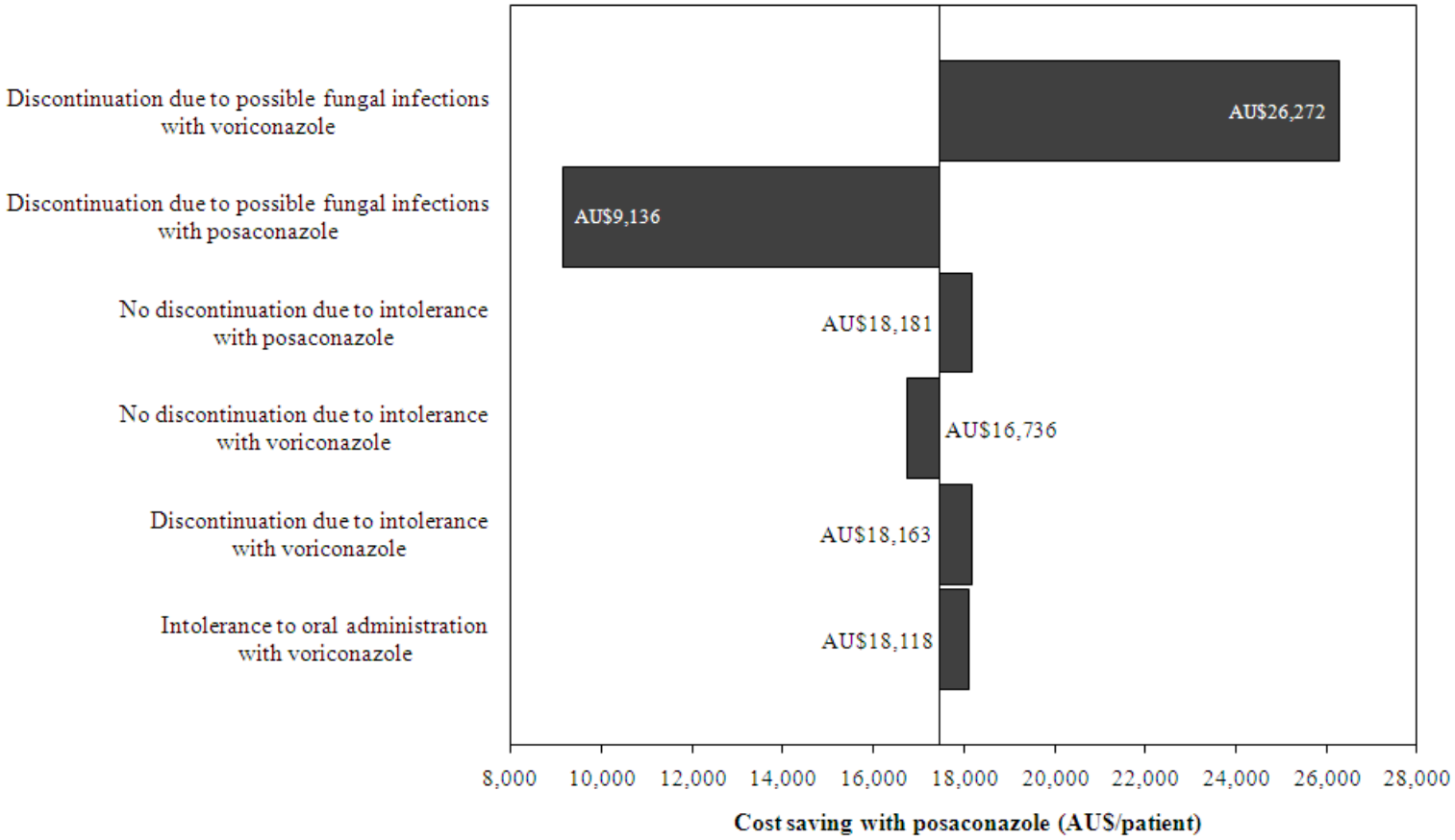

Figure 8-3. A tornado diagram of the variables as per their influence on the outcome of the Monte Carlo simulation.

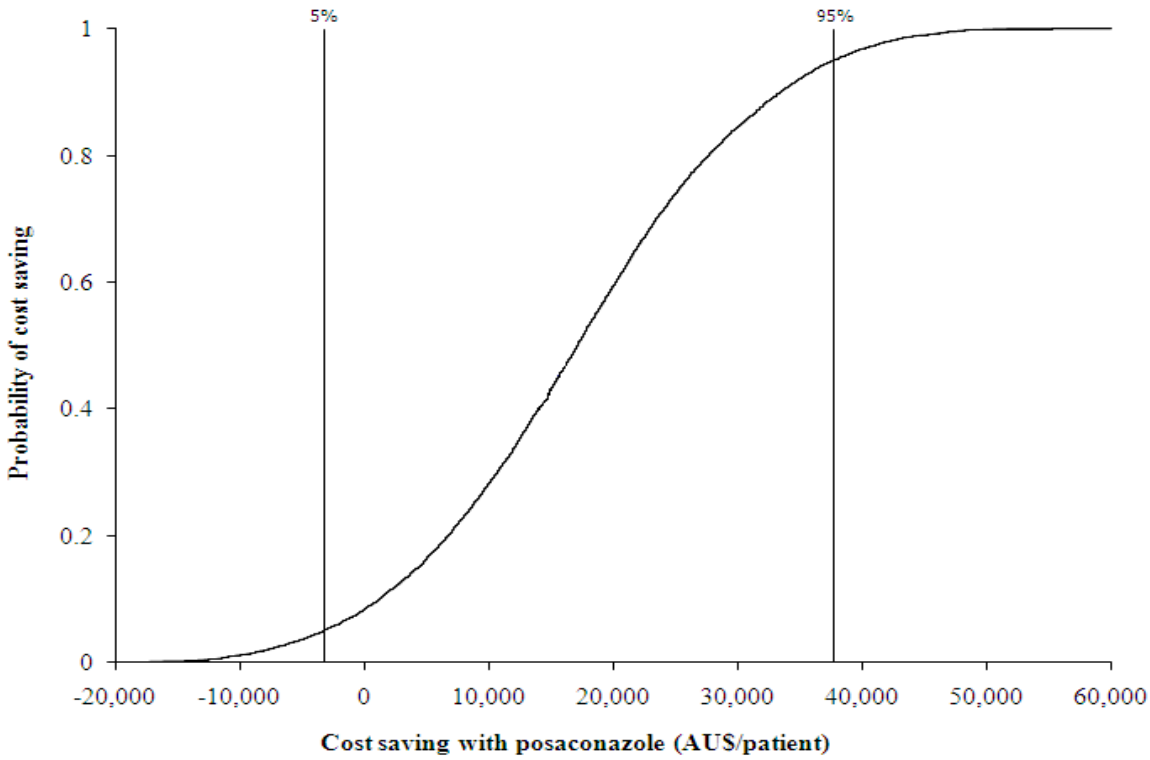

Figure 8-4. "Cost saving" probability curve of posaconazole.

The cost per patient associated with initial prophylaxis was higher for voriconazole as compared to posaconazole. This difference in cost was mainly due to fact that while posaconazole was only received as oral formulation, three of the patients on voriconazole received the iv formulation for the one month induction stage. This was clearly demonstrated in the one-way sensitivity analysis, whereby, the cost of initial voriconazole became less than that for posaconazole when all patients on voriconazole received the oral dosage form of initial voriconazole prophylaxis. The total cost of alternative therapies was also higher with voriconazole as compared to posaconazole. This was expected given that patients receiving posaconazole as initial therapy experienced less overall switching to alternative therapies, which meant that less alternative therapy and, ultimately, cost were consumed. Hospitalization costs associated with the posaconazole group were slightly higher than those associated for voriconazole. This is because, while overall average duration of hospital stay in the posaconazole and voriconazole groups was similar, the duration of administration of high-cost alternative medications was higher in the posaconazole group as compared to the voriconazole group. The impact of this cost advantage with voriconazole, however, was diminished by a superior cost advantage demonstrated by posaconazole, whereby,

posaconazole was associated with higher total costs of initial and alternative therapies. Consequently, the observed net cost difference was almost totally due to the difference in the costs of antifungal medications. These observations highlight the need for prescribers and other decision makers to consider both drug acquisition costs and secondary costs (i.e. cost of therapy failure), when determining the most appropriate medication for use.

While, for voriconazole, discontinuation because of intolerance to oral dosage form was the major clinical outcome that most influenced the therapeutic cost, for posaconazole, it was the rate of success among patients who did not discontinue because of intolerance that most influenced the therapy cost.

The cost of side effects that did not result in discontinuations was not included in the current study. It was not feasible to provide reliable estimations for the resources consumed in managing such side effects. However, these are usually moderate and do not cause therapy discontinuations, nor are they likely to significantly impact cost estimations. Furthermore, posaconazole has fewer reported side effects than voriconazole,[8] therefore, accounting for all side effects associated with the two antifungals would most likely increase the posaconazole economic advantage further.

An ideal economic evaluation would be based on data from a double-blinded randomised clinical trial,[21] from which the most robust evidence of efficacy can be drawn. Nonetheless, the current study is based on data that reflected relevant real-life clinical practice, especially at the RMH, and hence is important in confirming the value of the 2006 switch in prophylactic therapy at the RMH.

Importantly, sensitivity and uncertainty analyses demonstrated the cost advantage of posaconazole to be robust against large variations in key cost determinants.

The fact that posaconazole was not available as an option for alternative use after voriconazole is a limitation in the current model. However, simulating posaconazole as the sole alternative after intolerance to voriconazole side effects did not alter the study conclusion. Posaconazole and voriconazole have different side-effect profiles and, thus, are valid alternatives for one another.

As this was an observational study (no randomisation), it was subject to confounding. Therefore, the current study undertook the scenario of matching posaconazole patients with voriconazole patients according the patient age, deemed to be the demographic characteristic that may affect the effectiveness of antifungal prophylaxis in the AML population. This, however, did not change the study conclusion. It is important to emphasise here, however, that regardless of whether matching was performed or not, the baseline demographic characteristics were not significantly different between the two study cohorts.

Another limitation in the current model is that the threshold to discontinue voriconazole prophylaxis because of possible IFIs was possibly lower than that for

posaconazole. This is because the prophylactic use of voriconazole is not supported by clinical trials and, hence, clinicians were less certain of how to manage patients who are febrile whilst on voriconazole prophylaxis, whereby, voriconazole might have been more likely to be discontinued. In contrast, posaconazole was introduced after results from a clinical trial[10] on prophylactic posaconazole were available and demonstrated a low rate of breakthrough infections. Therefore, there mostly was an element of comfort with pushing on with posaconazole prophylaxis if patients did not have signs of IFIs, even if patients were febrile. In addition, in the duration 2006 onward, as compared to previous durations, higher resolution Computed Topography (CT) scans were more routinely available for screening tests. This might have resulted in higher confidence in screening outcomes and, thereby, clinicians might have become less likely to discontinue prophylaxis if results from the CT scan were negative, despite the presence of ongoing fever. To account for this potential limitation, an uncertainty range of 0-100% was assigned, as part of the probabilistic sensitivity analysis, to the probability of discontinuation because of possible IFIs associated with each of voriconazole and posaconazole. This enabled the analysis of the model under the scenario where both antifungals have similar probability to switch to alternatives because of possible IFIs. As per the outcomes from the Monte Carlo simulation, however, posaconazole was still associated with an average cost saving over voriconazole in the order of AU$17 159. In addition, the likelihood of posaconazole having a cost advantage over voriconazole was over 90%. The maximum expected cost saving with posaconazole was higher than that with voriconazole.

The small sample size in the current study is a limitation. Therefore, while the results of the current model are compelling, they warrant validation from other studies.

In conclusion, posaconazole appears to be a more cost-beneficial option as first-line prophylactic antifungal in AML, compared to voriconazole. It is associated with lower rate of discontinuations and lower direct medical costs. The current findings support the current use of posaconazole as the standard of care for prophylaxis therapy at the RMH and elsewhere.

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8.10 TRANSPARENCY DECLARATIONS

Associate Professor Monica Slavin serves on the advisory boards of Pfizer and Schering Plough. Associate Professor Andrew Grigg serves on the advisory board of Schering Plough.

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CHAPTER NINE: VORICONAZOLE EYE DROPS IN FUNGAL KERATITIS

As discussed in the outline of this thesis (**Chapter 1**), the current focus of interest with targeted antifungal therapy is the use of extemporaneously-prepared antifungal therapy for the localised fungal keratitis of the eye.

9.1 THE CORNEA

The cornea is the outermost portion of the eye. It is clear, lacking blood vessels, strong, durable and consists of a highly organised structure of cells and proteins. It obtains its nourishment from the tears and the aqueous humour, which fills the chamber located behind the cornea. This chamber is called the anterior chamber.[1, 2] The anatomy of the eye is illustrated in **Figure 9-1**.

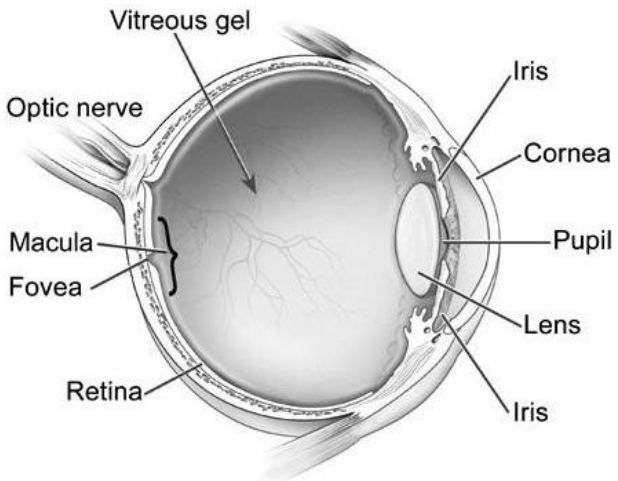

Figure 9-1. The human eye. Source: National Eye Institute,[3] by authorisation from authors.

The corneal tissues comprise three major layers of cells (**Figure 9-2**). The epithelium is the outer layer of the cornea. It is lipophilic, and comprises 10% of the corneal tissue thickness. The function of the epithelium is to provide a barrier against the passage of foreign materials and organisms into the eye. In addition, it provides a smooth surface that allows oxygen and

nutrients to be absorbed. With continuous cell regeneration, epithelial cells are rapidly restored if damaged.[1, 2, 4, 5]

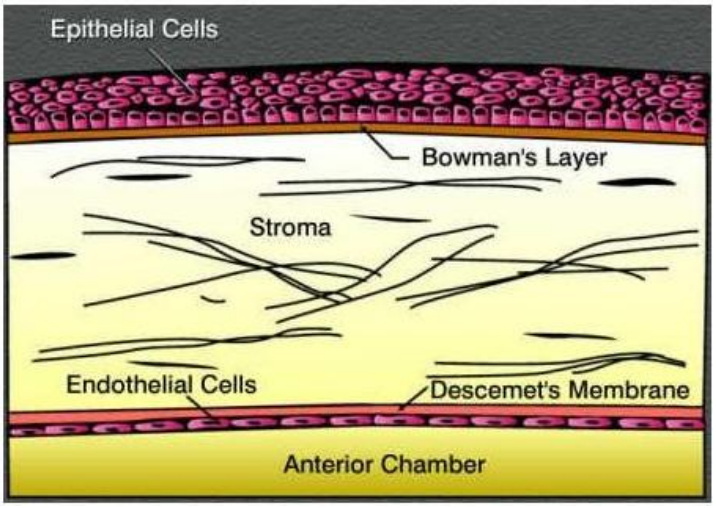

Figure 9-2. The structure of cornea. Source: Lasik Guider,[6] by authorisation from authors.

The stroma is the middle layer of the cornea. It is hydrophilic, and represents about 90% of the full thickness of the cornea. It consists of water and layers of protein fibres which give the cornea its strength, elasticity and form. The arrangement of cells within the stroma is critical to the light conductivity of the cornea. The final portion of the cornea is a layer of single cells called the endothelium. The function of the endothelium is to pump excess water out of the stroma to maintain its transparency. The endothelium does not regenerate and its injury can result in blindness. In addition to the above, the cornea also contains the Bowman's and Descemet's membranes. Bowman's membrane is a transparent sheet of collagen that underlies the epithelium. Whilst Bowman's membrane can regenerate, recovery from injuries to the membrane may leave scars, resulting in reduced visual acuity. Descemet's membrane is also a sheet of collagen, which underlies the stroma. This layer is flexible and strong, and is an important barrier against infections.[1, 2, 4, 5, 7]

The cornea is responsible for most of the refractive power of the eye. It focuses incoming light onto the retina, which in turn transmits the external visual stimuli (i.e. image) to the brain via the optic nerve. The other key function of the cornea is to protect the eye against foreign materials, including pathogens. The cornea lacks blood vessels; however, infections can induce extensive corneal neovascularisation. To a large extent, the cornea relies on immune elements present within the conjunctiva to protect it from pathogens. The conjunctiva lines the inside of the eyelid. It contains stratified epithelial cells comprising lymphocytes, T-cells, natural killer cells, mast cells and macrophages.[8-10] Upon injury or

infection in the cornea, blood vessels stretch from the conjunctiva into the corneal tissues, facilitating the mobilisation of the immune system at the site. Tears are also an important component of the corneal defence mechanism. In addition to providing nourishment to the cornea and maintaining a moist and smooth exterior of the eye, the tear film contains proteins such as lysozyme, lactoferrin, defensins and immunoglobulin, which are antimicrobial proteins capable of eradicating many pathogens from the corneal epithelium.[2, 5, 11]

The cornea heals quickly after minor damages. Upon injury, epithelial cells quickly regenerate before an infection occurs. Deeper injuries require longer duration to recover, leading to increased opportunity for pathogenic invasions to occur.[1, 2] Some of the major insults, which have an effect on the cornea, are ophthalmic microbial infections (i.e. keratitis), conjunctivitis, ophthalmic herpes (i.e. herpes simplex virus keratitis) and corneal dystrophies.[5, 12, 13] Failure to protect the eye from pathogens can cause serious visual impairment and blindness.

9.2 FUNGAL KERATITIS

The World Health Organization defines blindness as a visual acuity of 3/60 (10/200) or less.[14] Corneal disease is second only to cataract as cause of blindness worldwide, resulting in more than 1.5 million new cases of vision loss annually.[14] As a consequence of attention being directed towards the management of cataract, especially in developing countries, strategies for the management of traditional infections which causes blindness have been neglected.[15]

Ophthalmic mycosis is emerging as a major cause of morbidity and vision loss, and can be life threatening.[16, 17] Fungal keratitis is one of the major causes of ophthalmic mycosis,[18] accounting for more than 50% of proven ophthalmic mycoses in some countries.[19] Fungal keratitis is usually characterised by a corneal epithelial defect and inflammation of the corneal stroma. If untreated, fungal keratitis can lead to corneal scarring and vision loss.[14]

9.2.1 INCIDENCE OF FUNGAL KERATITIS

The first description of fungal keratitis was in the late 1870s.[20] Fungal keratitis is most common in tropical regions and developing countries, where it constitutes over 50% of keratitis.[21] In South India, about 44% of corneal ulcers are caused by fungi. Although lower, the prevalence of fungal keratitis is still relatively high in other countries. It is 17% in Nepal,

36% in Bangladesh, 38% in Ghana and 35% in South Florida (United States). In China, the incidence has been increasing in the past decade.[22] In contrast, fungal keratitis generally accounts for only 1-5% of the keratitis treated in developed countries and temperate regions such as Britain and northern United States.[22, 23] This also applies to Australia, where the incidence of fungal keratitis at the Royal Victorian Eye and Ear Hospital (RVEEH) in Melbourne (Victoria) was reported at 5%. The RVEEH is a tertiary referral eye hospital responsible for the care of most serious corneal infections in a population of about five million across Victoria, southern New South Wales and Tasmania.[23]

9.2.2 AETIOLOGY OF FUNGAL KERATITIS

Filamentous fungi were long considered as major cause of fungal keratitis.[24, 25] Ophthalmic infections from these fungi are most commonly associated with agricultural and outdoor activities.[26, 27] Of the filamentous fungi, infections from *Fusarium* and *Aspergillus* species are the most common. While *Fusarium* species are particularly prevalent in crop plants,[28] *Aspergillus* species are found in decaying vegetation and soil. *Aspergillus* is a contaminant in hospital air and has been involved in recent outbreaks of ocular infections in several hospitals.[29, 30] Keratitis caused by these filamentous fungi may involve any part of the cornea.[12, 31] Other less common keratitis-causative filamentous fungi include *Paecilomyces* and *Acremonium* species.[32] *Paecilomyces* species have been shown to be resistant to most common sterilising techniques, including those applied during surgical procedures.[33, 34] *Acremonium* species can be isolated from a variety of common sources, and can be associated with severe eye infections.[35, 36]

Dematiaceous fungi such as *Curvularia*, *Bipolaris* and *Exserohilum* species have also been reported to cause fungal keratitis. After *Aspergillus* and *Fusarium* species, *Curvularia* and *Bipolaris* species are the third most common keratitis-causative fungi worldwide.[32] *Curvularia*, *Bipolaris* and *Exserohilum* species usually cause persistent, but low-grade ulcerations near the epithelial part of the cornea. These ulcerations, if not appropriately treated or if associated with topical steroid use, can develop into resilient infections involving the deeper layers of cornea.[37-39] *Scedosporium* and *Lecytophora* species are also dematiaceous fungi[40] that are known to result in very severe keratitis infections that often do not respond to medical therapies.[37]

Whilst filamentous and dematiaceous fungi are the common causes of fungal keratitis at a global level, yeasts are the major cause of fungal keratitis in developed countries.[21] Yeasts are infrequent in tropical countries, characterised by major agricultural presence, which is

associated with higher prevalence of other types of fungal keratitis, such as the filamentous fungi.[32] Yeast infections have no geographical dominance and are most commonly caused by *Candida* species, especially *Candida albicans*.[21, 23, 32] *Candida* keratitis predominantly occurs in the stromal layer of the cornea. It is associated with epithelial defect and distinct infiltration, and is slow in development.[31] *Cryptococcus* species are another type of yeast that causes fungal keratitis, but less commonly than *Candida* species.[32]

Fungal keratitis can also be caused by zygomycetes fungi such as *Rhizopus* and *Mucorales* species,[17, 41, 42] and other fungi such as *Cladosporium*, *Cylindrocarpon*, *Penicillium* and *Chrysonilia* species.[19, 27, 43-45] Keratitis because of these fungi, however, is very low in occurrence.

The incidence of different types of fungal keratitis in different areas and countries is shown in **Table 9-1**.

Table 9-1. Studies of the incidence of types of fungal keratitis[21, 23, 26, 32, 46]

Place	Number of patients	Study duration	Principal pathogen (%)
Melbourne, Australia	56	18 months	*Candida albicans* (37), *Aspergillus fumigatus* (17), *Fusarium* spp.[a] (14)
Madurai, India	434	3 months	*Fusarium* spp. (47), *Aspergillus* spp. (16)
London, UK	65	13 years	*Candida albicans* (35), *Candida parapsilosis* (15), *Fusarium solani* (11), *Aspergillus fumigatus* (9)
Hyderabad, India	1352	10 years	*Fusarium* spp. (37), *Aspergillus* spp. (31)
Paraguay	45	1 year	*Fusarium* spp. (42), *Aspergillus* spp. (21)
Sri Lanka	66	2 years	*Aspergillus* spp. (25)
Florida, US	125	10 years	*Fusarium* spp. (68), *Candida* spp. (14), *Curvularia* spp. (9)
Bangladesh	142	11 months	*Aspergillus* spp. (37), *Fusarium* spp. (20), *Curvularia* spp. (18)
Ghana	199	NA	*Fusarium* spp. (52), *Aspergillus* spp. (15), *Lecytophora theobromae* (9)
New Delhi, India	211	5 years	*Aspergillus* spp. (40), *Fusarium* spp. (14), *Alternaria* spp. (10)
Singapore	29	5 years	*Fusarium* spp. (52), *Aspergillus flavus* (17)
Philadelphia, US	24	9 years	*Candida albicans* (46), *Fusarium* spp. (25)
Houston, US	32	30 years	*Curvularia senegalensis* (30), *Curvularia lunata* (25)

Table 9-1 *Continued*

Place	Number of patients	Study duration	Principal pathogen (%)
Qingdao, China	108	4 years	*Fusarium* spp. (65), *Aspergillus* spp. (14), *Candida* spp. (9)
Nepal	405	2 years	*Aspergillus* spp. (47), *Candida* spp. (13), *Fusarium* spp. (12)

[a]spp., species.

9.2.3 RISK FACTORS FOR FUNGAL KERATITIS

The general predisposing factors for fungal keratitis include ocular trauma, prolonged use of topical or systemic immunosuppressants, pre-existing corneal surface disease, underlying systemic disease (e.g. diabetes mellitus) and contact lens wear.[23, 32, 47]

The significance of these factors, however, varies among geographical areas. For instance, in Melbourne (Australia), ocular trauma, chronic steroid use and ocular surface disease were the most common risk factors,[23] whilst the common risk factors in Philadelphia (United States) were ocular surface disease, contact lens wear and topical steroids.[45] In southern United States, however, trauma was generally identified as the major risk factor for fungal keratitis. A similar trend was also observed in Singapore and Bangladesh, where ocular trauma was reported as the major risk factor.[48, 49] In contrast, in northern United States, ocular trauma was only reported as a secondary risk factor for fungal keratitis.[22]

The type of predisposing risk factors relates to the type of causative fungi for fungal keratitis. For example, keratitis associated with ocular trauma is commonly caused by *Aspergillus*, *Fusarium* and *Curvularia* species.[27] The use of lawn trimmers was found to be associated with *Fusarium* and *Curvularia* keratitis,[27, 50] while the use of topical steroids was linked to *Candida*, *Aspergillus*, *Acremonium* and *Curvularia* keratitis. Underlying chronic diseases were frequently related to keratitis caused by *Fusarium* and *Candida* species.[27] *Candida* keratitis is common where traumatic keratitis is infrequent.[32] Previous corneal ulceration resulting, for example, from previous keratitis or contact lens-related trauma, is particularly a risk factor for *Candida* keratitis.[31] Trauma by plant material, contaminated water or immune suppression is a risk factor for keratitis caused by *Scedosporium apiospermum.*[32] Keratitis caused by *Paecilomyces* species has been reported following surgical procedures.[33, 51]

9.2.4 DIAGNOSIS OF FUNGAL KERATITIS

A number of tools are currently in use for the diagnosis of fungal keratitis.

Clinical history and risk factors. Upon presentation, the initial investigation should include thorough review of the clinical history, including identification of predisposing risk factors such as trauma and lens wear, prior ocular diseases such as bacterial keratitis, concomitant antimicrobial and steroid use, and ocular or systemic defects that could have resulted in the development of keratitis.[32]

Smear. Direct microbiological examination of corneal scrapes (or corneal biopsies) is the most valuable and rapid diagnostic tool for the identification of the fungal elements in fungal keratitis.[22] The corneal scrapes can be subjected to a variety of conditions prior to examination. Wet smears of the scrape can be produced with the use of solutions such as potassium hydroxide or lactophenol cotton blue, reported to have sensitivities of up to 99% and 80%, respectively. Scrapes can also be prepared as stained smears for examination, involving the use of Giemsa and Gram stains (with a sensitivity of about 89%), Grocott methenamine silver stain (89% sensitivity), or calcofluor white (80-90% sensitivity).[22, 32]

Fungal culture. Fungal culture of corneal scrapes is essential to confirm fungal keratitis and the commencement of an appropriate antifungal therapy.[32] Under aseptic conditions, elements from the corneal scrape are inoculated on solid (or into liquid) media.[32] Fungal growth in blood agar and Sabouraud dextrose agar, kept at room temperature, can be observed within 48 to 72 hours.[22] The rate of positive fungal culture depends on the severity of infection, and has been reported to be in the range of 52-68%.[22]

Histopathology. Through histopathology, tissue penetration by fungal infection can be measured, and the outcome of surgical procedures can be predicted. With histopathology, a corneal biopsy with suspected fungal structures is collected and stained by techniques such as Gomori methenamine silver and periodic acid-Schiff. The presence of any fungi within the corneal tissue, and inflammatory cellular reactions (including leukocytes), can then be seen. Histological examination of biopsies has been found to give positive results despite negative fungal cultures of the same samples.[32]

Confocal microscopy. Confocal microscopy is a relatively new, non-invasive technique for imaging the cornea.[22] It allows optical sectioning of the corneal tissue and helps with establishing the diagnosis, evaluating the response to therapy and confirming eradication of the causative fungi. With confocal microscopy, the causative fungi are imaged as high-contrast structures and identified through their distinctive morphology.[32] Experimental comparative studies have demonstrated that confocal microscopy is more sensitive than examination of the fungal culture at different stages of fungal keratitis.[22]

9.2.5 TREATMENT OF FUNGAL KERATITIS

The ultimate goal in the treatment of fungal keratitis is to conserve vision. This depends on timely diagnosis of the infection and administration of the appropriate antifungal therapy.[52] Currently, the range of antifungal therapies available for fungal keratitis remains inadequate.[22, 53] The antifungal agents that are commonly used in fungal keratitis can be broadly divided into three main groups: polyenes (amphotericin B and natamycin), azoles (fluconazole, itraconazole, ketoconazole, voriconazole and posaconazole) and echinocandins (caspofungin).

Amphotericin B is marketed only as an intravenous (IV) formulation. It can be fungistatic or fungicidal, depending on its concentration relative to the susceptibility of the fungi.[54] For the treatment of keratitis, it has been administered as IV and topical preparations. The IV administration of amphotericin B is recommended with a minimum dose of 1 mg/kg/day, otherwise it may be ineffective.[32] As amphotericin B has poor ocular penetration after IV administration, the administration of higher doses may be required to ensure adequate concentration of amphotericin B in the eye;[32] however, IV administration of high-dose amphotericin B is known to cause severe renal toxicity which can occur in up to 80% of patients.[32, 54] To minimise renal toxicity, low-dose amphotericin B is often used, which in many cases, results in inappropriate suboptimal doses,[55] especially when taking its poor ocular penetration in consideration. As a commercial preparation of amphotericin B eye drops is not available, amphotericin B eye drops are often manufactured extemporaneously by hospital pharmacy departments. The most commonly prescribed concentration of the eye drops for fungal keratitis is 0.15%.[23] Although corneal irritation was documented with concentrations over 0.5%, the 0.15% solution is well tolerated.[32] Topical amphotericin B penetrates well into the stroma and can achieve sufficient concentrations against susceptible fungi;[32] however, its penetration through cornea with intact epithelium is poor. Whilst amphotericin B is active against *Aspergillus* and *Candida* keratitis, it has no activity against keratitis caused by *Fusarium* species.[22, 56] Amphotericin B has also been administered, less commonly, via the intra-cameral route for the treatment fungal keratitis.[23]

Natamycin is another polyene, and is the only Food and Drug Administration approved and commercially available topical antifungal preparation for ophthalmic use.[40, 57] It is insoluble in water and is stable in 5% suspension.[32] Natamycin is the standard of care in many countries, especially developed countries, including Australia.[22, 23, 32] It adheres well to the cornea surface, is well tolerated, and is routinely used for keratitis caused by filamentous fungi.[22, 32] This antifungal, however, has poor penetration into deeper structures of the eye and, hence, is generally effective against superficial infections that are not severe.[22] Not

surprisingly, it is less effective against fungal keratitis with deep stroma lesions.[58] In addition, only about 2% of the drug in the cornea is bioavailable after topical application.[59] The usefulness of topical natamycin is further complicated by the fact that it settles out (precipitate) on the cornea upon instillation and degrades easily.[40]

Fluconazole is fungistatic and is administered systemically and topically for fungal keratitis.[60] Oral and IV fluconazole are very safe, and penetrate well into the corneal tissue.[32] After systemic administration, the ocular concentration of fluconazole was shown to be more than 70% of the observed plasma concentration.[61] Whilst oral fluconazole is a commonly used agent for the treatment of fungal keratitis,[23] topical application of 0.2% fluconazole solution is as effective as systemic fluconazole. Fluconazole, when applied topically, penetrates well into the cornea, is safe, and has been used successfully against fungal keratitis.[62-64] A major limitation associated with fluconazole, however, is its narrow spectrum of antifungal activity. Fluconazole is inactive against *Aspergillus* and *Fusarium* species;[65] although active against *Candida* species, it is less active against *Candida glabrata* and *Candida Krusei* than *Candida albicans*.[57]

Itraconazole is available orally and, though commonly associated with gastrointestinal side effects, it is considered relatively safe.[66] Although it has activity against *Candida* and *Aspergillus* species, it is rarely used for the treatment of fungal keratitis.[40] Itraconazole is inactive against *Fusarium* species,[23, 40] but more importantly, it has poor penetration into the cornea after systemic administration.[67] Experimental use of topical itraconazole (1% solution) has been reported, but appears to demonstrate insufficient corneal penetration.[68]

Ketoconazole is an older generation azole antifungal, which has a broad spectrum of activity, including against *Aspergillus*, *Candida* and *Fusarium* species.[40] It is available orally and, although it has demonstrated good tissue distribution after administration,[57] it has not been used for fungal keratitis. Significantly, long-term administration of high-dose ketoconazole may result in impotence, gynecomastia or alopecia, which is problematic considering the long-term nature of keratitis therapy.[69]

Voriconazole, a more recent azole antifungal, is available commercially for systemic administration in the form of oral and IV formulations. It has an excellent broad spectrum of antifungal activity and is active against species that are known to be resistant to the other common antifungal agents used in fungal keratitis.[40] Voriconazole is increasingly being used, orally in particular, against fungal keratitis. Oral voriconazole is highly bioavailable (96%)[70] and has demonstrated good penetration into the different parts of the eye,[71] with sufficient concentrations achieved to cover a wide range of the keratitis-causative fungi.[40] However, oral voriconazole can be associated with side effects as well as significant drug interactions.[72] Topical 1% voriconazole eye drops, manufactured extemporaneously and used in an off-label

manner, have also been prescribed for the treatment of keratitis with promising results. With topical administration, voriconazole demonstrated good penetration through the cornea into the aqueous humour,[73] without compromising intraocular safety.[74]

Posaconazole is only available orally as a suspension. It has an excellent broad spectrum of activity and is as active as voriconazole, with added activity against zygomycetes.[75] It is safe, with mild gastrointestinal side effects being the most common adverse events.[76] Posaconazole was only recently introduced worldwide and, as such, studies on its ocular penetration are lacking. In a number of recent case reports involving the use of oral posaconazole alone as salvage therapy, or in combination with topical posaconazole, this antifungal agent demonstrated success against fungal keratitis.[77, 78] The formulation used for the topical posaconazole was the same formulation used for the oral suspension (10 mg/0.1 ml).[40]

Caspofungin is the first member of echinocandins to be marketed commercially. It is available in IV formulation, and has significantly less systemic toxicity than azoles. Systemically administered caspofungin does not penetrate well into the eye and, hence, it is not used for fungal keratitis.[79] Nonetheless, in one recent case report, when administered topically (with concentration of 0.5%), as adjunctive therapy, caspofungin demonstrated clinical success against fungal keratitis.[63] It is safe;[79] however, it lacks activity against *Fusarium* species.[22, 80]

Of the aforementioned the antifungal agents, amphotericin B, natamycin, fluconazole, itraconazole and ketoconazole have been used to treat fungal keratitis for quite some time. However, poor cornea penetration after topical administration, poor ocular penetration after systemic administration, limited spectra of antifungal activity and/or limited clinical success associated with these agents are major limitations[22] and have rendered these therapies challenging and inadequate for fungal keratitis. The limited clinical success is particularly true with the topical use of these agents, as they often require co-administration of an additional antifungal agent taken systemically,[32] which can introduce systemic toxicity and be costly. This has led to consideration of using newer available antifungal agents, such as voriconazole, posaconazole and caspofungin, and/or in-house preparations of them, as a means to overcome the shortcoming of the current antifungal therapies for fungal keratitis.

Through the rest of this chapter, particular emphasis is given to the use of voriconazole eye drops as a treatment for fungal keratitis.

9.3 TOPICAL ADMINISTRATION OF VORICONAZOLE IN THE TREATMENT OF FUNGAL KERATITIS

Voriconazole is ideal for use in the treatment of fungal keratitis, as it has a broad spectrum of activity with low minimum inhibitory concentrations (MIC), as well as a high systemic intraocular penetration profile.[40, 81]

Voriconazole is potent against a wide spectrum of keratitis-causative fungi, namely, the most common pathogens *Candida albicans*, *Candida parapsilosis*, *Candida tropicalis*, *Aspergillus fumigatus*, *Aspergillus flavus* and *Fusarium solani*,[81-83] and other less common pathogens from the *Paecilomyces*, *Histoplasma*, *Scedosporium*, *Curvularia* and *Acremonium* species.[81, 82] The in vitro MICs of voriconazole against typical keratitis-causative fungi are shown in **Table 9-2**.

Although the MIC of voriconazole against *Fusarium* species is higher than that for other fungi, compared to other antifungal agents, voriconazole has the best activity against *Fusarium* species.[84] In a study by Marangon *et al.*,[84] in which, the in vitro susceptibility of common pathogens to voriconazole was compared to that for amphotericin B, fluconazole, itraconazole and ketoconazole, voriconazole demonstrated the lowest MIC_{90}, as shown in **Table 9-3**. In addition, voriconazole was the only antifungal agent that demonstrated 100% antifungal activity against 541 different fungal isolates comprising *Candida*, *Aspergillus* and *Fusarium* species (**Figure 9-3**).

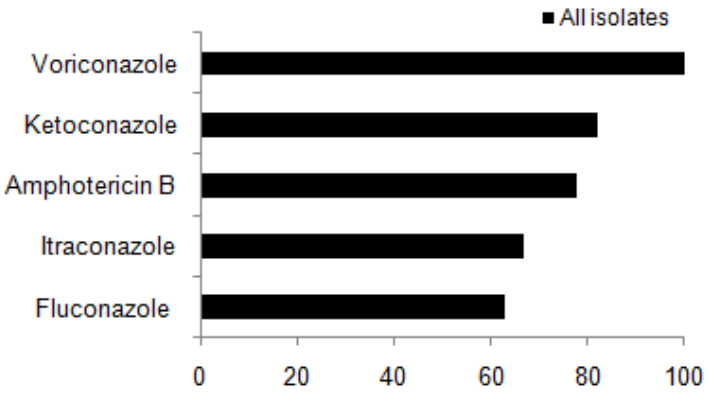

Figure 9-3. In vitro susceptibility of 541 fungal isolates to common antifungals.[84]

Table 9-2. In vitro minimum inhibitory concentrations (MIC_{90}) with voriconazole[73, 81, 85]

Organism	MIC_{90} (µg/ml)
Candida albicans	0.06
Candida parapsilosis	0.12-0.25
Candida tropicalis	0.25-> 16.0
Cryptococcus neoformans	0.06-0.25
Aspergillus fumigates	0.50
Aspergillus flavus	0.50
Fusarium species	0.25-8
Fusarium solani	2
Paecilomyces lilacinus	0.50
Acremonium alabamensis	0.25
Blastomyces dermatitidis	0.25
Coccidioides immitis	0.25
Histoplasma capsulatum	0.25
Penicillium marneffei	0.03
Cuvularia species	0.06-0.25
Scedosporium species	0.5
Scedosporium apiospermum	0.5

Table 9-3. In vitro minimum inhibitory concentrations (MIC_{90}) of common antifungals[84]

Antifungal agent	*Aspergillus* spp.[a] (µg/ml)	*Candida* spp. (µg/ml)	*Fusarium* spp. (µg/ml)
Voriconazole	0.5	0.016	2
Amphotericin B	2	0.5	2
Itraconazole	1	0.256	> 16
Fluconazole	> 256	0.5	> 256
Ketoconazole	4	0.032	> 16

[a]spp., species.

9.4 INTRAOCULAR PENETRATION OF SYSTEMIC VORICONAZOLE

In a prospective clinical study by Hariprasad *et al*.,[71] systemically administered voriconazole was demonstrated to achieve good penetration into the aqueous and vitreous humours of the human eye. Two 12-hourly 400 mg doses of voriconazole were given to 14 patients with non-inflamed eyes attending for elective surgery. The aqueous and vitreous humour samples were collected within three hours after drug administration. The mean measured plasma, vitreous and aqueous voriconazole concentrations were 2.13, 0.81 and 1.13 μg/ml, respectively. The voriconazole concentration in the aqueous humour was 53% of the concentration obtained in the plasma, and was sufficiently high to be effective against most common fungi associated with fungal keratitis. A similar outcome was reported in a case report by Nulens *et al*.,[86] where a case of *Scedosporium apiospermum* keratitis was successfully treated with oral voriconazole. The voriconazole concentration in the aqueous humour (1.8 μg/ml) was measured after 12 days of drug administration and was also 53% of the voriconazole concentration observed in the patient's plasma (3.4 μg/ml).

Although it has good intraocular penetration, systemic voriconazole may result in side effects (including ocular events), complications and interactions with concomitant medications.[72] Whilst mostly reversible, these side effects may lead to the discontinuation of therapy.[81] In addition, systemic voriconazole is very costly. The cheapest of its formulations (i.e. oral voriconazole tablets) costs about AU$3,000 (US$2,600) per month of therapy for fungal keratitis.[64] When administered intravenously, it can cost up to AU$11,400 (US$9,600) per month.[87] Therefore, an efficient, more effective and economical strategy of using voriconazole for the treatment of fungal keratitis is highly desirable and would be invaluable in clinical practice.

9.5 EYE DROPS AND OPHTHALMIC DRUG DELIVERY

The topical administration of medications to the eye is a typical strategy for treating disorders of anterior eye structures such as the cornea.[7, 88] Eye drops are the most common dosage form used,[88] as they are an economical and efficient method of delivering drugs into the eye, and have four main advantages.[7] Firstly, the drug effect is localised where it is needed and a minimal amount of the drug reaches the systemic circulation. Secondly, drug concentrations at the site, that are hard to achieve via systemic administration, can be achieved via topical

administration. Thirdly, topically administered drugs avoid hepatic metabolism. Lastly, topical administration is convenient, simple and painless.

Nonetheless, eye drops have their disadvantages. They have a very low drug bioavailability, usually less than 5%.[88] There are several factors that limit a drug's availability to penetrate through the cornea into deeper structures of the eye. The volume of a typical ophthalmic eye drop is 50 µL. The human eye, however, can maximally accommodate about 30 µL without spillage and, hence, a large amount of the drug is wasted.[7] The drainage rate of eye drops from the human eye surface is about 10 µL per minute.[89] Although to a lesser extent, another factor that can limit the amount of drug penetrating into the cornea is the constant turnover of the tear film.[7] The turnover rate of human tear film is 16%,[7] which is about 1.2 µL per minute.[89] Even after penetration into the aqueous humour, drugs are eliminated due to aqueous humour turnover and blood circulation.[89] The volume of the aqueous humour is about 0.3 mL,[89] and it has a turnover rate of about 3 µL per minute that is independent of the drug.[88] The drug's clearance from the eye via systemic circulation, however, depends on the lipophilicity of the drug and its ability to penetrate across membranes. Hence, the clearance of lipophilic drugs is higher than that for hydrophilic drugs and can range from 20 to 30 µL per minute.[88]

As mentioned previously (**Section 9.1)**, the cornea comprises both lipophilic and hydrophilic substances and, therefore, the cornea represents an effective barrier against delivering both lipophilic and hydrophilic drugs into the eye.[7] A lipophilic compound encounters minimal resistance in penetrating the outer epithelium of the cornea, but more resistance in infiltrating the stroma. The converse applies to hydrophilic compounds, which encounter more resistance to absorption from the epithelium and less by the stroma. Given that the corneal epithelium is the main and first barrier of the drug absorption into the eye,[89] it is not surprising that lipophilic compounds are more favourable for corneal absorption.[7]

9.6 FORMULATION OF VORICONAZOLE EYE DROPS

Whilst lipophilic compounds (or drugs) have higher corneal permeability, they usually have limited aqueous solubility. As such, formulating eye drops for drugs with low aqueous solubility can be challenging.[7] Voriconazole is a lipophilic compound with low solubility (0.061% at pH 7), and is unstable in aqueous environments.[7, 90] For the IV formulation of voriconazole to be feasible, the manufacturer (i.e. Pfizer) encapsulated voriconazole with a β-cyclodextrin derivative in the form of lyophilised powder of cyclodextrin-voriconazole complex.[72] This increases the solubility and stability of voriconazole in aqueous solutions,

while maintaining its lipophilicity and high corneal permeability.[7, 89] Cyclodextrins are a group of homologous cyclic oligosaccharides that, in complex formation with a drug, increase dissolution rate (solubility), aqueous stability and/or bioavailability of the drug.[89]

Currently, voriconazole eye drops are not commercially available and are aseptically manufactured on site, by the pharmacy department, by diluting the IV formulation of voriconazole. The IV voriconazole is available as a glass vial that holds a white lyophilised powder containing 200 mg voriconazole and 3,200 mg sulfobutyl ether β-cyclodextrin sodium. As per the voriconazole package insert, the powder is reconstituted with 19 mL of water for injection to produce a 20 mL aqueous voriconazole solution with a concentration of 10 mg/mL (1%), which is infused into the systemic circulation.[72] This voriconazole solution is what is typically being used as eye drops.[85, 91]

9.7 OCULAR PENETRATION OF VORICONAZOLE EYE DROPS – ANIMAL STUDIES

Several studies have been performed to assess the penetration and tolerability of voriconazole eye drops in animals. In an animal model by Sponsel *et al*.,[92] topical voriconazole (5 or 10 µg/mL) was evaluated against *Paecilomyces lilacinus* keratitis in ten rabbits (ten infected eyes). Voriconazole demonstrated good and deep penetration into the rabbits eyes. The measured tissue concentrations in the cornea were sufficiently high (24.3 and 51 ng/mL with topical 5 and 10 µg/mL voriconazole, respectively), and the experimental keratitis was treated successfully.

Topical application of voriconazole eye drops was also investigated in a horse model by Clode *et al*.,[93] where voriconazole eye drops (0.5, 1 and 3% solutions) were administered to seven healthy horses (four eyes for each concentration). With the measured aqueous humour concentrations being 1.43, 2.35 and 2.4 µg/mL, respectively, topical voriconazole was shown to effectively penetrate through the cornea and achieve detectable levels. Only the 3% solution was associated with ocular toxicity.

It is important to recognise, however, that extrapolating penetration data from animal models to humans may not be reliable. Rabbits, for instance, have a very low blink rate and large epithelial eye surface, which enhances the penetration of lipophilic and non-irritating drugs, such as voriconazole, into the cornea.[94] In addition, while the drainage rate of eye drops from the ocular surface in rabbits is about 4 µL per minute, it is over twice as much in humans.[89]

9.8 CORNEAL PENETRATION OF VORICONAZOLE EYE DROPS – HUMAN STUDIES

Two studies have investigated voriconazole penetration through the human cornea into the aqueous humour.[64, 85]

In a study by Vemulakonda *et al*.,[85] 13 patients scheduled for vitrectomy surgery were recruited to receive a two-hourly 1% voriconazole eye drop for 24 hours. Samples were taken 24 minutes after the last dose. Topical voriconazole was well tolerated by the eye, and the mean measured voriconazole concentration in the aqueous humour was 6.49 µg/mL, which is sufficiently high against common pathogens. The concentration, however, was a peak level concentration, as it was taken after 24 minutes of a two-hourly dosing regimen (peak concentration is reached after 20 to 30 minutes of eye drop administration).[88] This study did not demonstrate that the two-hourly dosing regimen results in sustained and adequate therapeutic trough voriconazole concentrations in the eye. Nonetheless, the ability of topically administered voriconazole eye drops to achieve high aqueous humour concentrations was demonstrated.

In another study, by Lau *et al*.,[64] ten patients scheduled for anterior segment surgery were recruited to receive a 1% voriconazole eye drop every six hours for three days, or every hour for four doses. The eye drops were well tolerated, but the aqueous humour concentrations achieved were not sufficiently high to be effective against all common pathogenic fungi. After the six-hourly and hourly dosing, the voriconazole concentrations were 0.94 and 1.9 µg/mL, with average sampling time of 2.1 and 1.1 hours after the last dose, respectively. If samples from the six-hourly regimen were to be taken six hours after the last dose (i.e. trough level), the concentrations measured would be even less than 0.94 µg/mL, suggesting that six-hourly dosing of 1% voriconazole eye drops may be ineffective. Samples taken by Lau *et al*.,[64] after the hourly dosing, were collected approximately one hour after the last dose, representing trough level concentrations. Although the measured 1.9 µg/mL concentration is effective against *Aspergillus* and *Candida* keratitis, it is ineffective against other common types of keratitis, such as *Fusarium* keratitis.

The studies by Vemulakonda *et al*. and Lau *et al*. were highly valuable and explored the penetration of 1% voriconazole eye drops into the human aqueous humour using different dosage regimens; however, it is important to recognise the major limitation that the eye drops, in these studies, were applied to non-infected eyes. It has been widely observed that corneal drug penetration will generally be enhanced with the destruction of the corneal epithelium.[95] For instance, the removal of the surface of the corneal epithelium is recommended to improve

the penetration of topical amphotericin B.[94] On the other hand, in the rabbit model by Sponsel *et al*.,[92] when the penetration of topical voriconazole into the infected eyes was compared with that into the non-infected eyes of the rabbits, it was found that the corneal concentration of voriconazole in the non-infected eyes (after topical administration) was higher than that in the rabbits with infected corneas. However, in a recent case series by Thiel *et al*.,[94] where voriconazole concentrations in the aqueous humour, following the administration of voriconazole eye drops, were compared among patients with different degrees of corneal injuries, measured voriconazole concentrations in the infected eyes depended neither on the size of the epithelial defect nor on epithelial removal. Accordingly, it was suggested that epithelial damage is not necessary for penetration of topical voriconazole into the eye. These, however, are preliminary findings. The effect of corneal damage on the penetration of voriconazole into the human eye remains to be elucidated.

To date, the penetration of topical voriconazole eye drops through the infected cornea in humans has only been reported twice, as case reports.

In the case reported by Klont *et al*.,[73] the aqueous humour voriconazole concentration was measured after 13 days of topical 1% voriconazole, co-administered with oral voriconazole, for the treatment of a patient with *Fusarium* keratitis. The advantage of topical voriconazole was demonstrated, whereby, the aqueous humour concentration was found to be 3.2 µg/mL, which was 160% of the voriconazole concentration in plasma (2 µg/mL).

In the previously mentioned case series by Thiel *et al*.,[94] six patients, including five patients with fungal keratitis, received IV and topical voriconazole for the treatment of *Aspergillus* and *Candida* infections. The aqueous humour samples were collected at stages of therapy where voriconazole eye drops were used alone. These resulted in voriconazole concentrations ranging from 0.61 to 3.3 µg/mL. The results were highly variable, but provided support for the benefit of using voriconazole eye drops.

9.9 EFFICACY OF VORICONAZOLE EYE DROPS – CASE REPORTS

Although voriconazole concentrations were detected in the aqueous humour after the topical administration of voriconazole eye drops, they may not necessarily correlate with efficacy in the clinical setting of fungal keratitis.[32] Well-designed clinical studies involving the use of voriconazole eye drops in patients with active fungal keratitis are difficult to perform and, therefore, lacking. The difficulties in conducting such studies relate to the low incidence of

fungal keratitis as well as the need for long treatment duration. In addition, in clinical settings, patients will mostly be receiving other antifungal therapies that will interfere with measured outcomes.

Currently, evidence of clinical efficacy of voriconazole eye drops in fungal keratitis is based solely on case reports. A review of published literature has identified seven reports on the use of voriconazole eye drops for the treatment of fungal keratitis.[73, 78, 96-99] The case reports are summarised in **Table 9-4**.

In all the reported cases, voriconazole eye drops were used in combination with systemic voriconazole. The 1% voriconazole eye drops were used in all cases, except that by Polizzi *et al*.,[96] where 2% voriconazole was used. Brief summaries of these cases are given below.

Table 9-4. Case reports of the use of topical voriconazole in fungal keratitis[73, 78, 96-99]

Author	Patient (age, sex)	Pathogen	Voriconazole concentration[b]	Treatment	Outcome
Reis *et al.*	16, female	*Fusarium solani*	1%	Salvage	Success
Tu *et al.*	29, male	*Fusarium* spp.[a]	1%	Primary	Failure
Tu *et al.*	43, female	*Fusarium solani*	1%	Primary	Failure
Prats *et al.*	19, male	*Scedosporium apiospermum*	1%	Salvage	Success
Jones *et al.*	52, female	*Aspergillus niger*	1%	Salvage	Success
Klont *et al.*	23, male	*Fusarium solani*	1%	Salvage	Success
Polizzi *et al.*	56, male	*Fusarium solani*	2%	Salvage	Success

[a]spp., species.

[b]Voriconazole concentration in eye drops.

The first of these cases, reported by Reis *et al*.,[98] involved a 16 year-old girl diagnosed with keratitis caused by *Fusarium solani* after swimming in a lake. After months of antifungal therapy, the fungal keratitis failed to respond to treatment. The patient was initially prescribed topical amphotericin B and fluconazole, followed by itraconazole at a later stage. These, however, had no effect on the infection and, hence, IV followed by oral voriconazole was administered. A significant improvement was noticed, followed by resolution upon the addition of topical voriconazole to therapy.

In the first of the two cases reported by Tu *et al*.,[78] a 29 year-old man received oral and topical voriconazole for the treatment of trauma-induced *Fusarium* keratitis. In the

second case, a 43 year-old woman received a combination of IV, topical and intravitreal voriconazole for keratitis caused by *Fusarium solani* that was associated with contact lens wear. In both of these cases, voriconazole was initially effective until it had to be discontinued because of severe hepatotoxicity. Patients were then switched to posaconazole as salvage therapy.

In the case report by Prats *et al*.,[97] a 19 year-old man was admitted with an incisive ocular wound, with the cornea totally sectioned upon trauma. *Scedosporium apiospermum* keratitis was diagnosed. Upon failure of the initial empirical antifungal therapy, systemic (IV and oral) and topical voriconazole were commenced. This was the first case report where voriconazole was used for the treatment of *Scedosporium apiospermum* keratitis. Five months after the incident, the infection resolved.

In the case report by Jones *et al*.,[99] voriconazole therapy was demonstrated to be effective against *Aspergillus* keratitis in a 52 year-old woman diagnosed with *Aspergillus niger* keratitis. The patient was initially treated with topical amphotericin B, which was not effective. When the patient was switched to a combination of oral and topical voriconazole, the infection improved rapidly and resolved after five weeks.

Similarly to the case reports by Reis *et al*. and Tu *et al*.,[78, 98] the case report by Klont at al[73] also reported the use of 1% voriconazole eye drops in the treatment of *Fusarium* keratitis. A 23 year-old man with *Fusarium solani* keratitis failed to respond to treatment despite initial topical amphotericin B and itraconazole therapies. The patient was then prescribed, as salvage therapy, concomitant IV and topical voriconazole followed by oral and topical voriconazole. The treatment was ceased at week six, with successful outcome.

In the case report by Polizzi *et al*.,[96] voriconazole eye drops were also used against *Fusarium* keratitis. This is the only case where 2% voriconazole eye drops were used. The 56 year-old man developed corneal ulceration caused by *Fusarium solani* upon accidental contact with vegetation. Systemic and topical amphotericin B and fluconazole were administered initially, but the patient did not improve. The therapy was then switched to IV and oral voriconazole given in combination with topical 2% voriconazole eye drops. No side effects were reported, and the patient completely recovered after 20 days of treatment with voriconazole.

The above cases highlight a number of important issues. One is that the use of voriconazole eye drops was associated with successful outcomes in most cases of fungal keratitis. Whilst the voriconazole therapy appeared to fail in the cases reported by Tu *et al*.,[78] the failure was not due to lack of voriconazole efficacy, but to severe side effects from systemically administered voriconazole, which required discontinuation of treatment. A second issue is that voriconazole eye drops were used as an adjunct to systemic voriconazole in all reported cases. None of the case reports has demonstrated the benefit of topical

voriconazole when used alone (i.e. monotherapy), either as primary or salvage therapy. Another issue is that, whilst the 2% voriconazole eye drops were effective,[96] the advantage of using 2% eye drops compared to 1% voriconazole eye drops remains unknown.

9.10 STABILITY OF VORICONAZOLE EYE DROPS

Despite the reports of the clinical use of voriconazole eye drops,[40, 81] with the eye drops being manufactured in-house for use in hospitals, there are negligible data in the literature related to the eye drops' long-term stability. Stability testing is an important part of the development of any extemporaneously-prepared eye drops. It maximises the clinical use of the eye drops and, importantly, helps minimise wastage. At the institutional level, long-term stability data for voriconazole eye drops can potentially result in major cost savings, especially because voriconazole eye drops appear to have clinical applications that extend beyond the use in fungal keratitis.[40, 63, 81, 100] The manufacturer of voriconazole recommended that, after the reconstitution of the lyophilised powder as per the package insert, the resulting voriconazole solution should be kept refrigerated for a maximum of 48 hours;[72] no further information was provided. The only stability study of voriconazole eye drops was performed by Dupuis *et al*.;[91] the stability of 1% voriconazole eye drops was only investigated over a period of four weeks when stored at 4 ºC and room temperature. The 1% voriconazole eye drops had a neutral pH of seven and was clear throughout the study duration.

9.11 COST MINIMISATION WITH VORICONAZOLE EYE DROPS

Voriconazole eye drops appear to be effective when used for the treatment of fungal keratitis; however, their current utilisation is less than optimal. Firstly, data on the long-term near-patient stability of voriconazole eye drops are lacking. The possibility of long-term storage of these extemporaneously prepared eye drops and, thus, minimising their manufacturing cost and wastage, is unknown. Secondly, if the voriconazole eye drops were to be used alone, they could result in significant cost savings and improved safety. However, it remains unknown whether voriconazole eye drops can be used effectively as monotherapy in humans for the treatment of fungal keratitis. Voriconazole eye drops have only been reported to be effective when used as an adjunct to other existing antifungal therapies. Thirdly, increasing the concentration of voriconazole eye drops may lead to increase efficacy and/or reduce dosing

frequency; however, the benefit of using greater than 1% concentrations of voriconazole eye drops has not been evaluated in humans beyond the case report by Polizzi *et al*.[96]

Accordingly, studies that evaluate the long-term stability of voriconazole eye drops, the use of voriconazole eye drops as monotherapy, as well as the use of higher concentrations of the voriconazole eye drops will provide important data to facilitate the optimal and cost-minimising use of voriconazole eye drops for the treatment of fungal keratitis. Such studies were performed as discussed in **Chapters Ten**, **Eleven**, **Twelve** and **Thirteen** of this thesis.

9.12 REFERENCES

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CHAPTER TEN: STABILITY OF EXTEMPORANEOUSLY PREPARED VORICONAZOLE OPHTHALMIC SOLUTION

As discussed in the previous chapter (**Chapter Nine)**, voriconazole eye drops are a promising option for the treatment of ocular fungal infections, such as fungal keratitis. However, despite their current use in clinical practice, long-term stability data for voriconazole eye drops remain insufficient. The availability of near-patient stability data will support the clinical use of the eye drops, with a view to minimising wastage and the cost associated with it, which could result in considerable cost savings at institutional level. The following work investigates the chemical and physical stability of two different concentrations (i.e. 1% and 2%) of extemporaneously manufactured voriconazole eye drops, containing the preservative benzalkonium chloride.

The following material is arranged in a manner suitable for publication in the American Journal of Health-System Pharmacy. Headings and tables are renumbered in order to generate a consistent presentation within the thesis.

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DECLARATION FOR THESIS CHAPTER TEN

In the case of Chapter Ten the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Conception and design. Literature search. Data collection. Statistical experience. Analysis and interpretation. Writing the article. Critical revision of the article.	85%

The following co-authors contributed to the work:

Name[a]	Nature of contribution
David CM Kong	Conception and design. Critical revision of the article. Final approval of the article.
Kay Stewart	Conception and design. Critical revision of the article.
Lok Leung	Critical revision of the article.
Geoffrey E Davies	Critical revision of the article.
Robert Fullinfaw	Design. Critical revision of the article.
Jian Li	Provision of materials, or resources. Analysis. Critical revision of the article.

[a]None of the co-authors is a student co-author.

Candidate's signature _____ Date _____

DECLARATION BY CO-AUTHORS

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.

(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;

(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;

(4) there are no other authors of the publication according to these criteria;

(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and

(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

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Geoffrey E Davies	[redacted]	17/11/2009.
Robert Fullinfaw	[redacted]	17 Nov 2009
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10.1 STUDY TITLE

Stability of extemporaneously prepared voriconazole ophthalmic solution.

10.2 AUTHORS

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10.3 ABSTRACT

Purpose: The stability of extemporaneously prepared voriconazole ophthalmic solution was studied.

Methods: Voriconazole solutions (2% and 1%) were reconstituted from the i.v. formulation. After thorough mixing, 3-mL samples of each of the resulting 2% and 1% solutions were filtered into eyedroppers. Three samples for both solutions were analyzed in triplicate at each time point. The 2% voriconazole ophthalmic solutions were stored at 2-8 °C, 25 °C, and 40 °C. The 1% voriconazole eye drops were stored at 2-8 °C. The 2% voriconazole solution samples were analyzed at time 0 and at weeks 1, 2, 4, 8, 16, and 32. The 1% solution samples

were analyzed at time 0 and at weeks 6 and 14. Stability was measured using high-performance liquid chromatographic analysis.

Results: The 2% voriconazole ophthalmic solution demonstrated excellent stability at 2-8 °C and 25 °C for up to 16 weeks. The voriconazole solution displayed no significant change in pH at all time intervals. No change in visual appearance or clarity was observed in the 2% voriconazole eye drops at any point of the study for all study temperatures. Voriconazole 1% solution was stable at 2-8 °C for up to 14 weeks.

Conclusion: Voriconazole 2% (20 mg/mL) solution preserved with 0.01% benzalkonium chloride prepared as alternative antifungal eye drops was stable for 16 weeks when stored at 2-8 °C and 25 °C and for 8 weeks when stored at 40 °C, while voriconazole 1% solution was stable at 2-8 °C for up to 14 weeks.

Index terms: Antifungals; Chromatography, liquid; Compounding; Control, quality; Hydrogen ion concentration; Solutions, ophthalmic; Stability; Storage; Temperature; Voriconazole.

10.4 INTRODUCTION

Ocular fungal infections (ophthalmic mycoses) are a major cause of morbidity and blindness.[1] Of these infections, fungal keratitis remains one of the most difficult to treat.[2] While a number of topical antifungal agents (e.g., commercially available natamycin, extemporaneous amphotericin B formulations) have been used to treat fungal keratitis, their effectiveness is limited, and they are generally considered inadequate for use as monotherapy.[3] Accordingly, orally administered or injectable antifungal agents are often coadministered to treat fungal keratitis. In addition to being costly, these systemic antifungals are often associated with adverse effects or interact with concomitant medications.[1-3] A more effective and economical strategy to manage ophthalmic fungal infections is needed.

A potential solution is to manufacture a new antifungal eye drop formulation using an antifungal known to effectively treat fungal keratitis but not marketed for direct application to the eye. Voriconazole (Vfend, Pfizer, New York, NY) was approved for marketing in the United States in 2002. It is a second-generation triazole with extended-spectrum antifungal activity.[4] Voriconazole is highly effective against *Candida*, *Aspergillus*, *Fusarium*, *Paecilomyces*, and *Scedosporium* species with a minimum inhibitory concentration required

to inhibit the growth of 90% of strains of 0.015, 1, 2, 0.5, and 0.25 µg/mL, respectively.[5-8] It is currently available only in oral and i.v. formulations.

The results of one study revealed that oral voriconazole penetrates the eyes to treat fungal keratitis.[9] However, oral voriconazole is costly and often associated with adverse effects (e.g., liver toxicity, visual disturbances), requiring treatment to be discontinued.[4,9,10] While oral voriconazole has been used to treat fungal keratitis,[9,11] little is known about the ophthalmic use of voriconazole to treat fungal infections. Direct application of voriconazole to ocular tissues has been demonstrated as safe in animal models,[12] but limited information has been reported regarding the use of voriconazole eye drops to treat fungal keratitis in humans. Numerous case reports have described promising results for the off-label use of voriconazole as a 1% topical eye drop preparation.[13-15] This formulation was prepared from i.v. voriconazole. The i.v. formulation is supplied as a vial of sterile lyophilized powder that contains 200 mg of voriconazole and 3200 mg of sulfobutyl ether β-cyclodextrin sodium.[4]

A recent study of the use of 1% voriconazole ophthalmic solution as monotherapy in patients undergoing elective eye surgery demonstrated that the concentration of voriconazole in the aqueous humor of the eye was sufficiently high to treat some types of fungal infections but may be inadequate for deep-seated infections that may involve, for example, the vitreous humor of the eye.[16] This finding is similar to that of a recent report by Vemulakonda et al.,[17] who studied the penetration of a topically administered 1% voriconazole solution into the eye. The results of these studies suggest that a higher concentration of voriconazole ophthalmic solution (e.g., 2%) may be required to achieve adequate levels of voriconazole in the eye.[16,17]

Despite several reports of the clinical application of voriconazole ophthalmic solution,[13-17] there are negligible data in the literature related to the formulation's long-term stability, thus limiting its clinical use. Long-term stability information on extemporaneously compounded voriconazole for ophthalmic use is not available from the manufacturer (Ellery K, Pfizer Australia, personal communication, 2009 Jun 1). The manufacturer recommends that reconstituted voriconazole for i.v. injection should be kept refrigerated for a maximum of 48 hours.[4]

In view of the limited stability data available to support the use of the 2% and 1% voriconazole ophthalmic solutions, this study investigated the stability of 2% and 1% voriconazole eye drops.

10.5 METHODS

10.5.1 SAMPLE PREPARATION

Voriconazole solution (20 mg/mL [2%], 10 mL) was prepared by reconstituting 200 mg of voriconazole lyophilized powder for injection[a] with 9 mL of water for injection[b] containing 0.01% benzalkonium chloride solution.[c] The 1% voriconazole solution was prepared, according to the manufacturer's instructions, by reconstituting 200 mg of voriconazole for injection[a] with sterile water for injection[b] (19 mL) containing 0.01% benzalkonium chloride solution[c] to obtain an extractable 20-mL volume of the solution.[4] The reconstituted solutions were clear and colorless.

When preparing samples for the stability study, voriconazole powder in each vial was reconstituted under aseptic conditions. After thorough mixing, 3-mL portions of each of the resulting 2% and 1% solutions were filtered through 0.22-µm mixed cellulose esters membrane filters[d] into amber high-density polyethylene (HDPE) eye drop bottles.[e] All eyedroppers were kept sealed until the time of testing. Three samples at each time point for both the 2% and 1% solutions were analyzed in triplicate by high-performance liquid chromatography (HPLC). The 2% voriconazole solution samples were analyzed at time 0, 1 week (7 days), 2 weeks (14 days), 4 weeks (28 days), 8 weeks (56 days), 16 weeks (112 days), and 32 weeks (224 days). The 1% solution samples were analyzed at time 0 and 6 weeks (43 days) and 14 weeks (99 days) after storage.

Samples of the 2% voriconazole ophthalmic solution were stored under refrigeration (2-8 °C), at room temperature (25 °C) in an environmental chamber, and in a dry oven (40 °C). The stability of the 1% voriconazole ophthalmic solution was only investigated for samples stored under refrigeration (2-8 °C). All solutions were stored in lightproof HDPE eyedroppers.

A 200-µL sample of the voriconazole ophthalmic solution was removed from an eyedropper at each testing time point and diluted with water[f] and methanol (50:50, v/v)[g] to a 10-mL volume (50-fold dilution) in a volumetric flask. To validate the dilution procedure of the 1% and 2% ophthalmic solution samples, quality-control solutions of 10-mg/mL (1%) and 20-mg/mL (2%) voriconazole pure substance[h] were prepared. The dilution of the eyedropper sample was deemed valid if the measured concentration of the dilution quality-control solution was within 20% difference from the quality-control samples.

10.5.2 HPLC METHOD

A modification of the HPLC methods described by Adams and Bergold[18] and Sahraoui et al.[19] was adapted for use. The instrumentation included a delivery pump,[i] a degasser,[j] an autoinjector,[k] a column oven,[l] a photodiode-array ultraviolet spectrophotometric detector,[m] and a controller[n] connected to a multiinstrument data acquisition and data-processing system.[o]

A 200-µL sample of the diluted solution was transferred into an HPLC autosampler vial, and 10 µL was injected into a C_{18} column[p] preceded by a C_{18} column guard,[q] both of which were contained in the column oven set at 25 °C. The mobile phase consisted of acetonitrile and water (60:40, v/v) delivered at a flow rate of 1 mL/min. The column eluent was monitored for ultraviolet absorbance (signal collected from 190 to 300 nm and processed at 255 nm), and the run time was 6 minutes. Voriconazole had a retention time of 4.6 minutes (**Figure 10-1-A**).

The stock solution of voriconazole pure substance (1 mg/mL) was prepared in methanol, and the working standard solutions were made by serial dilutions of the stock solution in water:methanol (50:50, v/v) to yield voriconazole concentrations of 62.5, 125, 250, 500, and 750 µg/mL. These correspond to 0.31%, 0.63%, 1.25%, 2.5%, and 3.75% voriconazole aqueous solutions, respectively, because concentrations of the aqueous solutions (i.e., samples stored in the eyedroppers) are measured by diluting (i.e., 50-fold) 200-µL portions of the samples taken from the eyedroppers to 10 mL and injecting 10 µL of the diluted solution into the HPLC column for quantification. Good linearity was observed with a linear regression equation of $y = 12152.3x - 1708.7$, where x was the concentration of voriconazole and y was the peak area; the goodness of fit (r^2) was 0.999.

Analysis of intraday quality-control samples with nominal concentrations of 83.0, 333, and 667 µg/mL had mean ± S.D. measured concentrations of 82.2 ± 1.71 µg/mL (n = 6), 352 ± 2.27 µg/mL (n = 6), and 708 ± 4.58 µg/mL (n = 6), with a variation of 0.93%, 5.70%, and 6.26%, and a coefficient of variation (CV) of 2.08%, 0.64% and 0.65%, respectively. The interday quality-control samples with nominal concentrations of 83.0, 333, and 667 µg/mL had mean ± S.D. measured concentrations of 81.1 ± 1.94 µg/mL (n = 3), 349 ± 5.66 µg/mL (n = 3), and 706 ± 7.74 µg/mL (n = 3), respectively. These had a variation of 2.31%, 4.61% and 5.95%, and a CV of 2.39%, 1.62% and 1.10%, respectively. All intraday and interday variations were within acceptable limits of the Food and Drug Administration's guidance for industry in relation to the use of HPLC for quantification (i.e., 15% among the measured high quality-control samples and 20% among the low quality-control samples).[20] The limit of quantification in this study was 62.5 µg/mL.

Forced-degradation and HDPE leaching studies were performed using base, acid, heat, and oxidation to provide an indication of the stability-indicating nature and the specificity of the analytic method.

Effect of acid and alkaline hydrolysis. Voriconazole solution (2%, 1.5 mL) was prepared and transferred to a glass test tube, and either 1 mL of alkaline 0.05 M sodium hydroxide or 6 mL of acidic 0.1 M hydrochloric acid was added. The alkaline solution was left at room temperature for 48 hours under continuous agitation, and the acidic solution was stored in a 40 °C oven for 48 hours. The alkaline and acidic samples were neutralized with equal volumes of 0.05 M hydrochloric acid or 0.1 M sodium hydroxide, respectively. All samples were then diluted in triplicate, as appropriate for the HPLC analyses.

Effect of heat. An HDPE eyedropper filled with 2% voriconazole solution was kept sealed in a 60 °C oven for 15 days to study the effect of heat. On days 0, 7, and 15, samples were taken and equilibrated to room temperature. The samples were then diluted as appropriate for HPLC analysis.

Effect of oxidation. An open HDPE eyedropper filled with 2% voriconazole solution was exposed to the open atmosphere for 7 days at room temperature. In a separate experiment, 0.5 mL of 3% hydrogen peroxide was added to 1 mL of 2% voriconazole in a glass test tube and stored at 25 °C for 23 days. Samples from both solutions were collected at the end of the experiment and processed as appropriate for HPLC analysis.

Leaching solutions. An HDPE eyedropper was filled with 0.01% benzalkonium chloride solution only (without voriconazole), and another dropper was filled with water for injection only (without voriconazole or benzalkonium chloride). Both eye-droppers were stored in a 60 °C oven for 14 days. Samples were taken and diluted in triplicate on days 0, 7, and 14 and analyzed by HPLC analysis.

10.5.3 SAMPLE AND DATA ANALYSES

The stability of the voriconazole ophthalmic solution was investigated by following changes in drug concentration, pH, and visual appearance and clarity of the ophthalmic solution over time. The stability of voriconazole in two ophthalmic solution formulations was determined by calculating the percentage of the initial concentration remaining at each time interval. Chemical stability at any time point was defined as ≥95% of the initial concentration (t = 0), which is above the usually acceptable stability limit for extemporaneous formulations of ophthalmic solutions (≥90% of the initial concentration).[21]

Changes in pH were monitored with a calibrated pH electrode.[r]

10.6 RESULTS

10.6.1 STABILITY-INDICATING NATURE OF THE ASSAY

After exposure to the alkaline condition, two significant additional peaks (retention times of 3.3 and 4 minutes) were detected, with the voriconazole concentration decreasing by about 90% (**Figure-1-B**). When exposed to the acidic condition, two negligible peaks (retention times of 3.3 and 4 minutes) appeared. There was no reduction in the measured voriconazole concentration (**Figure-1-C**), consistent with what was reported in previous studies (i.e., voriconazole is stable in an acidic environment).[19] Seven days after exposure to heat at 60 °C, a significant peak with a retention time of 3.3 minutes was detected, and the resulting voriconazole concentration was reduced to about 55% of its initial value. Fifteen days after exposure to heat, the degradation peak increased in size, while the voriconazole further decreased to about 22% of the initial concentration (**Figure-1-D**). When the voriconazole solution was exposed to the air at room temperature for seven days, no reduction in the voriconazole concentration was observed **(Figure-1-E**). There was a negligible degradation peak at 2.4 minutes, with no significant reduction in the voriconazole concentration (**Figure-1-F**) after exposure to hydrogen peroxide, consistent with previously reported data.[19]

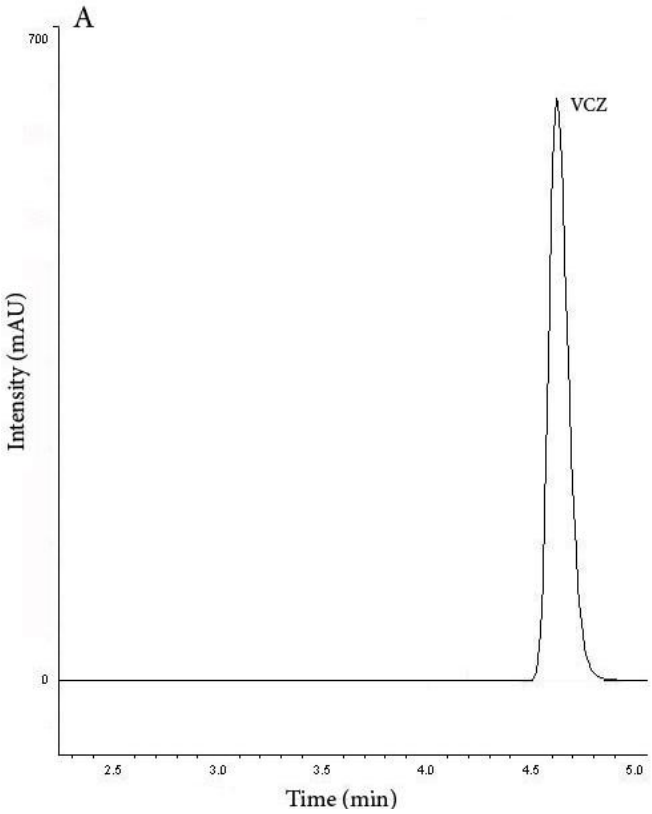
Photodiode array analyses of the spectra of all degradation samples ensured the purity of the voriconazole peak (retention time of 4.6 minutes). No peaks for impurities or byproducts overlapped with the voriconazole peak.

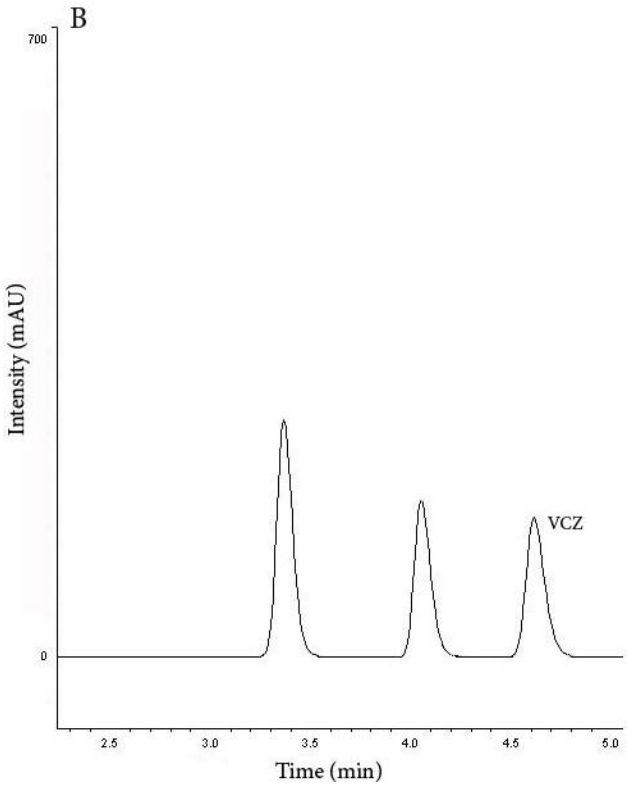
There were no peaks detected with the ophthalmic solution made of 0.01% benzalkonium chloride solution only or with water for injection only.

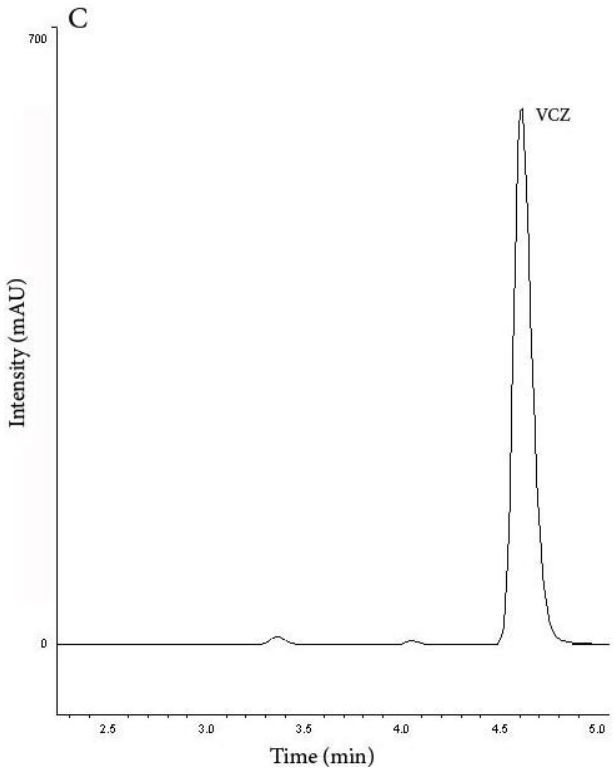
10.6.2 STABILITY DATA

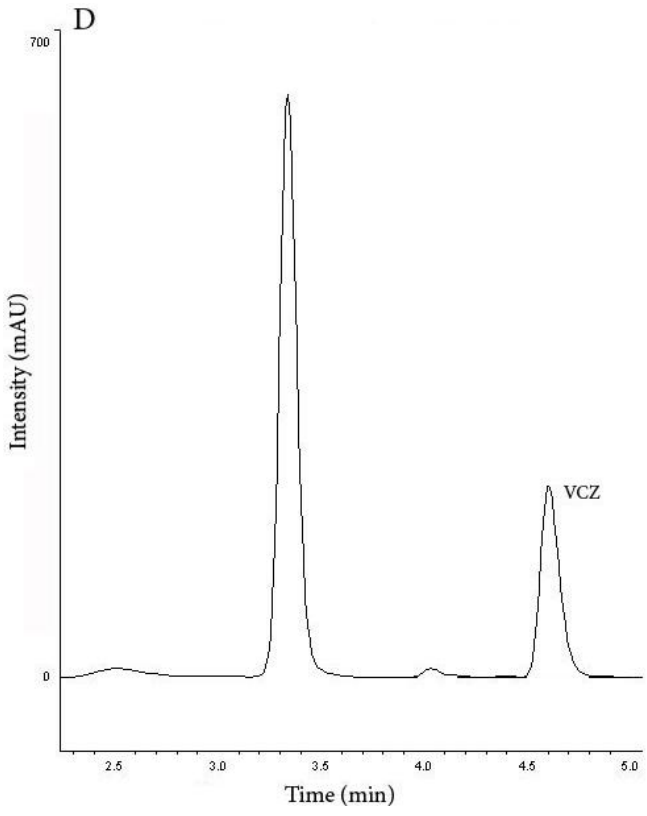
The 2% voriconazole ophthalmic solution stored in HDPE eyedroppers demonstrated excellent stability at 2-8 °C for up to 16 weeks. However, after 32 weeks of storage at 2-8 °C, the voriconazole concentration dropped to 94.35% of its initial concentration (**Table 10-1**). No loss in voriconazole concentration occurred throughout 16 weeks of storage at 25 °C. The voriconazole ophthalmic solution appeared to be more sensitive to degradation when stored at 40 °C; nevertheless, all measured concentrations remained above 97.88% of the initial concentration (**Table 10-1**).

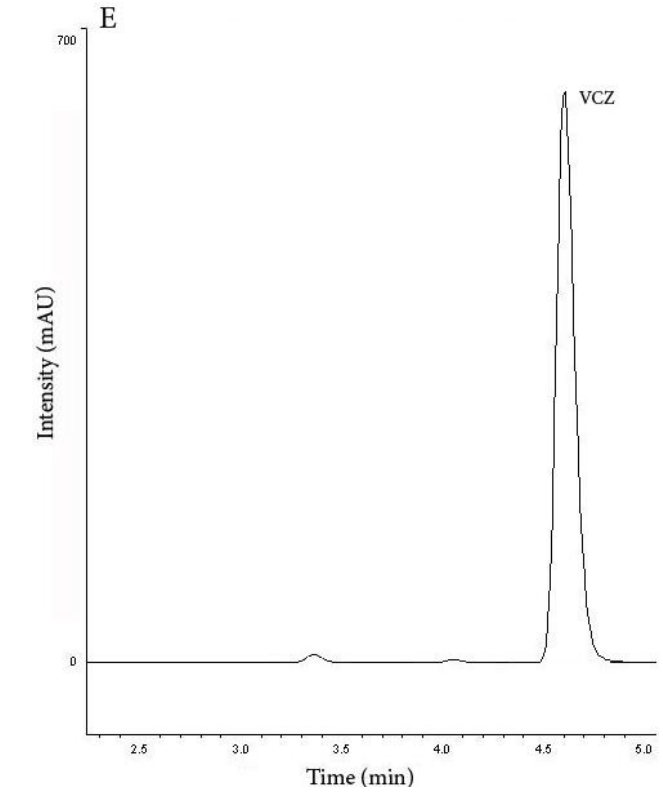
Figure 10-1. Typical chromatograms of voriconazole (VCZ) (**A**) and voriconazole exposed to alkaline (**B**), to acid (**C**), to heat (**D**), to atmosphere (**E**), or to hydrogen peroxide (**F**)






C
700
VCZ
Intensity (mAU)
0
2.5
3.0
3.5
4.0
4.5
5.0
Time (min)


D
700
Intensity (mAU)
VCZ
0
2.5
3.0
3.5
4.0
4.5
5.0
Time (min)


E
700
VCZ
Intensity (mAU)
0
2.5
3.0
3.5
4.0
4.5
5.0
Time (min)

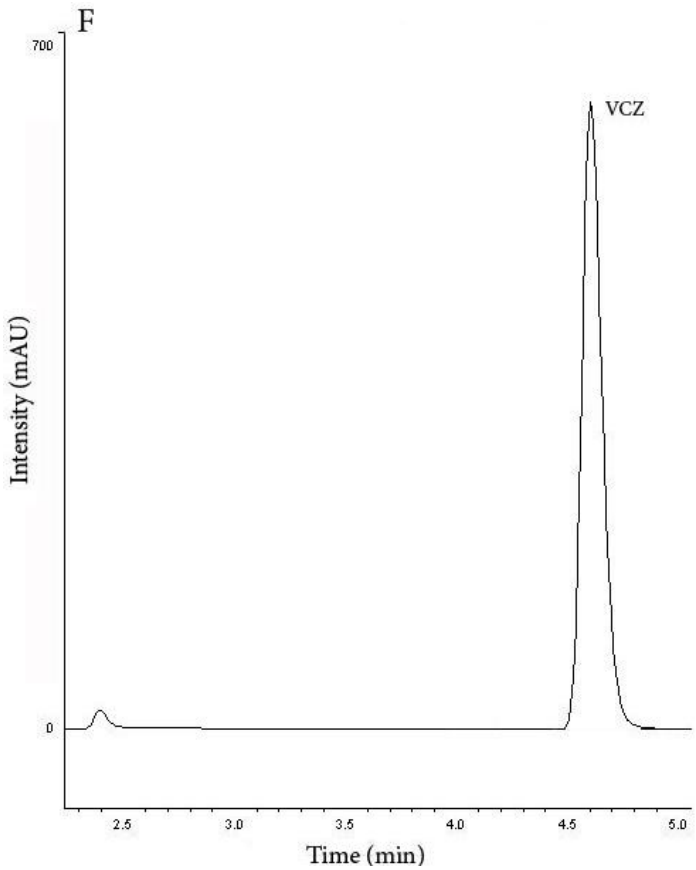

F
700
VCZ
Intensity (mAU)
0
2.5
3.0
3.5
4.0
4.5
5.0
Time (min)

Table 10-1. Stability of voriconazole 2% ophthalmic solution

	Mean ± S.D.						
Variable	Week 0[a]	Week 1	Week 2	Week 4	Week 8	Week 16	Week 32
Storage at 2-8 ºC							
Concentration (mg/mL)	19.37 ± 0.24	19.61 ± 0.04	19.48 ± 0.09	19.58 ± 0.09	19.60 ± 0.11	19.81 ± 0.67	18.27 ± 1.38
pH	6.14 ± 0.00	6.12 ± 0.03	6.15 ± 0.00	6.16 ± 0.01	6.16 ± 0.01	6.15 ± 0.01	6.10 ± 0.01
Storage at 25 ºC							
Concentration (mg/mL)	19.37 ± 0.24	19.64 ± 0.07	19.57 ± 0.05	19.62 ± 0.22	19.58 ± 0.13	20.02 ± 0.45	…..[b]
pH	6.14 ± 0.00	6.11 ± 0.02	6.14 ± 0.01	6.13 ± 0.01	6.13 ± 0.01	6.12 ± 0.01	…..
Storage at 40 ºC							
Concentration (mg/mL)	19.37 ± 0.24	19.66 ± 0.14	19.53 ± 0.10	19.17 ± 0.24	18.96 ± 0.13	…..	…..
pH	6.14 ± 0.00	6.12 ± 0.01	6.08 ± 0.03	6.06 ± 0.01	6.02 ± 0.02	…..	…..

[a]Triplicate determination for three samples (n = 3).

[b]Not measured.

The voriconazole solution displayed no significant change in pH at any time interval. No change in visual appearance or clarity was observed in the 2% voriconazole ophthalmic solution at any point of the study for all study temperatures.

The mean ± S.D. concentration and pH at baseline for the 1% voriconazole ophthalmic solution were 10.38 ± 0.04 mg/mL and 6.27 ± 0.00, respectively. These values did not change during the storage period and were 10.37 ± 0.04 mg/mL and 6.27 ± 0.00, respectively, after 6 weeks and 10.25 ± 0.11 mg/mL and 6.25 ± 0.01, respectively, after 14 weeks. In addition, the colorless and clear nature of the solution did not change throughout the duration of the study.

10.7 DISCUSSION

Stability testing is an important part of the development of any extemporaneously prepared medication. Voriconazole ophthalmic solutions are increasingly being compounded for routine use in hospitals worldwide. The current study is the first to examine the formulation of a preserved ophthalmic preparation of voriconazole and its long-term stability.

Low solubility (0.061% at pH 7) and instability in aqueous environments are established properties of voriconazole.[22] The manufacturer of the commercially available product for injection encapsulated voriconazole with a β-cyclodextrin derivative (solubilizing agent) in the form of lyophilized powder of cyclodextrin-voriconazole complexes. This approach significantly increases the solubility and stability of voriconazole in aqueous solutions while maintaining its lipophilicity and permeability characteristics through membranes.[22,23] However, the manufacturer has only reported on the preparation of the 1% voriconazole solution, recommending use of the i.v. formulation within 48 hours.[4] The current study has demonstrated that the 2% voriconazole solution is stable for an extended period in aqueous solutions. In addition, the results suggest that the 1% voriconazole solution is chemically stable for more than 48 hours.

The results from the forced-degradation and leaching studies suggest that the analytic assay was specific and detected changes in voriconazole concentrations in the ophthalmic solutions. Together with the high interday and intraday accuracy and reproducibility, these data indicate that the HPLC method was stability indicating.

Voriconazole was highly unstable in the alkaline environment, consistent with the results of other reports.[18,19] Practicing pharmacists should exercise caution when preparing extemporaneous voriconazole preparations that may result in the final products having an alkaline pH.

Importantly, up to week 16, all measured voriconazole concentrations in the 2% voriconazole ophthalmic solutions stored at 2-8 °C and 25 °C were negligibly different from the initial concentration. After 32 weeks of storage at 2-8 °C, a 5.65% loss in the voriconazole concentration was detected. The >5% degradation observed exceeds the ≤5% degradation limit used in the current study. This translates to the 2% voriconazole ophthalmic solution being considered unstable at 32 weeks of storage. Nevertheless, for most practices, a 5.65% loss in the voriconazole concentration will still be acceptable, as up to a 10% loss in the initial concentration is the widely accepted stability standard for extemporaneous preparations.[21]

Accelerated-degradation studies at a high temperature (i.e., 40 °C) can be used to predict the product's stability at room temperature; nonetheless, this is of supportive value only and should not be used as a substitute for the actual storage temperatures.[21] In the current study, the stability of 2% voriconazole ophthalmic solution at 40 °C was also investigated, and the voriconazole concentration remained over 97.88% of the initial concentration at all time points. This finding supports the stability data from the 2% samples stored at 2-8 °C and 25 °C. While the samples stored at 2-8 °C and 25 °C exhibited little change in the voriconazole concentrations over 16 weeks, the samples stored at 40 °C demonstrated a higher rate of degradation, indicating that the ophthalmic solution is more likely to have a shorter expiration date (i.e., chemically less stable) if stored at 40 °C.

As a prelude to a recent pilot clinical study[16] on the use of the 1% voriconazole solution in fungal keratitis, a small-scale stability study of the 1% solution was performed, where the study samples were only stored at 2-8 °C. The measured concentrations of the 1% voriconazole solutions remained constant throughout the study duration (14 weeks).

The pH of 1% and 2% voriconazole ophthalmic solutions ranged from 6.02 to 6.27, which is usually tolerated by the eyes.[24] Thus, it is unlikely that eye irritation resulting from the use of these eye drops will be a consequence of low pH. Recent studies have demonstrated that 1% voriconazole ophthalmic solution is well tolerated.[16,17]

Given the observed stability and tolerability of the voriconazole ophthalmic solutions, the potential for cost savings associated with their use as opposed to oral voriconazole tablets for the treatment of fungal keratitis should not be underestimated. The price of a voriconazole 200-mg i.v. vial (U.S.$146.34, AU$190.84) is the largest cost associated with preparation of the ophthalmic solution. Each vial can be used to prepare two 10-mL eyedroppers of voriconazole 1% eye drops. The bottle will hold approximately 200 drops, enough for 6-7 drops a day for a month. Together with the hospital personnel and other expenses, the cost per eyedropper and, hence, per month of treatment is less than U.S.$88.78 (AU$115). By contrast, the monthly cost of treatment with oral voriconazole is slightly under U.S.$2262 (AU$2950), making the extemporaneously prepared ophthalmic solutions 96% cheaper.

From a clinical perspective, these data suggest that the 2% voriconazole ophthalmic solution can be aseptically prepared or manufactured inhouse with a reasonably long shelf life if stored at 2-8 °C or 25 °C. Taking the microbial stability into consideration, the product should be stored at refrigerated temperature for up to 16 weeks and discarded 28 days after it is opened. The data also suggest that the 2% voriconazole ophthalmic solution will be sufficiently stable for patients to transport home without the need for cool containers. Results of the study indicate that the solutions are probably stable during short periods of exposure to temperatures of ≤40 °C. The stability of the solutions after being exposed to fluctuating temperatures will need to be confirmed with further studies.

10.8 CONCLUSION

Voriconazole 2% (20 mg/mL) solution preserved with 0.01% benzalkonium chloride prepared as alternative antifungal eye drops was stable for 16 weeks when stored at 2-8 °C and 25 °C and for 8 weeks when stored at 40 °C, while voriconazole 1% solution was stable at 2-8 °C for up to 14 weeks.

[a]Voriconazole for injection (Vfend I.V.), Pfizer Australia Pty Ltd., West Ryde, NSW, Australia, lot 6064303.

[b]Water for injection BP, 100-mL bottles, Pfizer (Perth) Pty Ltd., WA, Australia, lot CC08.

[c]Benzalkonium chloride 50%, 100-mL bottles, Professional Compounding Centers of America, Houston, TX, lot C117356.

[d]MF-Millipore membrane filter, Millipore, Bedford, MA, lot R5PN14033.

[e]Amber high-density polyethylene bottles with eyedropper, Plasdene Glass Pak Pty Ltd., Sydney, NSW, Australia, lot 070307-1.

[f]Distilled Milli-Q water, prepared by Ultra pure Organex cartridge, Quantum EX, Millipore, North Ryde, NSW, Australia, lot F4EN51817.

[g]Methanol gradient grade for liquid chromatography, 2.5-L bottles, Merck, Darmstadt, Germany, lot K37218918.

[h]Voriconazole (analytical grade), Pfizer, New York, NY, lot 052301-008-09.

[i]Model LC-10AT*vp*, Shimadzu Corporation, Kyoto, Japan.

[j]Model DGU-14A, Shimadzu.

[k]Model SIL-10AD*vp*, Shimadzu.

[l]Model CTO-10AC*vp*, Shimadzu.

[m]Model SPD-M10A*vp*, Shimadzu.

[n]Model RF-10A*xl*, Shimadzu.

[o]Class-VP 6.12 SP2, Shimadzu, Oceania, Japan.

[p]PhenoSphere-NEXT column, 5-µm particle size, 250 × 4.6 mm, Phenomenex, Lane Cove, NSW, Australia, serial number 121790-1.

[q]PhenoSphere-NEXT column, 5-µm particle size, 4.0 × 3.0 mm, Phenomenex.

[r]Microcombination electrode with calomel reference and BNC connector (6 in), Eutech, Vernon Hills, IL.

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The authors have declared no potential conflicts of interest.

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CHAPTER ELEVEN: SUCCESSFUL SALVAGE TREATMENT OF *SCEDOSPORIUM APIOSPERMUM* KERATITIS WITH TOPICAL VORICONAZOLE AFTER FAILURE OF NATAMYCIN

As discussed in **Chapter Nine**, evidence for the clinical effectiveness of voriconazole eye drops in the treatment of fungal keratitis has been based solely on published case reports. The typically used concentration of voriconazole eye drops in the reported cases was 1%. As reported in **Chapter Ten**, these eye drops are stable for at least 14 weeks when refrigerated at 2-8 °C. Case reports published to date (see **Chapter Nine**) have reported the successful use of 1% voriconazole eye drops as adjunct therapy to systemic antifungal agents in salvage circumstances; evidence for the successful use of voriconazole eye drops as monotherapy remains lacking. If successful when used alone, salvage voriconazole eye drops can produce substantial cost savings, and side effects and drug interactions associated with systemic administration of voriconazole or other antifungal agents could be avoided or substantially reduced. The following work is the outcome of a review of the use of 1% voriconazole eye drops in fungal keratitis at the Royal Victorian Eye and Ear Hospital in Melbourne, Australia, where a case of *Scedosporium apiospermum* keratitis was successfully treated using voriconazole eye drops alone as salvage therapy.

The following material is arranged in a manner suitable for publication in The Annals of Pharmacotherapy. Headings are renumbered in order to generate a consistent presentation within the thesis.

This chapter is a reproduction of the following publication:

Al-Badriyeh D, Leung L, Davies GE *et al*. Successful salvage treatment of *Scedosporium apiospermum* keratitis with topical voriconazole after failure of natamycin. *Ann Pharmacother* 2009; **43**:1139-42.

DECLARATION FOR THESIS CHAPTER ELEVEN

In the case of Chapter Eleven, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Conception and design. Literature search. Data collection. Analysis and interpretation. Writing the article. Critical revision of the article.	80%

The following co-authors contributed to the work:

Name[a]	Nature of contribution
David CM Kong	Conception. Critical revision of the article. Final approval of the article.
Kay Stewart	Conception. Critical revision of the article.
Lok Leung	Provision of materials, or patients. Interpretation. Critical revision of the article.
Geoffrey E Davies	Critical revision of the article.

[a]None of the co-authors is a student co-author.

Candidate's signature _____ Date _____

DECLARATION BY CO-AUTHORS

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.

(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;

(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;

(4) there are no other authors of the publication according to these criteria;

(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and

(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	Health Information Services - Royal Victorian Eye and Ear Hospital, Melbourne, Australia.

David CM Kong	[redacted]	Date 19/11/09
Kay Stewart	[redacted]	19/11/09
Lok Leung	[redacted]	18/11/2009
Geoffrey E Davies	[redacted]	17/11/2009

11.1 STUDY TITLE

Successful salvage treatment of *Scedosporium apiospermum* keratitis with topical voriconazole after failure of natamycin.

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11.3 ABSTRACT

Objective: To report successful management of *Scedosporium apiospermum* (previously known as *Monosporium apiospermum*) keratitis with topical voriconazole as monotherapy.

Case Summary: A 54-year-old previously well woman presented to the emergency department with a painful, injected right eye. There was no history of trauma or use of contact lenses. On examination, the right eye was estimated to have visual acuity of hand movement. Slit lamp examination detected a 2.5 x 3.5 mm dense, central corneal infiltrate with overlying epithelial defect. The eye had mild corneal edema with anterior chamber inflammation. Microbiology testing revealed *S. apiospermum* as the primary pathogen. Hourly administration of topical natamycin 5% resulted in initial improvement in visual acuity to 20/50, with reduction in the size of the central infiltrate. However, 1 month later, the eye infection relapsed, with recurrence of epithelial defect (3.1 x 3.1 mm) and decline in visual acuity to 20/100. Antifungal therapy was switched to topical voriconazole 1%, administered every 2 hours. Vision improved to 20/30 within 5 days, and the central defect had completely re-epithelialized within 1 week.

Discussion: Treatment of *S. apiospermum* keratitis remains inadequate. A high natamycin minimum inhibitory concentration is necessary to treat *S. apiospermum* infection, which may explain the persistence of central infiltration despite ongoing therapy. The combined use of topical and oral voriconazole for the treatment of *S. apiospermum* keratitis has been reported. However, this is the first report of a successful clinical experience using topical voriconazole without oral therapy to manage *S. apiospermum* keratitis. This eliminates some disadvantages associated with oral voriconazole such as high cost, potential significant toxicity, and drug interactions.

Conclusion: The voriconazole 1% eye drop used alone is a promising, cost-effective, safe option for managing fungal keratitis, even that caused by *S. apiospermum*. It may have a larger role to play than simply that of adjunctive therapy.

Key words: keratitis, *Scedosporium apiospermum*, topical voriconazole.

11.4 INTRODUCTION

Fungal keratitis, which accounts for 6-50% of all ocular infections, is difficult to treat.[1,2] *Scedosporium apiospermum*, previously known as *Monosporium apiospermum*, is a ubiquitous fungus frequently isolated from soil, polluted water, and decaying vegetable matter.[2,3] It is an opportunistic organism that rarely causes fungal keratitis in humans. However, keratitis is its most common clinical expression in immunocompetent patients.[3]

Voriconazole is a triazole antifungal agent that is commercially available only in oral and injectable forms.[4] Our report describes a case of fungal keratitis due to *S. apiospermum* that was successfully managed with extemporaneously prepared voriconazole eye drops.

11.5 CASE REPORT

A 54-year-old woman presented to the emergency department of the Royal Victorian Eye and Ear Hospital with a 3-day history of a painful, injected right eye. Systems review showed no preceding history of trauma or use of contact lenses. The patient did not have diabetes, hypertension, or arthritis and was not using any immunosuppressant medications. She had sought medical treatment from a general practitioner on day 2 but had failed to improve on topical chloramphenicol 0.5% therapy given every 6 hours.

Visual acuity was reduced to counting fingers. Slit lamp biomicroscopic examination revealed a dense central corneal infiltrate measuring 2.5 x 3.5 mm, with an overlying epithelial defect. There was mild corneal edema. Intraocular pressure was 18 mm Hg and there was mild anterior chamber inflammation. The patient underwent a corneal scrape. On day 5, empirical therapy with topical ofloxacin 0.3% every hour and topical homatropine 2% 3 times daily was initiated, with tentative diagnosis of bacterial keratitis.

Early microbiology report on the scrape revealed presence of filamentous fungi. As a result, natamycin 5% eye drops, given hourly day and night, were added to the regimen at the follow-up appointment (day 6). Growth of *S. apiospermum* was detected upon further analysis. *Micrococcus* spp. was isolated from the enrichment broth but failed to grow on standard culture. The microbiologist believed that *S. apiospermum* was more likely to be the primary pathogen, while *Micrococcus* spp. could be a contaminant from skin flora. Polymerase chain reaction (PCR) report on herpes simplex virus was negative.

There was gradual improvement over the next month. Visual acuity improved to 20/50, the central infiltrate had reduced in size, and the corneal defect had re-epithelialized. The woman was managed as an outpatient through the specialized corneal clinic within the hospital. Topical ofloxacin 0.3% was stopped and topical chloramphenicol 0.5% 4 times daily was commenced. Topical natamycin 5%, administered every 2 hours, was continued during the day only.

A few days later (week 5), the patient presented with signs of relapse (ie, recurrence of epithelial defect, increasing injection, stromal infiltration, and a decline in visual acuity to 20/100). On examination there was a central epithelial defect measuring 3.1 x 3.1 mm and a core stromal infiltrate measuring 1.7 x 2.0 mm. Another corneal scraping was performed that

confirmed *S. apiospermum* persistence. The antifungal therapy was changed to topical voriconazole 1% every 2 hours. The voriconazole eye drop was aseptically prepared by reconstituting voriconazole 200 mg (Vfend, 200-mg vial, Pfizer Australia Pty Ltd, NSW, Australia, batch number 6064303) with water for injection 19 mL (water for injection BP, 100-mL bottle, Pfizer, Perth Pty Ltd., WA, Australia, batch number CC08) containing 0.01% benzalkonium chloride solution (benzalkonium chloride 50%, 100-mL bottle, Professional Compounding Centers of America, Houston, TX; Australian Compounding Pharmacy, Australia, batch number C117356).

The patient recovered rapidly, and subsequent scrape failed to show any organism. Vision improved to 20/30 within 5 days and the central defect had completely re-epithelialized within 1 week. Within 2 weeks, a residual stromal scar measuring 3.6 x 4.1 mm was observed with mild corneal thinning. Voriconazole was stopped and the patient was started on regular ocular lubricants. Follow-up 6 months later showed no evidence of recurrence and vision remained stable at 20/30.

11.6 DISCUSSION

In our experience at the Royal Victorian Eye and Ear Hospital, bacterial keratitis accounts for the majority of presenting corneal infections.[5] For this reason, initial treatment protocols require a corneal scrape and the commencement of an empirical broad-spectrum antibiotic.

The most common mechanism for *S. apiospermum* keratitis is traumatic introduction of the fungus.[3] Our patient's case is atypical, as she did not recall any recent ocular injury. Filamentous fungi, such as *S. apiospermum*, are increasingly reported to cause invasive ocular infections.[3] The first reported corneal infection by *S. apiospermum* occurred in 1955[2]; the infected eye was eventually removed after treatment failure. To date, treatment of *S. apiospermum* keratitis remains inadequate. This is due primarily to the high minimum inhibitory concentration (MIC) required, which exceeds the unbound intraocular concentration of most of the current antifungal agents.[3] Successful identification of filamentous fungi on the initial slides confirmed the diagnosis in our patient. The role of organism identification cannot be overemphasized; it allowed for more directed antifungal therapy. *S. apiospermum* is slow-growing, and colonies usually take days to form. This could explain the fact that the fungal culture at the time of the original scrape failed to grow any significant pathogen. Despite isolation from enrichment broth, *Micrococcus* spp. failed to grow on standard culture. The presence of *Micrococcus* spp. as skin flora contaminant was

suggested by the microbiologist upon consultation. A negative PCR report excluded any potential underlying herpetic complications.

Natamycin is a polyene antifungal agent with activity against *Candida* and *Fusarium* spp.[6] It is the only Food and Drug Administration-approved and commercially available topical antifungal recommended for management of ocular infections caused by filamentous fungi.[3] Natamycin has poor penetration through the intact cornea, with therapeutic concentrations achieved usually in the stroma but not the intraocular fluid.[4] The presentation of superficial ulcer in this case may have allowed better absorption through a compromised corneal barrier.

A review of the literature showed variable responsiveness to natamycin.[7] *S. apiospermum* can require a relatively high natamycin MIC (>16 μg/mL), which is a major clinical concern, although there is little evidence suggesting a clear link between therapeutic efficacy and antifungal concentration. This may explain the persistence of central infiltration in our case, despite ongoing intensive therapy. On the other hand, the role of topical natamycin in reducing fungal load cannot be excluded. The use of natamycin may have facilitated the positive response to subsequent topical voriconazole therapy.

The failure to achieve complete clinical resolution with the use of natamycin implies that an alternative therapy needs to be sought. Amphotericin B has demonstrated an MIC comparable with that of natamycin for *S. apiospermum* and it has a similar penetration profile.[3,7] Terbinafine and flucytosine have no significant antifungal activity against *S. apiospermum*.[3] Of the echinocandins, caspofungin (MIC_{50} 0.5 μg/mL) is the most active in vitro, followed by anidulafungin (MIC_{50} 1 μg/mL).[3] However, little has been reported in the literature about the use of topical echinocandins for ocular infections, although encouraging results are available from animal models.[8] *S. apiospermum* has been shown to be susceptible to azole antifungal agents, except for fluconazole and ketoconazole. Voriconazole (MIC_{50} 0.25 μg/mL), miconazole (MIC_{50} 0.5 μg/mL), and posaconazole (MIC_{50} 1 μg/mL) have demonstrated the most potent in vitro activity.[3]

Recently, there has been increasing interest in the use of voriconazole for keratitis. Oral voriconazole is a relatively safe broad-spectrum agent that has become a standard of care for fungal keratitis.[4] An investigation of voriconazole concentrations following 12 days of oral therapy reported an aqueous humor concentration that was about 50% of the concentration measured in plasma (2 μg/mL).[4] However, when oral voriconazole therapy was combined with topical voriconazole 1% solution, the concentration in the aqueous humor increased to 3.2 μg/mL, which was 160% of the plasma concentration. Voriconazole is unavailable commercially for topical use; therefore, it is prepared extemporaneously. A recent study reported the penetration of voriconazole 1% eye drops administered hourly into the noninfected eye.[9] The eye drops demonstrated a favorable penetration profile, with a trough

aqueous humor concentration of 1.90 ± 1.12 μg/mL. The study suggested that further investigation in the clinical setting was needed.

Topical voriconazole has been used successfully as adjunctive therapy to oral and intravitreal therapy for the treatment of severe ocular fungal infections, especially when organisms of moderate in vitro susceptibility have been isolated in culture.[4] One published report described successful concomitant use of topical and systemic voriconazole for the treatment of *S. apiospermum* keratitis.[10] However, ours is the first case report demonstrating a successful clinical experience using topical voriconazole for the management of *S. apiospermum* keratitis without oral therapy. The stability profile of voriconazole in aqueous solution is another appealing feature. Voriconazole 1% solution has recently been shown to be stable for at least 14 weeks when stored between 2 and 8 °C.[11] The use of oral voriconazole can be costly and is potentially associated with increased levels of liver enzymes; in some cases, it can result in drug interactions.[12]

Significantly, this case demonstrates the effectiveness of topical voriconazole, as it resulted in the patient's good and rapid recovery when natamycin treatment was switched to voriconazole. We suggest that voriconazole 1% eye drops may be a good alternative treatment for patients with fungal keratitis in which progress has halted or regressed despite a regimen of natamycin.

Topical voriconazole may have a larger role to play than just as adjunctive therapy to systemic voriconazole. It is a promising, cost-effective option for the management of fungal keratitis, even when caused by *S. apiospermum*. Our report provides encouraging data regarding the potential of topical voriconazole 1% in the treatment of fungal keratitis.

11.7 FINANCIAL DISCLOSURE

None reported.

11.8 ACKNOWLEDGMENTS

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CHAPTER TWELVE: SUCCESSFUL USE OF TOPICAL VORICONAZOLE 1% ALONE AS FIRST-LINE ANTIFUNGAL THERAPY AGAINST *CANDIDA ALBICANS* KERATITIS

Chapter Eleven gave some preliminary evidence of the effectiveness of 1% voriconazole eye drops as salvage therapy when used alone. The evidence presented, however, is not indicative of the potential benefit of voriconazole eye drops when used as primary therapy, as it can be argued that the primary antifungal therapy facilitated the positive response to the subsequent use of voriconazole eye drops. As discussed in **Chapter Nine**, two published case studies have reported the failure of 1% voriconazole eye drops therapy when used as primary therapy; however, it is important to reiterate that the use of the eye drops in these cases was in combination with systemic antifungals, where the failure of therapy was the result of the need to cease treatment as a consequence of side effects associated with the systemic medications, and not due to lack of voriconazole efficacy. The successful use of voriconazole eye drops as primary monotherapy is likely to minimise treatment cost and potentially reduce the duration of therapy. The following work is the outcome of a review of the use of 1% voriconazole eye drops in fungal keratitis at the Royal Victorian Eye and Ear Hospital in Melbourne, Australia, where a patient with *Candida albicans* keratitis was successfully treated with 1% voriconazole eye drops used alone as primary therapy.

The following material is arranged in a manner suitable for publication in The Annals of Pharmacotherapy. Headings and figures are renumbered in order to generate a consistent presentation within the thesis.

This chapter is a reproduction of the following publication:

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DECLARATION FOR THESIS CHAPTER TWELVE

In the case of Chapter Twelve, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Conception and design. Literature search. Data collection. Analysis and interpretation. Writing the article. Critical revision of the article.	80%

The following co-authors contributed to the work:

Name[a]	Nature of contribution
David CM Kong	Conception. Critical revision of the article. Final approval of the article.
Kay Stewart	Conception. Critical revision of the article.
Lok Leung	Provision of materials, or patients. Interpretation. Critical revision of the article.
Geoffrey E Davies	Critical revision of the article.

[a]None of the co-authors is a student co-author.

Candidate's signature _____ Date _____

DECLARATION BY CO-AUTHORS

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.

(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;

(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;

(4) there are no other authors of the publication according to these criteria;

(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and

(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	Health Information Services - Royal Victorian Eye and Ear Hospital, Melbourne, Australia.

David CM Kong	[redacted]	Date 19/11/09
Kay Stewart	[redacted]	19/11/09
Lok Leung	[redacted]	18/11/2009
Geoffrey E Davies	[redacted]	17/11/2009

12.1 STUDY TITLE

Successful use of topical voriconazole 1% alone as first-line antifungal therapy against *Candida albicans* keratitis.

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12.3 ABSTRACT

Objective: To report the successful use of topical voriconazole 1% given alone as primary therapy against a case of *Candida albicans* keratitis.

Case Summary: A 48-year-old previously well man presented to the emergency department with pain and foreign body sensation in the left eye following exposure to dust while driving a forklift. He wore weekly disposable soft contact lenses. Anterior stromal scar and dense infiltrate were detected in the left eye. The anterior chamber remained deep, with flare and copious white cells. Intraocular pressure was 12 mm Hg and visual acuity was 20/200. The epithelial defect persisted, with progressive thinning despite topical fluorometholone and ofloxacin 0.3% therapy for 2 days. Microbiology testing revealed *C. albicans* as the affecting pathogen. Hourly administration of voriconazole 1% eye drops was initiated as antifungal therapy. The corneal infiltrate began to resolve and the epithelial defect decreased in size within 2 days. Visual acuity improved to 20/120. After 4 days of voriconazole use, the epithelial defect was completely healed and visual acuity was 20/30 in the affected eye. No fungi were isolated from a second eye scrape.

Discussion: Topical voriconazole as salvage monotherapy to manage fungal keratitis has been previously reported. It can be argued, however, that the primary therapy has facilitated the positive response to subsequent topical voriconazole. To date, there has been no solid evidence to suggest that topical voriconazole is effective when used as primary therapy. The current report provides evidence of topical voriconazole demonstrating clinical success when used as first-line therapy to treat *C. albicans* keratitis. The use of topical voriconazole can reduce the costs, toxicity, and drug interactions associated with common antifungal therapies.

Conclusion: Topical voriconazole 1% eye drops administered alone demonstrated success as first-line therapy against the most common fungal keratitis, *C. albicans* keratitis.

Key words: *Candida albicans*, eye drops, voriconazole.

12.4 INTRODUCTION

Fungal keratitis refers to the fungal infection that occurs in the cornea.[1] It has the potential to cause devastating consequences, including blindness.[2] The etiology of keratomycosis varies with geographical location. *Candida albicans* is the most frequently isolated etiologic agent of fungal keratitis in Australia.[3,4] At the Royal Victorian Eye and Ear Hospital (RVEEH) in Melbourne, Australia, *C. albicans* is found in 37% of cases. Similar trends can be observed in other countries such as England and the US.[2,5] *C. albicans* is an opportunistic organism that

can cause keratitis, with risk factors being ocular surface disease and prolonged corticosteroid use.[4]

Common topical antifungal agents, such as amphotericin B, natamycin, and fluconazole, have an established history of use in fungal keratitis. Nonetheless, these agents have limitations, including poor topical penetration, limited spectrum of activity, and limited clinical response.[6] Among other antifungal drugs, voriconazole has been developed to address the limitations of currently available agents. Voriconazole is a triazole antifungal agent that is available in oral and intravenous forms.[2] Its off-label topical preparation has been increasingly used as salvage and/or adjunctive therapy against fungal keratitis.[7,8] Interestingly, there have been no reports of voriconazole eye drops being used as first-line therapy in the management of fungal keratitis. We describe a case of *C. albicans* keratitis that was successfully treated with extemporaneously prepared voriconazole eye drops administered alone as first-line therapy.

12.5 CASE REPORT

A healthy 48-year-old man presented to the emergency department of the RVEEH with pain and foreign body sensation in the left eye. The patient reported that dust had entered his left eye on the same day while he was operating a forklift. He was not wearing protective eyewear and was wearing soft contact lenses to correct myopia. The patient was using disposable Acuvue soft contact lenses (Johnson & Johnson, Jacksonville, FL), which he changes on a weekly basis. He did not wear the lenses when sleeping. Upon initial contact with the dust, the patient removed the contact lenses and irrigated his eyes with tap water. The patient is a smoker (20 cigarettes/day). He has a history of skin allergy (ie, peeling) when exposed to acetaminophen 500 mg and codeine phosphate 30 mg (Panadeine Forte). There was no other previous medical history, including diabetes, hypertension, or arthritis, and the patient was not using any regular medications, including immunosuppressants. He had no previous ocular surgery, but 1 year prior to the incident, he had developed bacterial keratitis in the left eye, which was successfully treated with 3 weeks of topical antibiotic therapy. At that stage, despite the absence of fungal keratitis, microbiology testing reported a positive *Candida* culture. There was no other history of ocular trauma.

On examination, the patient had significant ciliary injection in the affected eye. The slit lamp biomicroscopic examination revealed a dense anterior stromal grey-white infiltrate with fluffy edges and an overlying epithelial defect (**Figure 12-1**).

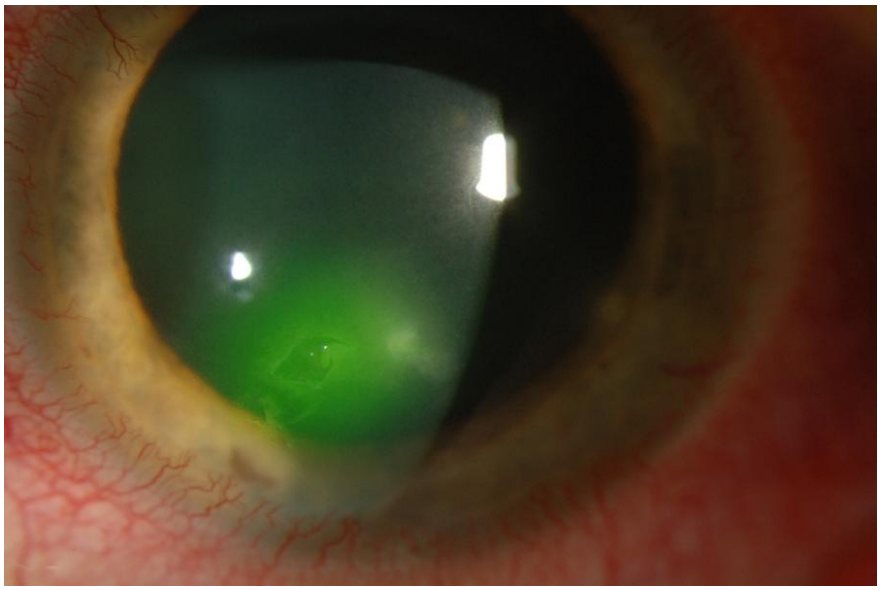

Figure 12-1. The left eye of the patient on presentation.

The anterior chamber demonstrated significant inflammation, with 3+ white cells (the number of cells in a 1-mm highest intensity light beam, which occurs when there is underlying pathology in the anterior chamber) and 1+ flare (the visible brightness of the highest intensity light beam in the anterior chamber, which occurs when there is increased protein content of aqueous humor as sign of iris and/or ciliary body inflammation). No hypopyon was present. Intraocular pressure was 12 mm Hg in both eyes. Visual acuity was reduced in the left eye to 20/200. The right eye visual acuity was 20/25. Posterior segment examination was unremarkable. Topical steroid treatment with fluorometholone acetate was initiated for a primary diagnosis of posttraumatic allergic reaction. Topical ofloxacin 0.3% therapy, administered hourly during the day and every 2 hours at night, was also initiated for prudent bacterial cover.

On day 2, despite ongoing topical antibacterial therapy, the infiltrate progressed and the epithelial defect enlarged. The corneal inflammation continued to worsen. Signs of photophobia developed. White cells were still abundant. Corneal scraping and culture and sensitivity (C&S) was performed.

On day 3, an early microbiology report on the corneal scraping revealed high presence of fungal elements. The patient was subsequently admitted to the corneal unit and voriconazole 1% eye drops administered hourly, day and night, were added to the regimen. The voriconazole 1% eye drop was aseptically prepared on site by the pharmacy department, by diluting a 200-mg vial of lyophilized voriconazole with 19 mL of benzalkonium chloride 0.01% in water for injection. The eye drop was 0.05 mL in volume and was administered via

a 10-mL eyedropper bottle (Plasdene Glass Pak Pty Ltd, NSW, Australia, B/N 070307-1). Topical ofloxacin 0.3% was reduced to every 2 hours, and 3-times-daily topical homatropine 2% was commenced. No topical steroids were used.

Two days later (day 5), the patient reported improvement in comfort. No adverse effects were noted from the eye drops. The corneal infiltrate began to resolve and the overlying epithelial defect decreased in size. The patient's visual acuity began to improve to 20/120. The fungal element was identified in the full microbiology report to be *C. albicans*. Coagulase-negative *Staphylococcus* spp. was also isolated from the enrichment broth, but was considered clinically insignificant. Polymerase chain reaction (PCR) report on herpes simplex virus was negative. On the following day (day 6), a second corneal scraping (C&S) was done, and the treatment regimen was continued.

On day 7 (after 4 days of voriconazole therapy), the anterior chamber was quiet (the absence of cells and flare in the anterior chamber of the eye), with significant reduction in the size of the infiltrate. Results from the second corneal scrape were negative for any fungal organisms. The administration of topical voriconazole 1% was tapered to every 2 hours during the day. The administration of topical ofloxacin was changed to 4 times daily and the topical homatropine was discontinued. Discharge was scheduled for the following day.

On the day of discharge, the patient was subjectively well. The epithelial defect was healed, with visual acuity of 20/30 in the affected eye. All inpatient medications were ceased except for the voriconazole 1% eye drops (administered every 2 hours), which were continued (postdischarge in an outpatient setting) for another week, followed by topical voriconazole administered every 6 hours for a further 2 weeks. Twenty-five days after discharge, no signs of active infection were observed during the outpatient review.

12.6 DISCUSSION

One of the most common mechanisms for *C. albicans* keratitis is traumatic introduction of the fungus, particularly those related to contact lens wear.[8] Our patient's case, with a history of recent ocular injury and probable epithelial defect caused by the exposure of the cornea surface to dust while wearing soft contact lenses, is a typical example. Irrigation with tap water may have been a potential source of this ubiquitous yeast. Given that *Candida* was detected in the same eye a year prior to this episode, the patient could have been carrying *Candida* chronically in his eye. This is the most likely source of *Candida*. Topical fluorometholone acetate was initiated on day 1 due to the rapid progression of ciliary injection, dense anterior infiltrate, and overlying epithelial defect; allergic inflammation was

considered as the reason for the symptoms. Topical ofloxacin, but not antifungal, therapy was also initiated on day 1. This is because, in our experience at the RVEEH, bacterial keratitis is the major cause of all the presenting ocular infections. Therefore, it is common at the RVEEH to commence broad-spectrum antibiotic therapy for ocular infections before microbiologic results from the scrape are available. The combined effect of the established *Candida* colonization in the eye and the immunosuppressive effect of the topical steroid might have accelerated the fungal infection. At the RVEEH, antifungal treatment is generally not initiated unless fungal elements are observed or cultured. In our patient, despite 2 days of steroid and antibacterial therapies, the infiltration, epithelial defect, and corneal inflammation continued to progress. In addition, photophobia developed and white cells persisted. This raised the suspicion of an atypical cause of keratitis and triggered the first corneal scrape (C&S) on day 2. The preliminary isolation of fungal elements in the first scrape (day 2 scrape for which the results were made available to the clinician on day 3) triggered the antifungal treatment. The role of positive identification could not be overemphasized, as it allowed directed antifungal therapy to be introduced promptly and topical steroids to be withheld. A negative PCR report excluded any potential underlying herpetic keratitis.

A commonly used topical treatment for *Candida* keratitis is amphotericin B 0.15% eye drops, a polyene antifungal agent, with a 90% minimum inhibitory concentration (MIC_{90}) of 0.5 μg/mL against *C. albicans*.[3,4] Although often thought to be the most efficacious agent clinically available to treat yeast keratitis, amphotericin B does not penetrate well into the cornea, and thus, has limitation in use.[3,4,8] Topical natamycin 5% suspension, a polyene, and the only Food and Drug Administration–approved and commercially available topical antifungal, has an MIC_{90} and penetration profile similar to that of amphotericin B.[8] The usefulness of topical natamycin is further complicated, given the fact that crystal films develop on the ocular surface upon intensive repeated instillation, presenting a hazy view for subsequent slit lamp examinations. The impact of crystallization on clinical efficacy is unclear. Topical fluconazole (MIC_{90} 0.5 μg/mL) penetrates well into the cornea.[3] It is safe and its success against mycotic keratitis has been reported.[9,10] There is a dearth of information on the topical application of caspofungin in fungal keratitis. *C. albicans* has in vitro susceptibility to caspofungin (MIC_{90} 0.06 μg/mL).[11] However, use of topical caspofungin 0.5% has only been reported once,[10] where it was used as adjunct therapy to intrastromal voriconazole with success against *Alternaria* keratitis.

Oral voriconazole is relatively safe and has demonstrated excellent intraocular penetration over other systemic antifungal agents.[6] It has been used successfully as an adjunct to topical antifungals for fungal keratitis.[6,8] However, as with other systemically administered antifungals, its use can be costly, associated with adverse effects (ie, increased levels of liver enzymes), and, in some cases, result in clinically significant drug–drug interactions.[12]

Voriconazole is currently not commercially available for topical use, and hence, it is prepared extemporaneously when used as eye drops. The topical 1% formulation has been shown to be a useful adjunctive therapy to oral and intravitreal therapies against ocular fungal infections.[8] There has been one case report focusing on the monotherapy use of voriconazole eye drops in patients with fungal keratitis.[7] In this case report, topical voriconazole 1%, administered alone, demonstrated success against *Scedosporium apiospermum* keratitis. However, the report did not provide solid evidence to suggest that topical voriconazole can be effective as first-line therapy. This was because the topical voriconazole was used as salvage therapy in fungal keratitis; it can be argued that the administered primary antifungal therapy (ie, natamycin) had facilitated the positive response to subsequent therapy with voriconazole eye drops.

In our case, topical voriconazole therapy was given empirically due to its good safety profile and broad spectrum of antifungal activity. Voriconazole is less toxic than topical amphotericin B, with better cornea penetration.[6,8] It has excellent activity against the most common typical causative organisms (ie, *Candida*, *Aspergillus*, *Fusarium* spp.) of fungal keratitis encountered at our institution and by others.[2,8] While amphotericin B and natamycin have excellent activity against *Candida* spp., these agents are only moderately active against *Aspergillus* and *Fusarium* spp.[6,8] Topical fluconazole, with its excellent activity against *Candida* spp., is ineffective against *Aspergillus* and *Fusarium* spp.

Our report provides some evidence for the use of topical voriconazole 1% alone as first-line therapy against voriconazole-sensitive *C. albicans* (MIC_{90} 0.016 μg/mL).[3] Indeed, the use of topical voriconazole monotherapy as first-line therapy in our patient resulted in a complete and rapid eradication (within 4 days) of the keratitis-causative fungus as evidenced by the negative culture on rescraping. This was consistent with the total and rapid recovery previously observed with the salvage use of topical voriconazole 1% as monotherapy.[7]

The current report, together with evidence on good corneal penetration of voriconazole eye drops, provides some reassurance with respect to the use of voriconazole eye drops alone as first-line antifungal therapy against sensitive fungal keratitis. We and others have reported the penetration of voriconazole 1% eye drops into the aqueous humor of noninfected eyes.[3,13] Four doses of hourly eye drops demonstrated a favorable penetration profile, with a trough aqueous humor concentration of 1.90 ± 1.12 μg/mL (mean ± SD).[3] A similar trend was observed with 12 doses of 2 voriconazole eye drops administered every 2 hours, where the peak concentration in the aqueous humor was as high as 6.49 ± 3.04 μg/mL (mean ± SD).[13]

According to one stability study, voriconazole 1% eye drops, prepared in sterile benzalkonium chloride 0.01% solution, are stable for at least 14 weeks when stored at 2–8 °C.[14] In another stability study of voriconazole 1% eye drops, prepared in sterile water for

injection alone, the eye drops were stable for at least 4 weeks when stored at 4 °C.[15] A complete description of the formulation and stability of the voriconazole eye drops used in our report was reported previously.[14] The stability data will help minimize wastage; in the absence of stability data, most extemporaneously prepared products at our institution are given a short shelf-life of less than 1 month. Indeed, the use of topical voriconazole can result in major cost savings. At the RVEEH, the approximate monthly cost of topical voriconazole 1% treatment administered every 2 hours is $170 (US$)/patient. By contrast, the monthly cost of oral voriconazole treatment is about $2160/patient, which translates into a monthly $1990 cost saving when using the eye drop formulation.

Accordingly, in the absence of further clinical data, our report suggests that monotherapy with topical voriconazole 1% is potentially a viable effective primary therapy for patients with voriconazole-sensitive keratitis. In the case presented here, topical voriconazole 1% solution administered alone, without adjunctive antifungal therapy, demonstrated success as first-line therapy against *C. albicans* keratitis. This suggests that voriconazole eye drops (as monotherapy) might be useful as first-line antifungal treatment for the management of fungal keratitis.

12.7 FINANCIAL DISCLOSURE

None reported.

12.8 ACKNOWLEDGMENTS

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CHAPTER THIRTEEN: PROSPECTIVE OPEN-LABEL STUDY OF THE ADMINISTRATION OF TWO-PERCENT VORICONAZOLE EYE DROPS

In the preceding **Chapters Ten** to **Twelve**, the long-term stability of voriconazole eye drops, and the potential benefits of 1% voriconazole eye drops as monotherapy were investigated as cost-minimising strategies. As discussed in **Chapter Nine**, the use of voriconazole eye drops at concentrations higher than 1% may lead to increased efficacy and/or reduction in dosing frequency. Also discussed in **Chapter Nine** is a single case report that demonstrated the successful use of 2% voriconazole eye drops in fungal keratitis, when used in combination with systemic antifungals. Evidence for the clinical effectiveness of 2% voriconazole eye drops remains inadequate; it is unknown whether topical administration of 2% voriconazole eye drops will result in a higher concentration of voriconazole in the human aqueous humour compared to 1% eye drops. In **Chapter Ten**, it was demonstrated that 2% voriconazole eye drops have tolerable pH and are stable for up to 16 weeks when stored at 2-8 and 25 °C. The following work investigates the penetration of topically administered 2% voriconazole eye drops into the human aqueous humour.

The following material is arranged in a manner suitable for publication in the journal Antimicrobial Agents and Chemotherapy. Headings and tables are renumbered in order to generate a consistent presentation within the thesis.

This chapter contains the reproduction of the following publication:

Al-Badriyeh D, Leung L, Roydhouse T *et al*. Prospective open-label study of the administration of two-percent voriconazole eye drops. *Antimicrob Agents Chemother* 2009; **53**: 3153-5.

DECLARATION FOR THESIS CHAPTER THIRTEEN

In the case of Chapter Thirteen, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Conception and design. Literature search. Statistical experience. Data analysis and interpretation. Writing the article. Critical revision of the article.	65%

The following co-authors contributed to the work:

Name[a]	Nature of contribution
David CM Kong	Conception and design. Critical revision of the article. Final approval of the article.
Kay Stewart	Conception and design. Critical revision of the article.
Lok Leung	Design. Provision of materials, or resources. Critical revision of the article.
Geoffrey E Davies	Design. Critical revision of the article.
Robert Fullinfaw	Sample analysis. Critical revision of the article.
Trent Roydhouse	Design. Provision of patients.
Mark Daniell	Design. Data collection.

[a]None of the co-authors is a student co-author.

Candidate's signature _____ Date _____

DECLARATION BY CO-AUTHORS

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.

(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;

(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;

(4) there are no other authors of the publication according to these criteria;

(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and

(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	Department of Pharmacy - Royal Victorian Eye and Ear Hospital, Melbourne, Australia.

David CM Kong	[redacted]	Date 19/11/09
Kay Stewart	[redacted]	19/11/09
Lok Leung	[redacted]	18/11/2009
Geoffrey E Davies	[redacted]	17/11/2009
Robert Fullinfaw	[redacted]	17Nov2009
Trent Roydhouse	[redacted]	23/11/9
Mark Daniell	[redacted]	20.11.09

13.1 STUDY TITLE

Prospective open-label study of the administration of two-percent voriconazole eye drops.

13.2 AUTHORS

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13.3 ABSTRACT

Thirteen human subjects scheduled for elective anterior segment eye surgery received hourly 2% voriconazole eye drops 4 hours presurgery. No side effects were reported. Significantly, the voriconazole concentration in the aqueous humor of the eye was similar to that reported for the 1% voriconazole solution, suggestive of concentration-independent absorption.

13.4 INTRODUCTION

Fungal keratitis accounts for 6 to 50% of all ocular infections and is one of the most difficult infections to treat (13). Seventy percent of fungal keratitis infections are attributed to *Candida albicans*, *Aspergillus fumigatus*, and some *Fusarium* species (2). At the Royal Victorian Eye

and Ear Hospital (RVEEH), Melbourne, Victoria, Australia, *Candida albicans* is the causative fungus in 37% of the treated cases (2).

Voriconazole (Vfend) is effective (**Table 13-1**) against common pathogens associated with fungal eye disease (i.e., *Candida*, *Aspergillus*, and *Fusarium* species [3, 6, 8]) and some less common keratitis-causative fungi such as *Paecilomyces* spp., *Histoplasma* spp., *Scedosporium* spp., *Curvularia* spp., and *Acremonium* (3, 8). The typical corneal fungal pathogens (8) are shown in **Table 13-1**.

Table 13-1. In vitro MICs at which 90% of isolates are inhibited by voriconazole

Organism	MIC_{90} (mg/liter)	Reference
Yeast and yeastlike species		
Candida albicans	0.06	16
Candida parapsilosis	0.12-0.25	16
Candida tropicalis	0.25->16.0	16
Cryptococcus neoformans	0.06-0.25	16
Moniliaceous molds		
Aspergillus fumigates	0.50	16
Aspergillus flavus	0.50	16
Fusarium species	0.25-8	8
Fusarium solani	2	10
Paecilomyces lilacinus	0.50	16
Acremonium alabamensis	0.25	16
Dimorphic fungi		
Blastomyces dermatitidis	0.25	16
Coccidioides immitis	0.25	16
Histoplasma capsulatum	0.25	16
Penicillium marneffei	0.03	16
Dematiaceous fungi		
Cuvularia species	0.06-0.25	16
Scedosporium species	0.5	16
Scedosporium apiospermum	0.5	16

Voriconazole is available commercially in oral and intravenous forms (Vfend package insert; Pfizer Inc., New York, NY). Case reports relating to the use of topical 1% voriconazole for ocular fungal infections are promising but limited (8). A recent study by Lau et al. reported that the concentration of voriconazole in the aqueous humor (after topical administration with 1% voriconazole solution) was sufficiently high to treat some common types of fungal infections but may be inadequate for common but less-sensitive keratitis-causative fungi (12).

To date, there has only been one case report on the topical application of 2% voriconazole solution (14). The solution was used in combination with intravenous voriconazole and was successful against *Fusarium solani* keratitis. Importantly, the extent of the role played by the 2% solution in the reported case and the extent of penetration of topically applied 2% voriconazole solution into the aqueous humor remain unknown.

The aim of the current study was to investigate the penetration of 2% voriconazole eye drops into the aqueous humor as a potential alternative therapy for the management of ophthalmic fungal keratitis.

(Preliminary data of the work described in this paper were presented at the 13th International Congress on Infectious Diseases, Kuala Lumpur, Malaysia, June 2008.)

The current study was an open-label prospective study conducted between July 2007 and August 2008 at the RVEEH. The study was approved by the human ethics committee of RVEEH and Monash University.

Participants ≥18 years old scheduled to undergo routine anterior eye segment surgery were recruited. Exclusion criteria were liver or kidney failure, breast feeding, pregnant, trying to conceive, allergy to voriconazole or benzalkonium chloride, use of latanoprost or medications contraindicated for voriconazole (Vfend package insert; Pfizer Inc., New York, NY), and active ocular inflammatory conditions. Written informed consent was obtained from each participant before enrolment.

In accordance with previous studies (12, 16), for an expected standard deviation of ± 1.0 mg/liter and a ± 0.5-mg/liter margin of error of the mean associated with a 95% confidence level, the required sample size was 13 participants.

The 2% solution was manufactured aseptically by the RVEEH Pharmacy Department. It was prepared by reconstituting Vfend IV (200-mg vial; Pfizer Australia Pty. Ltd., Sydney, NSW, Australia) with 9 ml of water for injection (Pfizer Pty. Ltd., Perth, WA, Australia) containing 0.01% benzalkonium chloride solution (benzalkonium chloride 50%; Professional Compounding Centers of America, TX; Australian Compounding Pharmacy, Australia).

A single drop (0.05 ml) of the 2% voriconazole solution was administered by a nurse to the eye to be operated on every hour for 4 hours prior to operation. The last dose was administered approximately 1 hour before surgery. A drug administration diary was used to document the date and time of administration and any side effects experienced.

At the start of surgery and before infusion of any intraocular irrigation solution, 0.1 to 0.2 ml of aqueous humor was aspirated through a paracentesis site with a 30-gauge needle attached to a syringe. Samples were immediately refrigerated at 4°C and analyzed within 7 days of collection.

Voriconazole levels in the aqueous humor were quantified by a validated high-performance liquid chromatography assay with photodiode array detection. Working standards with concentrations of 0.5, 1, 2, 4, and 8 mg/liter were prepared in water from a 100 mg/liter stock solution. Working standards, quality controls, and samples were prepared by deproteinising 200 µL of plasma (or 50 µL of aqueous fluid) with equi-volume acetonitrile. Following vortex mixing and centrifuging, 50 µL of supernatant was injected on to a C18, 5-micron, 100 x 2.0-mm column (Hypersil C18; Thermo Electron Corporation, Waltham, Massachusetts, USA). A Hewlett Packard high-performance liquid chromatograph (Model 1090A; Hewlett Packard, Avondale, Pennsylvania, USA) was used for the analyses. The eluent was monitored at 255 nm and the column was maintained at 50°C. The mobile phase consisted of 30% acetonitrile and 70% 0.01-mol/L potassium dihydrogen orthophosphate buffer adjusted to pH 3.0 with phosphoric acid. Flow rate was maintained at 0.5 ml/min with a resultant voriconazole retention time of 3.3 min. The assay is linear to at least 16 mg/liter and has a limit of detection of 0.04 mg/liter, which covers the range typically seen in patients' aqueous samples. All peaks were verified for authenticity by cross matching the ultraviolet spectra data of the peak against the voriconazole spectrum in the detector's library. Blank aqueous humor samples were run to investigate any overlapping peaks with the voriconazole peak, and spiked aqueous humor, plasma, and water were run at 8 mg/liter to confirm that there were no significant differences in recoveries.

The Mann-Whitney test was used to investigate any significant difference in measured voriconazole concentrations between participants with and without diabetes mellitus. Student's *t* test was used to compare differences between means.

The 13 participants had a mean age (± standard deviation) of 70 ± 7.7 years (**Table 13-2**). All participants had phakic lens status and required unilateral cataract surgery in a noninflamed eye. No side effects or toxicities were reported.

The mean voriconazole concentration in the aqueous humor was 1.67 ± 0.97 mg/liter, while the mean sampling time after the last eye drop administration was at 1.3 ± 0.3 h (**Table 13-2**). There was no statistical difference ($P = 0.67$) in the mean aqueous humor voriconazole concentrations between the 10 nondiabetic participants (1.72 ± 1.03 mg/liter) and the 3 diabetic participants (1.50 ± 0.91 mg/liter).

Table 13-2. Patient characteristics and voriconazole concentrations in aqueous humor

Age (yr)	Sex	Diabetes mellitus	Sampling time after last voriconazole dose (h)	Voriconazole concn in aqueous humor (mg/liter)
65	Male	No	1.2	0.9
79	Female	No	1.3	1.0
69	Male	Yes	1.1	1.0
61	Female	Yes	1.3	0.9
82	Male	Yes	1.2	2.6
73	Male	No	1.3	1.3
73	Male	No	1.9	3.6
56	Male	No	1.6	0.8
67	Male	No	1.5	1.4
61	Male	No	1.6	1.0
77	Male	No	1.0	1.5
69	Male	No	0.9	3.4
75	Male	No	1.3	2.4

The mean aqueous humor voriconazole concentration in this study (using 2% voriconazole solution) was not significantly different ($P = 0.68$) from that reported by Lau et al. (12) using 1% voriconazole solution.

In the Lau et al. study (12), the mean aqueous humor voriconazole concentration was 1.90 ± 1.12 mg/liter and the mean sampling time after the last dose was 1.1 ± 0.5 h. Results from the current study are comparable with those of Lau et al. (12). Both studies had identical numbers and frequencies of doses administered. In both studies, the trough voriconazole levels were measured (samples were collected approximately 1 h after the last one-hour drop). Furthermore, both studies administered the same volumes (~0.05 ml) of eye drops at each dose (11) and used benzalkonium chloride (a transcorneal penetration enhancer [9]) as the preservative. The eye drops prepared in this study and those used by Lau et al. contained the same concentration of benzalkonium chloride (0.01%).

The results from this study are consistent with previous studies (12, 16), demonstrating that topically administered voriconazole solutions achieve therapeutic concentration in the aqueous humor for treatment of fungi in **Table 13-1**, including those encountered at RVEEH. Importantly, the concentration resulting from the 2% voriconazole eye drops is not significantly different from that reported by Lau et al. for the 1% solution (12). This appears counterintuitive, and challenges the hypothesis of the study, but is consistent with observations in a recent animal study, where the voriconazole levels in the

corneas of horses with fungal keratitis did not change when the voriconazole concentration was changed from 1% to 3% (4). The measured aqueous humor voriconazole concentrations in the current study were highly variable (0.9-3.6 mg/liter). The study by Lau et al. reported similar variability (0.5-3.5 mg/liter) (12). This suggests the possibility that, although the penetration of voriconazole through the cornea may be due to a rate-limiting mechanism, it may just be that the corneal absorption is erratic. Nonetheless, this is difficult to confirm in the present study, given the small sample size. In either case, within the measured ranges of voriconazole concentration in the current study and that by Lau et al., it appears that the penetration of voriconazole through an intact infection-free cornea is not concentration dependent, at least for the eye drop's concentration range studied (1% to 2%).

While the precise mechanism of fluid/drug transport through the cornea remains obscure (5), it is important to recognize that, in this and previous studies (12, 16), the eye drops were applied to noninfected eyes. To attempt this study in patients with active fungal keratitis would be difficult, given the very low incidence of fungal keratitis and the need for long-term treatment. Nonetheless, the voriconazole concentration in the infected eye depends neither on the size of the epithelial defect nor on epithelial removal, and thus it has been suggested that epithelial damage is not necessary for voriconazole penetration (15).

We have previously demonstrated that the 2% eye drops are stable for up to 16 weeks when stored between 2 to 8°C and at 25°C (1). Furthermore, the 2% solutions have a pH range of 6.02 to 6.16 (1), which is usually well tolerated by the eye (7). It is unlikely, therefore, that any eye irritation resulting from the use of these eye drops (none reported in our study) would be a consequence of low pH. Systemic side effects resulting from the topical administration of the 2% voriconazole solution will be negligible as each administered dose (0.05 ml) contains approximately 1 mg of voriconazole, which, compared to the standard systemic daily dose of 400 mg, is unlikely to result in a systemic concentration that will cause side effects.

In conclusion, the 2% voriconazole eye drops appear to be well tolerated. The concentration of voriconazole achieved in the aqueous humor was adequate (at least theoretically) to treat typical keratitis-causative fungi. Our data suggest that the penetration of voriconazole through an intact noninflamed cornea is unlikely to be concentration dependent for the concentration range 1 to 2%.

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CHAPTER FOURTEEN: SUMMARY AND CONCLUSION

This thesis has explored different aspects (i.e. empirical, prophylactic and targeted therapies) within the topic of optimising the utilisation of high-cost antifungal agents in Australian hospitals.

14.1 ECONOMICS OF EMPIRICAL ANTIFUNGAL THERAPY IN FEBRILE NEUTROPENIA

Chapter Four discusses work investigating the economics of voriconazole versus liposomal amphotericin B (LAmB) as primary empirical therapy in patients with febrile neutropenia. A decision analytic model was constructed by using clinical and probability data obtained from the only available clinical trial on voriconazole versus LAmB as empirical therapies in febrile neutropenia. One-way sensitivity analysis, alternative scenario analysis and uncertainty analysis (i.e. Monte Carlo simulation) were undertaken. Compared to voriconazole, LAmB was associated with overall cost savings, as well as higher probability of success and lower probability of death. LAmB was a dominant empirical therapy over voriconazole. The economic model was demonstrated to be robust, with over 90% chance that LAmB will have cost savings over voriconazole. Despite a considerably lower acquisition cost for voriconazole than for LAmB, LAmB was associated with lower overall costs. This is because voriconazole was associated with higher probability of failure and discontinuation and, hence, secondary costs, which were high enough to supersede the difference in acquisition costs.

In **Chapter Five**, an economic evaluation of caspofungin versus LAmB for empirical therapy in febrile neutropenia is presented. The economic model was based on clinical and probability inputs extracted from the only clinical trial available on the comparative effectiveness between caspofungin and LAmB for empirical use in febrile neutropenia. One-way sensitivity, alternative scenario and Monte Carlo simulation analyses were performed. With economic advantage over LAmB, higher rate of success and lower rate of death, caspofungin demonstrated dominance over LAmB for empirical use. The model was robust, with caspofungin having cost savings over LAmB in more than 90% of cases. Both agents had similar secondary costs. The overall difference in cost was mostly due to the lower acquisition cost associated with caspofungin relative to LAmB.

In **Chapter Six**, the cost-benefit of voriconazole compared to caspofungin for empirical use in febrile neutropenia is reported. The decision model was based on two clinical

trials that provided indirect comparative data between voriconazole and caspofungin. One-way sensitivity analysis, alternative scenario analysis and Monte Carlo uncertainty analysis were undertaken as appropriate. Caspofungin was dominant over voriconazole as empirical therapy. It was more cost-beneficial, and had higher probability of success and lower probability of death. The model was robust, with caspofungin having over 60% chance of a cost advantage over voriconazole. The acquisition cost of voriconazole is considerably lower than that of caspofungin; however, the difference in the secondary costs between the two was higher than the difference in acquisition costs, and was to the advantage of caspofungin. Voriconazole was associated with higher failure and discontinuation rates.

The three studies were performed from the perspective of the Australian hospital system, with only direct medical costs included. Independent expert panels were used to obtain data that were not available from the clinical trials or other sources. Costs were collected from Australian representative data sources, and were according to the financial year 2008-09. Persistent fever was the clinical outcome that contributed most to overall costs.

In conclusion, caspofungin is the most cost-beneficial among the approved antifungal agents for the empirical use in febrile neutropenia. Voriconazole had the least cost-benefit. This is contrary to current Australian practice, in which LAmB is the standard of care for empirical therapy in febrile neutropenia. The conclusion is also contradictory to the current Australian practice of recommending voriconazole as an equally effective alternative to LAmB, with assumed economic advantage. The current role of caspofungin in the empirical setting in Australia may need to be reviewed.

Future clinical trials to directly compare the effectiveness of these agents within the same patient setting, while prospectively collecting economic data, would be valuable and would address the limitations associated with the current studies. Limitations included the use of expert panels and the assumption in the decision models that there was only a single switch to an alternative after a failure, and that the duration of use of the subsequent alternative agent was similar to that for the discontinued initial therapy. These limitations were necessary, however, given the retrospective nature of the studies.

14.2 ECONOMICS OF ANTIFUNGAL PROPHYLAXIS IN ACUTE MYELOID LEUKAEMIA

Chapter Eight reports a study to evaluate the cost-benefit of using posaconazole versus voriconazole for prophylaxis in patients with acute myeloid leukaemia (AML) in Australia. The decision analytic modelling depicted the downstream option and consequences as

extracted from a six-year (June 2003-June 2009) review of hospital medical records of all AML patients at the Royal Melbourne Hospital, Melbourne, Australia. Patients on either posaconazole or voriconazole were followed up for the duration of the induction stage of chemotherapy. The analysis was from the hospital perspective, with only direct medical costs included. Costs were collected from available Australian sources for the financial year 2008-09. One-way sensitivity analysis, alternative scenario analysis and probabilistic sensitivity analysis via Monte Carlo simulation were performed. Ninety-four patients were eligible for inclusion in the analysis, 38 of whom were initially given posaconazole and 56 received voriconazole. Baseline demographic characteristics were not significantly different between the two groups. The total duration of antifungal therapy was similar for both groups; however, patients in the posaconazole group had fewer documented possible invasive fungal infections (IFIs) and fewer discontinuations because of side effects or intolerance to oral administration. Fewer proven IFIs were reported by the patients in the voriconazole group. Posaconazole was associated with 31% lower cost than voriconazole. The model demonstrated robustness, where posaconazole was associated with over 90% chance of costing less than voriconazole. The difference in the overall costs between the two groups was the result of both lower acquisition cost with posaconazole and lower costs associated with alternative antifungal agents in the posaconazole group compared to the voriconazole group.

In conclusion, posaconazole has a cost-benefit over voriconazole for prophylaxis. It resulted in a lower rate of discontinuation as well as lower overall costs. This conclusion supports the recently adopted Australian practice of recommending posaconazole in preference to voriconazole for prophylaxis in patients with AML.

Although the observational design of this study enabled representation of the real clinical practice situation, future randomised clinical studies could minimise confounding factors, especially those related to the fact that data on posaconazole and voriconazole in the current study were obtained from different chronological periods. Future studies should have larger sample sizes to achieve enhanced power to further validate the results. In addition, while follow-up in the current model was limited to the induction stage of chemotherapy (i.e. one month), the prophylactic use of antifungals is lengthy, extending for months. Future studies, therefore, should also involve the collection of long-term survival data based on durations beyond induction, such as the consolidation stage of chemotherapy. Because patients on prophylaxis are not necessarily inpatients, studies that evaluate quality of life data would also be valuable and could add a social perspective to the analysis.

14.3 VORICONAZOLE EYE DROPS IN FUNGAL KERATITIS

In **Chapter Ten**, the long-term stability of extemporaneously prepared voriconazole eye drops, with benzalkonium chloride as preservative, was evaluated to support the clinical use of 1% and 2% voriconazole eye drops against fungal keratitis, with a view to minimising their wastage and the associated cost. The voriconazole eye drops demonstrated physical stability and a pH that is tolerable by the eye. The 1% voriconazole eye drops were stable at 2-8 °C for up to 14 weeks, and the 2% voriconazole eye drops were stable for 16 weeks when stored at 2-8 °C and 25 °C, and for eight weeks when stored at 40 °C.

Chapter Eleven discussed the 1% voriconazole eye drops when used alone as salvage therapy. A 54 year-old female presented with keratitis that was later identified as a rare *Scedosporium apiospermum* keratitis. Primary antifungal therapy with natamycin 5% was not successful. The natamycin therapy was switched to 1% voriconazole eye drops that were manufactured as described in **Chapter Ten**. Vision improved, and the corneal defect completely reepithelialised.

In **Chapter Twelve**, 1% voriconazole eye drops used alone were demonstrated to be successful as first-line therapy. A 48 year-old male presented with a case of keratitis, the cause of which was later identified as *Candida albicans*. Despite empirical antibacterial therapy, the epithelial defect persisted. One-percent voriconazole eye drops were prepared as described in **Chapter Ten**, and were initiated as primary antifungal therapy. The corneal infiltrate resolved, the epithelial defect was completely healed, and the visual acuity restored.

Chapter Thirteen reports a study of the potential usefulness of 2% voriconazole eye drops in fungal keratitis, with a view to further enhancing the cost-minimising role of voriconazole eye drops. The penetration of 2% voriconazole eye drops through the cornea and into the aqueous humour of the eye was compared with that reported for 1% voriconazole eye drops. An open-label prospective study was conducted at the corneal unit of the Royal Victorian Eye and Ear Hospital, Melbourne, Australia. Thirteen human subjects scheduled for elective anterior segment eye surgery were recruited according to a set of inclusion criteria. The 2% voriconazole eye drops were manufactured as described in **Chapter Ten**. The eye drops were well tolerated by patients, and voriconazole penetrated into the aqueous humour. The mean voriconazole concentration in the aqueous humour was found to be not significantly different from that reported after the administration of 1% voriconazole eye drops at the same dosing frequency.

In conclusion, the preparation of preserved 1% and 2% voriconazole eye drops is feasible and the formulations are tolerated by the eye. The 1% and 2% voriconazole eye drops demonstrated physical and chemical stability for up to 16 and 18 weeks of storage,

respectively. This extends the shelf-life beyond the existing recommendations, as discussed in **Chapter Nine**. The extended stability data will enable bulk in-house preparation of the eye drops, resulting in considerable cost savings. While the stability of 2% voriconazole eye drops was investigated at 2-8, 25 and 40 °C, the stability of 1% voriconazole eye drops was only investigated at 2-8 °C. More emphasis was given to the 2% voriconazole eye drops over the 1% voriconazole eye drops, because the 2% eye drops were initially expected to perform better than the 1% voriconazole eye drops in terms of corneal penetration and, hence, have an important role in clinical practice. Future stability studies should evaluate the stability of the 1% voriconazole eye drops at other temperatures such as 25 °C and 40 °C. This is important because the eye drops are used by patients outside the hospital environment.

From a clinical perspective, 1% voriconazole eye drops have a potential role that extends beyond current adjunctive role to systemic antifungal agents in the treatment of fungal keratitis. The eye drops demonstrated a promising cost-minimising role as monotherapy for both salvage and first-line therapies, and against both the rare *Scedosporium apiospermum* keratitis and the more common *Candida albicans* keratitis. Nonetheless, these positive outcomes are based on two case reports only. Future studies in form of audits or large case series on the standalone use of voriconazole eye drops are necessary to confirm current findings and establish the extent of effectiveness against other types of fungal keratitis.

Regarding the use of more concentrated voriconazole eye drops, resulting penetration of voriconazole from 2% eye drops into the aqueous humour was contradictory to the initial hypothesis, in which it was expected that increasing the concentration of the eye drops from 1% to 2% would increase the amount of voriconazole penetrating through the cornea. This result suggests concentration independent penetration of voriconazole through the cornea and, consequently, it appears that administering 2% over 1% voriconazole eye drops in fungal keratitis is unlikely to give any additional benefit. Although, as discussed in **Chapter Nine**, studies have suggested that epithelial damage is not necessary for voriconazole penetration, future studies that evaluate the penetration of 2% voriconazole eye drops, compared to 1%, despite being difficult to perform, will be important. Future studies should also consider investigating the extent of clearance of voriconazole from the human eye after topical administration, with a view to optimising the dosing regimen of the eye drops.

14.4 PLACE IN PRACTICE

Current protocols for the use of antifungal agents in Australia are mainly based on the only Australian guidelines available on the use of systemic antifungal agents, which were first

released in 2004, by Slavin *et al.*[1] The guidelines were widely used and adapted throughout Australasia. These guidelines were recently updated, also by Slavin *et al.*,[2] based on a more recent review of available evidence, and were published in 2008. Both versions of the guidelines were generated using the recommendations of the National Health and Medical Research Council in Australia, for development of evidence-based clinical practice guidelines in Australian hospitals.[3] The recommendations, however, were based solely on the published clinical evidence, assessed according to strength of evidence, size of effect, and relevance of evidence, and did not incorporate the economic impact of medications. Added to this is the fact that no pharmacoeconomic evaluations of antifungals from the Australian perspective existed. (Slavin M, leading and corresponding author of current Australian guidelines on the use of antifungals, personal communication, 14 May 2010, Peter MacCallum Cancer Centre and Royal Melbourne Hospital, Australia).

This thesis suggests that the use of antifungal agents is currently less than optimal in the management of fungal infections, and confirmed that treatment protocols for the different indications should consider the burden of outcomes, especially in term of costs. Future update of the guidelines for the use of antifungal agents in Australia is expected to reference economic data generated from this thesis (Slavin M, leading and corresponding author of current Australian guidelines on the use of antifungals, personal communication, 14 May 2010, Peter MacCallum Cancer Centre and Royal Melbourne Hospital, Australia).

In summary, this analysis from the Australian hospital system perspective suggests the potential favourable cost-effectiveness of using caspofungin and posaconazole for empirical therapy and prophylaxis, respectively. LAmB has also demonstrated relative benefit as empirical therapy, although to a lesser degree. The estimated benefit of voriconazole for empirical therapy and prophylaxis was less than that for other available agents. As eye drops, voriconazole appeared promising for the effective management of fungal keratitis, while mitigating the cost of treatment. The current data allow the development of practices and procedures to improve the efficiency of the use of these eye drops in the future.

The work undertaken in this thesis provides evidences to support decisions regarding the optimal utilisation of several high-cost antifungal agents in Australian hospitals.

14.5 REFERENCES

1. Slavin MA, Szer J, Grigg AP *et al.* Guidelines for the use of antifungal agents in the treatment of invasive Candida and mould infections. *Intern Med J* 2004; **34**: 192-200.

2. Slavin MA, Szer J, Morrissey O *et al.* Introduction to the updated Australian and New Zealand consensus guidelines for the use of antifungal agents in the haematology/oncology setting, 2008. *Intern Med J* 2008; **38**: 457-467.
3. NHMRC 2008/2009. NHMRC additional levels of evidence and grades for recommendations for developers of guidelines. Canberra: National Health and Medical Research Council. www.nhmrc.gov.au/publications/synopses/cp65syn.htm.

APPENDIX A: Chapters Four to Six – Questions to Expert Panel

Cost-effectiveness of Empirical Voriconazole, Ambisome & Caspofungin in Febrile Neutropenia
-Discussion Questions for Expert Panel-

1. In the 2002 paper comparing Voriconazole and Ambisome, the authors reported the median and range of the duration of voriconazole and ambisome administration, as shown below (ie. table1 in the paper). In your estimation, what would the **mean** duration of administration for each drug be?

	Voriconazole (N=415)	Ambisome (N=422)
Median (days)	7	7
Range (days)	1-113	1-81
Mean (days)	( )	( )

2. In your experience, during a hospital stay for neutropenia with fever, how often would a patient spend a day in the **ICU**? (Average number of days per week or month)

   If receiving Voriconazole:
   If receiving Ambisome:
   If receiving Caspofungin:

3. In the 2002 paper, lowering the Ambisome dose from 3mg to **1.5mg/kg/day** was permitted due to side effects. Based on your clinical experience, out of 416 patients with **NO base-line** fungal infections receiving **3mg/kg/day Ambisome**, what percentage of patients would be likely to receive a **dose reduction from 3mg to 1.5mg/kg/day** because of the side effects?

4. If lowering the Ambisome dose from 6mg to **1.5mg/kg/day** was permitted due to side effects, out of 6 patients with **base-line** fungal infections receiving **6mg/kg/day Ambisome**, how many patients would experience a **dose reduction from 6mg to 1.5mg/kg/day** because of side effects?

5. From your clinical experience, to moderate fever and neutropenia associated with the underlying diseases, what **antibiotics and colony stimulating factors** would you usually prescribe, concomitantly with the empirical use of the following antifungals? What are the **dose and duration** of each?

   With Voriconazole:

   With Ambisome:

   With Caspofungin:

6. Which of the following **screening methods** would you use to diagnose fungal infections during febrile neutropenia, and **how often** do you use the diagnostic test for the same patient (per day, week or month)? (check all that apply)

   - Chest X-ray:
   - CT scan:
   - Bronchoalveolarlavage (BAL):
   - Fungal cultures (not blood): - What kind of sample?
   - Galactomannan assay (ELISA):

Panel Members: Drs Monica Slavin, David Ritchie, Karin Thursky and Orla Morrissey.
14 June 2008

7. If there is a **switch from primary therapy to an alternative therapy**, would the frequency of using the screening tests listed above (ie. question 6) be the same or different? If different, what's the new 'frequency'?

8. During antifungal therapy for fever, which of the following **monitoring tests** would you use and **how often** for the same patient (per day, week or month)? (check all that apply)

   - Complete blood count:
   - Renal function:
   - Liver function:

9. During antifungal therapy for febrile neutropenia, do you request for therapeutic **drug monitoring** for the following? If yes, **how often** are the drug levels requested?

   Voriconazole:
   Ambisome:
   Caspofungin:

10. **During ICU stay** of a patient, would there be **any special procedures and tests** needed to be done in addition to those listed in Questions 6 & 8?

11. What interventions would you use to **moderate the side effects usually related to**:

    Voriconazole:

    Ambisome:

    Caspofungin:

12. In your experience, how many patients (total patient number is given below) will **prematurely discontinue** therapy because of each of the following **side effects**? With no patient having more than one side effect (exclusive data).

    - **Voriconazole** (**19** patients in total)
      Infusion-related reactions:
      Nephrotoxicity:
      Hepatotoxicity:

    - **Ambisome** (**100** patients in total)
      Infusion-related reactions:
      Nephrotoxicity:
      Hepatotoxicity:

    - **Caspofungin** (**27** patients in total)
      Infusion-related reactions:
      Nephrotoxicity:
      Hepatotoxicity:

Cost-effectiveness of Empirical Voriconazole, Ambisome & Caspofungin in Febrile Neutropenia
-Discussion Questions for Expert Panel-

13. After successful treatment of fever in neutropenia, is there a **post-therapy observational inpatient period** that is related to the fever and/or antifungal therapy? If yes, for **how long**?

14. What antifungal therapy would you give as an **alternative** in the following circumstances (Tables A, B & C)?

- **Table A:**

Drug	1st circumstance of treatment failure		Alternative	Dose	Frequency	Duration	Management of side effects
Voriconazole	Premature discontinuation due to severe:	Infusion-related reactions					
		Nephrotoxicity					
		Hepatotoxicity					
Ambisome	Premature discontinuation due to severe:	Infusion-related reactions					
		Nephrotoxicity					
		Hepatotoxicity					
Caspofungin	Premature discontinuation due to severe:	Infusion-related reactions					
		Nephrotoxicity					
		Hepatotoxicity					

- -**Table B:**

Drug	2nd circumstance of treatment failure		Alternative	Dose	Frequency	Duration	Management of side effects
Voriconazole	Premature discontinuation due to lack of efficacy against:	Suspected fungal infection					
		Persistent fever					
Ambisome	Premature discontinuation due to lack of efficacy against:	Suspected fungal infection					
		Persistent fever					
Caspofungin	Premature discontinuation due to lack of efficacy against:	Suspected fungal infection					
		Persistent fever					

Cost-effectiveness of Empirical Voriconazole, Ambisome & Caspofungin in Febrile Neutropenia
-Discussion Questions for Expert Panel-

Table C

Drug	3rd circumstance of treatment failure			Alternative	Dose	Frequency	Duration	Management of side effects
Voriconazole	Therapy failure due to:	Breakthrough fungal infection	Aspergillus species (lungs)					
			Candida species (disseminated, blood)					
			Zygomycetes (lungs, nasal passages)					
		Non responding base-line fungal infections	Aspergillus species					
			Candida species					
			Zygomycetes (disseminated)					
		Persistent fever						
Ambisome	Therapy failure due to:	Breakthrough fungal infection	Aspergillus species (lungs, sinuses, CNS or skin, disseminated, pneumonia)					
			Candida species (blood, chronic disseminated candidiasis, disseminated fungal infection, fungemia)					
			Dematiaceous molds (blood, lungs)					
			Mold, not identified (disseminated fungal infection & pneumonia)					
		Non responding base-line fungal infections	Aspergillus species (disseminated, pneumonia, sinusitis)					
			Candida species (disseminated, fungemia, empyema, pneumonia)					
			Trichoderma fungemia					
			Fusarium species (disseminated, sinusitis)					
			Mold, not identified (disseminated, pneumonia)					
		Persistent fever						
Caspofungin	Therapy failure due to:	Breakthrough fungal infection	Aspergillus species (disseminated, pneumonia, sinusitis)					
			Candida species (chronic disseminated candidiasis, disseminated fungal infection, fungemia)					
			Zygomycetes (hepatic & pneumonia & disseminated fungal inf.)					
			Fusarium species (disseminated fusarial infection & sinusitis)					
			Trichosporon species (fungemia)					
		Non responding base-line fungal infections	Aspergillus species (pneumonia, sinusitis)					
			Candida species (chronic disseminated candidiasis, disseminated fungal infection, fungemia)					
			Dipodascus capitatus (fungemia)					
			Zygomycetes (hepatic & pneumonia & disseminated fungal inf.)					
		Persistent fever						

APPENDIX B: Chapter Eight – Approvals of Ethics Committees

The Human Research Ethics Committee operates in accordance with the *NHMRC National Statement on Ethical Conduct in Human Research 2007*

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MELBOURNE HEALTH

RESEARCH DIRECTORATE

Research Directorate - Human Ethics Committee Approval Form

Telephone: 9342 8530 Facsimile: 9342 8548

This is to certify that

HREC Project No: 2007.125 **Approval date: 15/08/2007** **Expiry date: 15/08/2010**

Project Title: Pilot Economic Evaluation of Posaconazole Versus Voriconazole for Prophylactic Therapy in Acute Myeloid Leukemia Patients

Principal Investigator: Dr. David Kong
Pharmacy Practice
Monash University
381 Royal Parade
PARKVILLE VIC 3052

Sponsored by:

Protocol No:

Participant Information and Consent Form:

Investigator Brochure:

Other enclosures:(please describe eg advertisement etc.)

Conducted at: Royal Melbourne Hospital **has been approved**

It is now your responsibility to ensure that all people conducting this research project are made aware of which documents have been approved.

This approval is subject to ongoing, current and valid insurance coverage throughout the duration of the conduct of the study.

You are required to notify the Secretary of the Human Research Ethics Committee of

- Any change in the protocol and the reason for that change together with an indication of ethical implications (if any) by submitting an amendment to the study.
- Serious adverse effects on subjects and the action taken to manage them, including amended Plain Language Statement and Consent Form where appropriate.
- Any unforseen events.
- Your inability to continue as Principal Investigator, or any other change in research personnel involved in the study
- A delay of more than 12 months in the commencement of the project.
- The actual date of commencement of the study.

You are required to submit to the Human Research Ethics Committee

- An Annual Report every twelve months for the duration of the project.
- A detailed Final Report at the conclusion of the project.

The Human Research Ethics Committee may conduct an audit at any time.

An extension of the project beyond the stated conclusion date should be sought from the Human Research Ethics Committee.

Signed: [redacted]
Dr. Angela Watt
Secretary – Human Research Ethics Committee

MONASH University

Standing Committee on Ethics in Research Involving Humans (SCERH)
Research Office

Human Ethics Certificate of Approval

Date	6 September 2007
Project Number	2007001775
Project Title	Pilot economic evaluation of posaconazole versus voriconazole for prophylactic therapy in acute myeloid leukemia patients
Chief Investigator	Dr David Kong
Approved	From 6 September 2007 To 15 August 2010

Terms of approval

1. Approval is only valid whilst you hold a position at Monash University.
2. It is the responsibility of the Chief Investigator to ensure that all pending information (such as permission letters from organisations) is forwarded to SCERH. Research cannot begin at an organisation until SCERH receives a permission letter from that organisation.
3. It is the responsibility of the Chief Investigator to ensure that all investigators are aware of the terms of approval and to ensure the project is conducted as approved by SCERH.
4. You should notify SCERH immediately of any serious or unexpected adverse effects on participants or unforeseen events affecting the ethical acceptability of the project.
5. The Explanatory Statement must be on Monash University letterhead and the Monash University complaints clause must contain your project number.
6. **Amendments to the approved project:** Requires the submission of a Request for Amendment form to SCERH and must not begin without written approval from SCERH. Substantial variations may require a new application.
7. **Future correspondence:** Please quote the project number and project title above in any further correspondence.
8. **Annual reports:** Continued approval of this project is dependent on the submission of an Annual Report. This is determined by the date of your letter of approval.
9. **Final report:** A Final Report should be provided at the conclusion of the project. SCERH should be notified if the project is discontinued before the expected date of completion.
10. **Monitoring:** Projects may be subject to an audit or any other form of monitoring by SCERH at any time.
11. **Retention and storage of data:** The Chief Investigator is responsible for the storage and retention of original data pertaining to a project for a minimum period of five years.

[redacted]

Dr Souheir Houssami
Executive Officer, Human Research Ethics (on behalf of SCERH)

Cc: Assoc Prof Kay Stewart, Dr Danny Liew, Mr Daoud Al-Badriyeh

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APPENDIX C: Chapters Eleven and Twelve – Approvals of Ethics Committees

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March 3, 2008

Mr Geoff Davies
Director of Pharmacy
RVEEH - Box 12

Dear Mr Davies

Re: **Human Research & Ethics Committee – NEW PROJECT**
Research Project - An audit on the use of voriconazole eye drops for the treatment of fungal keratitis

The Human Research & Ethics Committee considered the above project at it's 28 February 2008 meeting. I am pleased to inform you that ethical approval was granted.

The project number **08/780H** was allocated, and this number should be used in all future correspondence. The Committee requires an annual progress report, and must approve any proposed amendments to the protocol. All serious or unexpected adverse effects on participants or any unforeseen events that might affect continued ethical acceptability of the trial must be reported to the Committee.

The Human Research & Ethics Committee of the Royal Victorian Eye & Ear Hospital is constituted and operates in compliance with the National Health & Medical Research Council National Statement on Ethical Conduct in Human Research (2007).

The Committee requires you to preserve the confidentiality of information about research subjects, and to ensure the confidentiality of records. Information obtained for your research that is confidential or personal must not be used for purposes other than those specified in the approved protocol.

Ethical approval is valid from the date of this letter until 28 February, 2013. At the end of this period, or at the conclusion of the research, a final report is required along with a copy of any publications.

On behalf of the Committee, I wish you every success with your project.

Yours sincerely

[redacted]

Kerryn Baker
Secretary
Human Research & Ethics Committee

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MONASH University

Standing Committee on Ethics in Research Involving Humans (SCERH)
Research Office

Human Ethics Certificate of Approval

Date:	**1 May 2008**
Project Number:	**2008000569**
Project Title:	**An audit on the use of voriconazole eye drops for the treatment of fungal keratitis**
Chief Investigator:	**Dr David Kong**
Approved:	**From: 1 May 2008 To: 1 May 2013**

Terms of approval

1. The Chief investigator is responsible for ensuring that permission letters are obtained and a copy forwarded to SCERH before any data collection can occur at the specified organisation. **Failure to provide permission letters to SCERH before data collection commences is in breach of the National Statement on Ethical Conduct in Human Research and the Australian Code for the Responsible Conduct of Research.**
2. Approval is only valid whilst you hold a position at Monash University.
3. It is the responsibility of the Chief Investigator to ensure that all investigators are aware of the terms of approval and to ensure the project is conducted as approved by SCERH.
4. You should notify SCERH immediately of any serious or unexpected adverse effects on participants or unforeseen events affecting the ethical acceptability of the project.
5. The Explanatory Statement must be on Monash University letterhead and the Monash University complaints clause must contain your project number.
6. **Amendments to the approved project:** Requires the submission of a Request for Amendment form to SCERH and must not begin without written approval from SCERH. Substantial variations may require a new application.
7. **Future correspondence:** Please quote the project number and project title above in any further correspondence.
8. **Annual reports:** Continued approval of this project is dependent on the submission of an Annual Report. This is determined by the date of your letter of approval.
9. **Final report:** A Final Report should be provided at the conclusion of the project. SCERH should be notified if the project is discontinued before the expected date of completion.
10. **Monitoring:** Projects may be subject to an audit or any other form of monitoring by SCERH at any time.
11. **Retention and storage of data:** The Chief Investigator is responsible for the storage and retention of original data pertaining to a project for a minimum period of five years.

[redacted]

Professor Ben Canny
Chair, SCERH

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APPENDIX D: Chapter Thirteen – Participant Information Sheet and Consent Form

PARTICIPANT INFORMATION AND CONSENT FORM

Version 2: Dated 13/03/2007
Site: The Royal Victorian Eye and Ear Hospital

Investigation of Voriconazole Eye Drops for the Treatment of Fungal Keratitis

Principal Researchers **Mr Geoff Davies**

Associate researchers: **Dr Mark Daniell**
Mr Lok Leung
Mr Robert Fullinfaw
Dr David Kong
A/Prof Kay Stewart
Mr Daoud Al-Badriyeh
Dr Trent Roydhouse

Subject Identification Number: _____

This Participant Information and Consent Form is 9 pages long. Please make sure you have all pages.

1. Your consent

You are invited to take part in this research project.

This Participant Information contains detailed information about the research project. Its purpose is to explain to you as openly and clearly as possible all the procedures involved in this project before you decide whether or not to take part in it.

Please read this Participant Information carefully. Feel free to ask questions about any information in the document. You may also wish to discuss the project with a relative or friend or your local health worker. Feel free to do this.

Once you understand what the project is about and if you agree to take part in it, you will be asked to sign the Consent Form. By signing the Consent Form, you indicate that you understand the information and that you give your consent to participate in the research project.

You will be given a signed and dated copy of the Participant Information and Consent Form to keep as a record.

2. Purpose and background

The purpose of the study is to investigate whether eye drops are a suitable way to deliver the drug voriconazole to eye tissues.

Voriconazole is only approved and available for use in Australia in injectable and tablet form. The voriconazole eye drops are not approved for marketing by the Australian Therapeutic Goods Administration. Therefore, the use of voriconazole as eye drops in this study is experimental in nature. There are several reports in the medical literature about individual patients that have benefited from having it prepared as an eye drop for the treatment of fungal eye diseases.

Treatment of fungal infections usually requires a prolonged period of treatment using oral or injectable voriconazole, and this can be associated with liver toxicity. This is because when administered as tablets or injections, the drug is found all over the body. We, the investigators, believe that delivering a small amount of voriconazole directly to the eye will be effective for the treatment of fungal eye disease, without the need to treating the whole body (ie. no drug in the rest of the body).

In a recent study done by us last year (also in the Royal Victorian Eye and Ear Hospital), we administered voriconazole eye drop at 1% concentration (ie. 1 g of voriconazole in 100 mL of eye drops) to a number of consenting participants who were also scheduled to undergo routine anterior segment (eg. cataract) surgery by the RVEEH Corneal Unit. The voriconazole eye drops were very well tolerated amongst the study participants, but we found that there was not enough voriconazole that actually gets into the eye (ie. into the aqueous humor of the eye). We believe this is due to us using a low concentration of voriconazole eye drop (ie. 1%).

The above finding has lead us to believe that by administering a higher concentration of voriconazole eye drops, for example, a 2% voriconazole solution, we will be able to increase the amount of voriconazole that actually gets into the eye tissue, and that the amount that actually gets into the eye will be sufficient to treat most fungal infections.

To test our theory, we need to administer the voriconazole eye drops for a short period, and then take samples of eye tissue (ie. aqueous humor).

In this study, participants will be assigned to be administered either voriconazole 2**%** eye drops 4 times a day for 3 days, or the same drops every hour for 4 doses only. These drops will be administered in the immediate lead up to scheduled surgery. Tissue samples will be taken during surgery for analysis. The tissue sample that we will take is tissue that would normally be taken and discarded by your doctor as part of your scheduled surgery.

A total of 40 subjects will participate in this study.

You are being invited to take part because you are:

- Over 18 years of age
- Scheduled to undergo routine anterior segment surgery by the RVEEH Corneal Unit (eg. corneal transplantation or cataract surgery).
- Not taking any of the following medicines: terfenadine, astemizole, cisapride, pimozide, quinidine, ergotamine, dihydroergotamine, rifampicin, carbamazepine, phenobarbitone, or sirolimus.
- Not breast feeding, pregnant, or trying to get pregnant.
- Not allergic or sensitive to the study medication or any of its components.

This trial has been initiated by Mr Geoffrey Davies, Director of Pharmacy at RVEEH. The results of this research will be used to help Mr Daoud Al-Badriyeh to obtain a PhD degree from Monash University.

3. Procedures

Participation in this project will involve no additional visits to the hospital other than those normally needed to prepare yourself for your surgery.

If you choose to participate in this study, you will be assigned (by the investigators) to one of two groups: one group will receive the voriconazole eye drops 4 times a day for the 3 days prior to surgery and the other group will receive the eye drops every hour for 4 doses on the day of surgery. You will be told which group you are in.

The last dose of study medication will be administered approximately 1 hour before your operation.

During the operation, samples of eye tissues that would normally be discarded as part of your treatment will be retained for drug level testing.

We will also be asking you questions about your symptoms of tearing, itchiness, discharge, eye discomfort and light sensitivity while you use the eye drops. Please ask your study doctor if you have any questions about any of the examinations mentioned above.

You will be asked about your medical and eye history during this visit and will need to let your study doctor know about any medications or vitamin supplements that you are taking before the start of the study, and during the study.

At any pre-admission visits, report any changes in your medications (over-the-counter and prescription), report any missed doses of the study medication, and report any changes in your general health to your study doctor.

To be eligible to participate in this study, all women of childbearing potential will need to be using a reliable form of contraception. Your doctor will discuss this with you at this visit if it is relevant to you.

4. Collection of Tissue Samples for Research Purposes

By consenting to take part in this study, you also consent to the collection, storage and use of tissue samples as specified below.

- If you are scheduled to have routine anterior segment surgery by the RVEEH Corneal Unit, samples of aqueous humor and cornea will be taken from the eye. Each sample will be about half the size of a grain of rice. This sample will be made entirely of tissue that would normally be removed and discarded as part of your normal operation.
- All tissue taken will only be used to determine the amount of voriconazole present in it.
- Tissue samples will be de-identified.
- Tissue samples will be stored until all trial samples have been taken. This is expected to be no more 12-months. They will then be processed by a laboratory to determine voriconazole levels, and then destroyed at the completion of the trial.
- This research does not involve the establishment of a tissue bank.
- There are no commercial uses of this tissue.

5. Possible Benefits

We do not believe you will receive any direct medical benefit from participating in this study. The possible benefits to humanity include more information about the use of voriconazole as an eye drop, and the development of future treatments of fungal eye disease.

6. Possible Risks

Possible risks, side effects and discomforts from oral voriconazole when given for several weeks and at about 50 times the daily dose we will be using include:

- *Greater than 10%* - Visual disturbances, fever, rash, vomiting, nausea, diarrhoea, headache, swelling of the arms and legs, and abdominal pain.

Between 1% and 10% - sinusitis (inflammation of nasal sinuses), chills (body feels cold and possible shivering), muscle weakness, chest pain, flu-like symptoms, accumulation of fluids in lungs, inflammation of the lips, gastroenteritis (stomach or bowel upset), abnormal liver function tests (damage to the liver), jaundice (yellowish discoloration of the whites of the eyes and skin), thrombocytopenia (reduction of numbers of platelets in circulating blood; which may cause easy bruising or episodes of excessive bleeding), anaemia (low number of red blood cells in circulating blood), leucopoenia (low number of white blood cells in circulating

blood), pancytopenia (low numbers of both red and white blood cells in circulating blood), hypokalaemia (low concentration of potassium ions in circulating blood), hypoglycaemia (low level of glucose in circulating blood), back pain, dizziness, tremor, paraesthesia (tingling sensation of body parts), hallucination, confusion, depression, anxiety , agitation, facial oedema (accumulation of fluid on the face), pruritus (itching feeling on the skin), maculopapular rash (flat red rash), photosensitivity (unusual skin reactions to light), alopecia (hair loss), exfoliative dermatitis (scaling and shedding of skin), purpura (purplish discolorations of skin caused by internal bleeding close to skin surface), hypotension (reduced blood pressure), thrombophlebitis (inflammation of a vein caused by blood clots), phlebitis (inflammation of a vein), acute renal failure (failure of kidneys to excrete wastes, concentrate urine and conserve electrolytes, usually associated with elevated creatinine level in circulating blood), haematuria (presence of blood in urine).

The total dose of voriconazole which you will receive as part of this study will be between 4mg and 12mg. This is between 2% and 6% of the daily oral dose. For this reason, generalised side effects are not expected to be common or severe.

Voriconazole eye drops have been reported widely in the medical literature as very safe with no to minimal side effects. Only in two patients, was the medication discontinued because of a burning sensation in the eye after one day and four weeks, respectively.

If you experience any illness or discomfort during the study, you should notify your Investigator. Your Investigator will then evaluate you to determine if you should continue in the study. If necessary, your study medication may be stopped, and other appropriate therapy may be started.

There may be side effects or discomforts from the study treatment which are not yet known.

The effects of voriconazole on the unborn child and on the newborn baby are not known. Because of this, it is important that study participants are not pregnant or breast-feeding and do not become pregnant during the course of the study. You must not participate in the study if you are pregnant or trying to become pregnant, or are breast-feeding.

If you are male, you should not father a child. If you are female and child bearing is a possibility, you will be required to undergo a pregnancy test prior to commencing the study. Both male and female participants are strongly advised to use effective contraception during the course of the study and for a period of one month after completion of the study. You should discuss methods of effective contraception with your doctor. If you do become pregnant whilst participating in the study you should advise your treating doctor immediately. He/she will withdraw you from the study and advise on further medical attention should this be necessary. You must not continue in the study if you become pregnant.

7. Other Treatments Whilst on Study

It is important to tell your doctor and the research staff about any treatment or medications you may be taking, including non-prescription medications, vitamins or herbal remedies and any changes to these during your participation in the study.

8. Alternatives to Participation

Participation in this study is voluntary, and choosing not to take part will not affect your treatment in any way.

9. Privacy, Confidentiality and Disclosure of Information

This study will involve the collection and processing of personal data about you, including sensitive data regarding your health and other personal details. Any personal data removed from RVEEH will be de-identified and will only be marked with your initials and a patient number that will be assigned to you at the beginning of the study.

The de-identified data will be used for purposes related to this study and any other studies arising out of this study, such as research and development, statistical analysis, the licensing and registration of pharmaceutical products, the provision of healthcare, and other related purposes.

It may be necessary to disclose your de-identified personal data to third parties involved in the study, such as companies affiliated to RVEEH, clinicians, research staff and government licensing and health authorities. Some of these third parties may be located outside of Australia. By agreeing to participate in this study, you are giving your permission:

1. for RVEEH to process your de-identified personal and sensitive data for purposes related to this study; and
2. for RVEEH to disclose such de-identified data to third parties and to transmit such data to countries outside of Australia.

Any information obtained in connection with this research project that can identify you will remain confidential and will only be used for the purpose of this research project. It will only be disclosed with your permission, except as required by law. A report of the results of this study may be published or sent to the appropriate health authorities in any country in which this product may ultimately be used, but your name will not be disclosed in these documents. In any publication, information will be provided in such a way that you cannot be identified. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information.

RVEEH is committed to respecting the privacy of all patients taking part in this study, and to this end upholds the provisions and principles of Health Records Act 2001 (Vic). In particular, where RVEEH does receive identifiable personal information about you it will respect your rights in relation to that data, including your right to correct your personal data and your right to have access to your personal data in RVEEH's possession.

By signing the attached Consent Form, you authorise release of, or access to, this confidential information to the relevant study personnel and regulatory authorities as noted above.

All appropriate precautions will be taken to maintain confidentiality of medical records and personal information. Study data will be stored securely in a locked room and will be accessed only by personnel directly involved in the study. At the end of the study, study data will be stored at the RVEEH for a minimum of 15 years from the end of the study. At the end of the 15 years the study data can be shredded or erased.

It is desirable that your family doctor be advised of your decision to participate in the research project. By signing the Consent Form, you agree to your family doctor being notified of your decision to participate in this research project.

In accordance with the Freedom of Information Act 1982 (Vic), you have the right to access and to request correction of information held about you by the Royal Victorian Eye and Ear Hospital.

10. New Information Arising During the Project

During the research project, new information about the risks and benefits of the project may become known to the researchers. If this occurs, you will be told about this new information. This new information may mean that you can no longer participate in this research. If this occurs, the person supervising the research will stop your participation.

In all cases, you will be offered all available care to suit your needs and medical condition.

11. Results of Project

Upon completion of the study, the Investigator will be given access to individual patient results and can share these with you on an individual basis.

12. Further Information or any Problems

If you require further information or if you have any problems concerning this project (for example, any side effects,) you can contact the Investigators.

Mr Geoffrey Davies	03 9929 8204 (business hours)
Dr Mark Daniell	03 9387 1000 (business hours)
Emergency Department	03 9929 8333 (after hours)

13. Other Issues:

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about your rights as a research participant, then you may contact the Kerryn Baker (Secretary of the Human Research & Ethics Committee at the RVEEH) on (03) 9929 8547.

14. Participation is Voluntary

Participation in any research project is voluntary. If you do not wish to take part you are not obliged to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

Your decision whether or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with the RVEEH.

Before you make your decision, a member of the research team will be available so that you can ask any questions you have about the research project. You can ask for any information you want. Sign the Consent Form only after you have had a chance to ask your questions and have received satisfactory answers.

If you decide to withdraw from this project, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to inform you if there are any health risks or special requirement linked to withdrawing.

15. Reimbursement for your Costs

You will not be paid for participating in this study. The study medication and the medical management surrounding trial participation will be provided free of charge while you remain in the study.

16. Ethical Guidelines

This project will be carried out according to Good Clinical Practice Guidelines, the International Conference of Harmonisation and the "National Statement on Ethical Conduct in Research Involving Humans" (June 1999) produced by the National Health and Medical Research Council of Australia (this statement has been developed to protect the interests of people who agree to participate in human research studies).

The ethical aspects of this research project have been approved by the Human Research and Ethics Committee of the Royal Victorian Eye and Ear Hospital and Monash University's Standing Committee for Ethical Research into Human.

17. Injury

In the event that you suffer an injury as a result of participating in this research project, hospital care and treatment will be provided by the public health service at no extra cost to you.

18. Termination of the Study

This research may be stopped for a variety of reasons. These may include reasons such as: unacceptable side effects, the drug being shown to not be effective, the drug being shown to work and not need further investigation. The Investigator may also stop your participation in the study at any time, and may stop this study at any time for reasons he determines appropriate.

19. The Royal Victorian Eye And Ear Hospital Experimental Subject's Statement Of Rights

The Royal Victorian Eye and Ear Hospital considers it important that you know:

Any patient who is asked to participate in a research study involving medical experiment, or who is requested to consent on behalf of another, has the right to:

1. Be informed of the nature and purpose of the experiment.
2. Be given an explanation of the procedures to be followed and any drugs used in the medical experiment.
3. Be given a description of discomforts and risks reasonably expected from the experiment, if applicable.
4. Be given an explanation of any benefits to the subject reasonably to be expected from the experiment, if applicable.
5. Be advised of appropriate, alternative procedures, drugs, or devices that might be advantageous to the subject, and their relative risks and benefits.
6. Be informed of the avenue of medical treatment, if any, available to the subject after the experiment if complications should arise.
7. Be given an opportunity to ask questions concerning the experiment or the procedures involved.
8. Know that consent to participate in the medical experiment may be withdrawn at any time, and that the subject may discontinue participation in the medical experiment without prejudice.
9. Be given a copy of the signed and dated written consent form when one is required.
10. Be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion or undue influence.

PARTICIPANT CONSENT FORM

Version 1: Dated 02/02/07
Site: Royal Victorian Eye and Ear Hospital

Investigation of Voriconazole Eye Drops for the Treatment of Fungal Keratitis

I have read, or have had read to me in my first language, and I understand the Participant Information version 1 dated 02/02/07

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this project according to the conditions in the Participant Information.

I will be given a copy of the Participant Information and Consent Form to keep.

I understand that the researcher has agreed not to reveal my identity and personal details if information about this project is published or present in any public form.

Participant's Name (printed): _____

Signature: _____ Date: _____

Name of Witness to Participant's Signature (printed): _____

Signature: _____ Date: _____

Declaration by researcher*: I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood the explanation.

Researcher's Name (printed): _____

Signature: _____ Date: _____

*A senior member of the research team must provide the explanation and provision of information concerning the research project.

Note: All parties signing the Consent Form must date their own signature.

REVOCATION OF PARTICIPANT CONSENT FORM

Investigation of Voriconazole Eye Drops for the Treatment of Fungal Keratitis

I hereby wish to WITHDRAW my consent to participate in the research proposal named above and understand that such withdrawal WILL NOT jeopardise any treatment to my relationship with the Royal Victorian Eye and Ear Hospital (RVEEH).

Participant's Name (printed): _____

Signature: _____ Date: _____

APPENDIX E: Chapter Thirteen – Staff Protocol

Appendix 1

Instructions for Medical, Pharmacy and Nursing staff

Medical Staff:

1. Identify suitable trial subject as per study protocol.
2. Ask subject if they would like to participate.
3. Explain procedures and obtain written consent.
4. Contact RVEEH Pharmacy and obtain a Patient number. The Pharmacy will confirm over the phone the Patient Number and whether the subject is to be on the hourly or 6-hourly arm of the trial.
5. If hourly:
    a. Book patient for PM surgery, and ask patient to arrive at least 5 hours before.
    b. Write a prescription for “Voriconazole Trial Drops”, the patient’s study number, the frequency of drop administration, and the eye it is to be administered in. Ask the patient to present this to RVEEH Pharmacy today.
    c. The patient is under the care of the Corneal Unit, and the surgery must be completed by Dr Mark Daniell, or the Corneal Fellow only.
    d. Ensure that when the patient is admitted on the day of surgery, an order is written on the drug chart for “Voriconazole Trial Drops”, to be administered hourly in the eye to be operated on at -4hours, -3hours, -2hours, and -1hour before operation time.
6. If 6-hourly:
    a. Book the patient for AM surgery.
    b. Write a prescription for “Voriconazole Trial Drops”, the patient’s study number, the frequency of drop administration, and the eye it is to be administered in.
    c. Ask the patient to visit RVEEH Pharmacy to discuss an appropriate date for drop collection, and for explanation of administration directions.
    d. The patient is under the care of the Corneal Unit, and the surgery must be completed by Dr Mark Daniell, or the Corneal Fellow only.
7. Notify Pharmacy once the booking date and time is known.
8. If contacted to assess the severity of any side effects experienced, record your assessment in the main Patient Notes, and contact Pharmacy to notify them of the outcome. If you believe it is in the patient’s best interest to be withdrawn from the trial, then they should be immediately.
9. During the surgical procedure, the aqueous humor sample should be taken and stored in a pathology specimen tube. This should be labeled with the patient’s initials, DOB, Study Number, and date and time of tissue collection, and then immediately transported to the RVEEH Pharmacy.

Pharmacy staff:

1. On receiving notice of a subject's inclusion from a doctor, assign the next Patient Number available to the specific patient.
2. Inform the doctor what the Subject Number is and confirm the dose regimen that the patient is to receive.
3. Ask the doctor to send the patient to Pharmacy once the consultation is complete.
4. If patient is assigned to hourly drops, complete points 6-12, skip points 13-19, then continue from point 20.
5. If assigned to 6-hourly drops, skip points 6-12.

Hourly drops

6. If the patient is assigned to receive the hourly drops, tell the patient that the medication will be provided to the admitting ward on the day of the surgery, for administration by nursing staff.
7. If necessary, mark in the manufacturing diary a suitable day for manufacturing to occur. Usually this will be one day before they are needed.
8. When dispensing, the eye drops should be labeled with the patient's name and their Study Number.
9. If randomised to hourly drops, directions should read: Instil ONE drop into the <INSERT> eye at FOUR hours, THREE hours, TWO hours, and ONE hour before your operation.
10. On the morning of surgery, issue to the admitting ward the drops and an Administration Log, marked with the patient's details and Study Number.
11. Ask the ward to return the used bottle and Log to Pharmacy that day.
12. File the Log filed in the Trial Folder, and used bottle in the refrigerator.

6-Hourly drops

13. When the patient arrives, and if the patient is assigned to receive the 6-hourly drops, negotiate a date and time for the drops to be collected or delivered. This can be anytime up until 4 days before surgery, provided that the drops will be less than its expiry date on the day of surgery.
14. If necessary, mark in the manufacturing diary a suitable day for manufacturing to occur. Usually this will be one day before they are needed.
15. When dispensing, the eye drops should be labeled with the patient's name and their Study Number.
16. If randomised to 6-hourly drops, directions should read: Instil ONE drop into the <INSERT> eye FOUR times a day for the THREE days before your operation.
17. On the day of issue, give also to the patient an Administration Log, marked with the patient's details and Study Number.
18. Ask the patient to bring in to hospital on the day of surgery both the used bottle, and the Log. This should be given to admitting ward staff and returned to Pharmacy.
19. File the Log filed in the Trial Folder, and used bottle in the refrigerator.
20. On the day of surgery, you will receive from theatre a pathology specimen tube containing a tissue sample. Store this in the refrigerator.

21. On the Tuesday following a trial patient receiving surgery, any tissue samples should be packed securely with an ice brick and sent by courier to:

    Robert Fullinfaw
    Senior Scientist
    Special Chemistry CMR 210
    Pathology Department
    Royal Melbourne Hospital
    Royal Parade
    Parkville

22. Once the package is ready phone Robert to know it is on its way. His phone number is 9342 7042.
23. The remainder of the used bottle in (19) is to be then packed and stored in refrigerators until the trial ends, to be discarded properly after that.

Nursing staff:

1. Only to be followed if patient is on the hourly drop administration arm of the trial.
2. Instil a single drop into the eye to be operated on at:
    a. -4 hours to the scheduled operation time
    b. -3 hours to the scheduled operation time
    c. -2 hours to the scheduled operation time
    d. -1 hours to the scheduled operation time
3. At 5 minutes after drop administration, ask if the patient feels any tearing, itchiness, discharge, eye discomfort, light sensitivity, or any other side effects. If any are noted, ask the patient to rate the severity of the effect noted on a scale of 1 to 10. Record this information below, taking note of the time the symptom(s).
4. If you are concerned about any side effect, the Corneal Fellow should be contacted immediately to evaluate whether the patient should continue in the trial.
5. The Administration log sheet provided should be completed, in addition to the drug chart.
6. Send this form to the RVEEH Pharmacy Department within 3 hours of the last administrated dose, along with the used drop bottle.

Appendix 2

Investigation of Voriconazole eye drops for the treatment of Fungal Keratitis

Administration Log

PLACE BRADMAR LABEL HERE

This Log is THREE (3) pages long. Please ensure that you have all pages and that they are securely attached.

Please return this form to the Pharmacy Department along with the remainder of the drops on the day of your operation

Pharmacy note: Cross out section that does not apply. (Section A or B)

Section A: 1-hourly drop administration

Instil ONE drop only per dose administration time. A second drop may be administered if the first drop does not reach to eye.

Date administered: _____

Hours before surgery	Time administered	Signature
4-hours		
3-hours		
2-hours		
1-hour		

Section B: 6-hourly drop administration

Instil ONE drop only per dose administration time. A second drop may be administered if the first drop does not reach to eye.

Day of administration	**Date (Pharmacist to complete)**	**Time administered**	**Signature**
3-days prior to surgery, **morning**			
3-days prior to surgery, **midday**			
3-days prior to surgery, **evening**			
3-days prior to surgery, **night**			
2-days prior to surgery, **morning**			
2-days prior to surgery, **midday**			
2-days prior to surgery, **evening**			
2-days prior to surgery, **night**			
1-day prior to surgery, **morning**			
1-day prior to surgery, **midday**			
1-day prior to surgery, **evening**			
1-day prior to surgery, **night**			

Section C: Adverse reactions or other comments

Please record whether you experience any symptom or adverse reaction that might be the result of your trial drops. If you do not experience an adverse reaction, please record that here.

If you experience any adverse reaction that you are concerned about, contact Mr Geoff Davies on 9929 8204 or 9929 8202 during business hours, or else the Emergency Department at the Royal Victorian Eye and Ear Hospital on 9929 8333 after hours

Date	Time	Symptom

APPENDIX F: Chapter Thirteen – Approvals of Ethics Committees

The Royal Victorian Eye & Ear Hospital
caring in every sense

The Royal Victorian Eye & Ear Hospital

32 Gisborne Street
East Melbourne
Victoria 3002 Australia

Locked Bag 8
East Melbourne
Victoria 8002 Australia

Telephone +61 3 9929 8666
TTY +61 3 9929 8052
Facsimile +61 3 9663 7203

info@eyeandear.org.au
www.eyeandear.org.au

ABN 81 863 814 677

February 26, 2007

Mr Geoff Davies
Director of Pharmacy
RVEEH - Box 12

Dear Mr Davies

Re: **Human Research & Ethics Committee – NEW PROJECT**
Research Project - Investigation of Voriconazole eye drops for the treatment of Fungal Keratitis

The Human Research & Ethics Committee considered the above project at it's 22 February 2007 meeting. I am pleased to inform you that ethical approval was granted subject to approval from the Hospital's Insurers.

The project number **07/731H** was allocated, and this number should be used in all future correspondence.

I will advise you in due course on the outcome of your application. Please note, you cannot commence until final approval is granted.

Yours sincerely

[redacted]

Kerryn Baker
Secretary
Human Research & Ethics Committee
kerryn.baker@eyeandear.org.au
Telephone +61 3 9929 8525

Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

File Number: 07/3121

ROYAL VICTORIAN EAR & EYE HOSPITAL
32 GISBORNE ST

EAST MELBOURNE VIC 3002
Attention: Geoff Davies

CTN Scheme (Drugs): Acknowledgement of New Trial

Your notification to conduct a clinical trial under the Clinical Trial Notification (CTN) Scheme, pursuant to Schedule 5A of Regulation 12 of the Therapeutics Goods Regulations, has been received by the Drug Safety and Evaluation Branch (DSEB).

Trial Number: 2007/202
Protocol Number: 07/731H
Drug Name(s): voriconazole

It is noted that:

i. the approval of the goods for this trial was given in accordance with Item 3 of Schedule 5A of the Therapeutic Goods Regulations by the body or organisation conducting the trial at each site.

ii. the representative of the Ethics Committee for each site has certified that the Committee is constituted and operates in accordance with the NH&MRC "National Statement on Ethical Conduct in Research Involving Humans", has considered this clinical trial, and has provided advice to the body or organisation conducting the trial.

The Therapeutic Goods Administration has not carried out an assessment of the quality, safety or efficacy of any drug product in relation to this notification.

Please note that, in the event that the Secretary of the Commonwealth Department of Health and Ageing becomes aware that to undertake or continue the clinical trial would be contrary to the public interest, the Secretary has the authority to direct that use of the drug product(s) for this clinical trial must cease.

A form for "CTN Scheme (Drugs): Trial Completion Advice" is enclosed. Please fill out and return this form after the Clinical Trial has completed.

Please direct enquiries to the Experimental Drugs Section on (02) 6232 8106 (phone) or (02) 6232 8112 (fax).

[redacted]
Rachael Smith
Experimental Drugs Section
Drug Safety & Evaluation Branch

11/04/07

Address: PO Box 100 Woden ACT 2606 Website: www.tga.gov.au
Telephone: 02 6232 8111 Facsimile: 02 6232 8112 ABN 40 939 406 804

Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

CTN Scheme (Drugs): Clinical Trial Site List

This document lists all sites acknowledged to date for the following clinical trial:

Sponsor: **ROYAL VICTORIAN EAR & EYE HOSPITAL**

Protocol Number: **07/731H**

Trial Number: **2007/202**

Date Acknowledged	Site Name	State
11-APR-07	Royal Victorian Eye & Ear Hospital	VIC

Address: PO Box 100 Woden ACT 2606 Website: www.tga.gov.au
Telephone: 02 6232 8111 Facsimile: 02 6232 8112 ABN 40 939 406 804

The Royal Victorian Eye & Ear Hospital
caring in every sense

The Royal Victorian Eye & Ear Hospital

32 Gisborne Street
East Melbourne
Victoria 3002 Australia

Locked Bag 8
East Melbourne
Victoria 8002 Australia

Telephone +61 3 9929 8666
TTY +61 3 9929 8052
Facsimile +61 3 9663 7203

info@eyeandear.org.au
www.eyeandear.org.au

ABN 81 863 814 677

March 22, 2007

Mr Geoff Davies
Director of Pharmacy
RVEEH - Box 12

Dear Mr Davies

Re: **Human Research & Ethics Committee – NEW PROJECT**
Research Project - Investigation of Voriconazole eye drops for the treatment of Fungal Keratitis

I acknowledge receipt of the revised Participant Information and Consent Form for this project. Your project has therefore been approved by the Executive Director Medical Administration.

I am pleased to inform you that ethical approval has now been granted. The project number **07/731H** was allocated, and this number should be used in all future correspondence. The Committee requires an annual progress report, and must approve any proposed amendments to the protocol. All serious or unexpected adverse effects on participants or any unforeseen events that might affect continued ethical acceptability of the trial must be reported to the Committee.

The Committee requires you to preserve the confidentiality of information about research subjects, and to ensure the confidentiality of records. Information obtained for your research that is confidential or personal must not be used for purposes other than those specified in the approved protocol.

Ethical approval is valid from the date of this letter until 22 February, 2012. At the end of this period, or at the conclusion of the research, a final report is required along with a copy of any publications.

Attached is the signed CTN form. Evidence of TGA submission must be sent to the HREC prior to recruitment at this site. Please ensure that a copy of the TGA notification is forwarded on to the HREC Secretary.

On behalf of the Committee, I wish you every success with your project.

Yours sincerely

[redacted]

Kerryn Baker
Secretary
Human Research & Ethics Committee
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Telephone +61 3 9929 8525

MONASH University

Standing Committee on Ethics in Research Involving Humans (SCERH)
Research Office

Dr David Kong
Department of Pharmacy Practice
Faculty of Pharmacy
Parkville - VCP Campus

6 June 2007

CF07/1434 - 2007/0389MC - Investigation of voriconazole eye drops for the treatment of fungal keratitis

Dear Researchers,

The above research project has been considered by the Standing Committee on Ethics in Research Involving Humans and approval has been given. This approval will be ratified at meeting A4/2007 on 19 June 2007. It is possible that issues may be raised by the Committee at that meeting. If you do not hear anything further you may assume that approval for the project is confirmed.

Terms of approval

1. This project is approved from 6 June 2007 to 22 February 2012 and this approval is only valid whilst you hold a position at Monash University.
2. It is the responsibility of the Chief Investigator to ensure that, if relevant, all information that is pending is forwarded to SCERH. You will then receive a letter from SCERH confirming that we have received the information.
3. It is the responsibility of the Chief Investigator to ensure that all investigators are aware of the terms of approval and to ensure the project is conducted as approved by SCERH.
4. You should notify SCERH immediately of any serious or unexpected adverse effects on participants or unforeseen events affecting the ethical acceptability of the project.
5. **Amendments to the approved project:** Changes to any aspect of the project require the submission of a Request for Amendment form to SCERH and must not begin without written approval from SCERH. Substantial variations may require a new application.
6. **Future correspondence:** Please quote the project number and project title above in any further correspondence.
7. **Annual reports:** Continued approval of this project is dependent on the submission of an Annual Report. Please provide the Committee with an Annual Report determined by the date of your letter of approval.
8. **Final report:** A Final Report should be provided at the conclusion of the project. SCERH should be notified if the project is discontinued before the expected date of completion.
9. **Monitoring:** Projects may be subject to an audit or any other form of monitoring by SCERH at any time.
10. **Retention and storage of data:** The Chief Investigator is responsible for the storage and retention of original data pertaining to a project for a minimum period of five years.

All forms can be accessed at our website www.monash.edu.au/research/human-ethics

We wish you well with your research.

[redacted]

Mrs Lyn Johannessen
Acting Human Ethics Officer (on behalf of SCERH)

Cc: Mr Daoud Al-Badriyeh

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