

**School of Pharmacy**

**An Evaluation of Intravenous Antifungal Medications in Patients in  
a Paediatric Hospital**

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## **Declaration**

This thesis titled “An Evaluation of Intravenous Antifungal Medications in Patients in a Paediatric Hospital” contains no material which has been accepted for the award of any other degree or diploma in any University.

To the best of my knowledge and belief this thesis contains no material previously published by any other person except where due acknowledgement has been made.

Signature .....

(Remya Raj)

Date

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## Abstract

**Objective:** To retrospectively evaluate intravenous antifungal medications in paediatric patients in a public hospital for children.

**Method:** Data relevant to the antifungal prescription were collected for all the patients <18 years of age who had been prescribed IV antifungal therapy. All paediatric patients prescribed intravenous antifungal treatment for one year (July 2006 to 30<sup>th</sup> June 2007) at PMH were evaluated retrospectively. The data collected were evaluated against the Australian Therapeutic Guidelines: Antibiotic Version 13 and hospital in house guidelines for IV antifungal therapy from the microbiology department at the hospital.

**Results:** There were 59 patients included in the study and the most frequently diagnosed disease was leukemia. Of the total 59 patients, liposomal amphotericin B (L-AmB) was prescribed for 47 patients, conventional amphotericin B (C-AmB) for four patients, caspofungin for two patients and voriconazole for one patient. Five patients received combination antifungals. The dose of C-AmB was 1 mg/kg/day. Voriconazole dose of 5 mg/kg/day was given for a period of four days for one patient. Nine patients included in this study were neonates and they were prescribed L-AmB, C-AmB and a combination of Voriconazole and L-AmB. 34 patients out of 47 were prescribed 3mg/kg/day of L-AmB and the highest L-AmB dose prescribed was 5 mg/kg/day and the lowest dose was 1 mg/kg/day. The median number of days for L-AmB treatment was found to be 11 days and the maximum was 51 days. Additionally 6% of patients who received L-AmB had oral fluconazole recommended r five days after cessation of L-AmB. It was found that 27% of patients had a low potassium level and a significantly higher proportion of patients had abnormal alanine aminotransferase and 11(18.6%) of the 59 patients had abnormal serum creatinine levels. It was found that the mean temperature decreased to 37.0°C from a 38.3°C from commencement to the cessation of the IV antifungal treatment. The longest duration of antifungal treatment in this study period was L-AmB prescribed for a period of 102 days.

The estimated treatment cost for the longest treatment in this study was found to be AUD 34,222 if prepared in the pharmacy (CIVAS) and AUD 43,784 if prepared in the ward setting. Estimated total treatment cost for a four year old patient with a bodyweight of 21 kg on L-AmB for a period of 21 days was found to be AUD 7,803 when prepared in Pharmacy (CIVAS) and AUD 12,029 for Ward reconstitution.

Conclusion: The data from this study indicated a satisfactory quality of IV antifungal treatment; however the remaining requirements for appropriate use required additional education. This study found that L-AmB was the antifungal agent of choice. Considerable savings could be made for pharmacy reconstituted IV antifungals by CIVAS over a ward setting where wastage occurs from unused antibiotic vials. At present the understanding of newer antifungal agents in children is limited. In future children should be included in the studies of new antifungal drugs and combination therapy and stratify the results by age, given the potential differences in pharmacokinetics, pharmacodynamics, efficacy and safety and cost.

## Abbreviations

IFI	Invasive fungal infections
SFI	Systemic fungal infection
L-AmB	Liposomal amphotericin B
C-AmB	Conventional amphotericin B
VCZ	Voriconazole
PCZ	Posaconazole
AML	Acute myeloid leukemia
FDA	Food and drug administration
CIVAS	Centralized Intravenous Additive Service
MIC	Minimum inhibitory concentration
EORTC	European Organisation for Research and Treatment of Cancer
IV	Intravenous
ALT	Alanine Aminoetransferase
AST	Aspartate Aminotransferase
ALK	Alkaline Phosphatase

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# 1 Introduction

The incidence and severity of invasive fungal infections (IFIs) in immunocompromised patients has dramatically increased worldwide during the last two decades.<sup>1</sup> Mortality and morbidity in patients with life-threatening conditions have reduced due to the advances in supportive medical care, cancer therapy, stem cell and solid organ transplantation. However these advances have also contributed to an increased population of patients vulnerable to IFIs.<sup>2</sup>

The incidence of invasive fungal infection (IFIs) in USA has increased 307% from 5231 cases in 1979 to 16,042 cases in 2000.<sup>3</sup> The fourth commonest nosocomial bloodstream pathogen with the highest crude mortality (40%) in the USA is the *Candida* spp.<sup>4</sup> New and emerging fungal pathogens such as *Zygomycetes*, *Fusarium* spp. or *Scedosporium* spp. have become increasingly important in addition to *Candida* spp. and *Aspergillus* spp. Empirical antifungal therapy has become the standard of care in neutropenic patients in whom fever persists despite treatment with broad spectrum antibiotics.<sup>5</sup> Despite the development of novel antifungal drugs and advances in medical interventions the crude and attributable mortality of IFIs has remained largely unchanged over the past 20 years.<sup>6,7</sup>

The new age of opportunistic fungal pathogens extends to paediatric patients with immunodeficiencies especially those with disorders of neutrophil function.<sup>8</sup> Unfortunately there are only a few paediatric focused studies on the epidemiology and treatment of IFIs in children although knowledge of newer antifungals has been expanded by recent studies. Many recommendations for the use of antifungals in children are derived from experience in adult patients.<sup>2</sup>

Three treatment strategies are available, dependent on whether an IFI is possible, probable or proven: prophylactic, empiric and specific. Two new triazoles and three new echinocandins have been approved by FDA for use in the last 6 years increasing the options for prophylaxis and treatment of IFIs. Amphotericin B deoxycholate (C-AmB) remains the 'gold standard' for the management of many invasive fungal infections in adults and children, as well as the comparative agent for all newer antifungal agents.<sup>9</sup> At

the beginning of the 1990s, the pace of drug development accelerated with the introduction of triazoles. Amphotericin B (C-AmB) was incorporated in three lipid formulations, whilst itraconazole and first generation triazoles changed the epidemiology of *Candida* infections and offered new treatment options.<sup>10</sup> In many cases these antifungals have proven to be less toxic and more effective than C-AmB.<sup>11</sup> The choice of the most appropriate drug should be guided by efficacy, safety and economic criteria.<sup>12</sup> Voriconazole is a second generation triazole antifungal agent approved by FDA in May 2002 available as both IV and oral formulations.<sup>13</sup> It has added a new and improved therapeutic option for primary therapy of invasive aspergillosis and demonstrated survival benefit and superior efficacy with C-AmB followed by other antifungal therapy.<sup>14</sup>

Antifungal therapy is influenced by a multiplicity of factors including patient risk profile, based on the underlying condition versus relapsing episodes of fever, whether antifungal prophylaxis has been used, clinical presentation, documentation of bacterial infection and results of non-invasive diagnostic tools.<sup>12</sup>

### *1.1 Fungal infections*

The fungal infections which are increasing in frequency are responsible for most fatal infections in patients with acute leukemia and other cancers.<sup>15</sup> Factors leading to increased incidence of fungal infections in cancer patients include more irradiation leading to long term granulocytopenia (>14 days), more aggressive cancer chemotherapy and complicated surgical procedures, damage of mucosal barriers, invasive treatments and procedures, use of potent broad spectrum antibiotics, prolonged serious illness and pharmacological doses of corticosteroids.<sup>15,16</sup>

The incidence of fungal infections in cancer patients is 15-25% for patients with leukemia or those undergoing bone marrow transplant, 10% for those with lymphoma, and 5% for those with solid tumors. Autopsy studies have shown that these infections are primarily due to either *Candida* or *Aspergillus* species.<sup>17,18</sup> Knowledge and management of patients with Systemic fungal infection (SFI) has improved concurrently with the emergence of new therapeutic compounds and with an improved understanding of the nature of the disease, although there remains problems in diagnosis and prevention.<sup>19</sup>

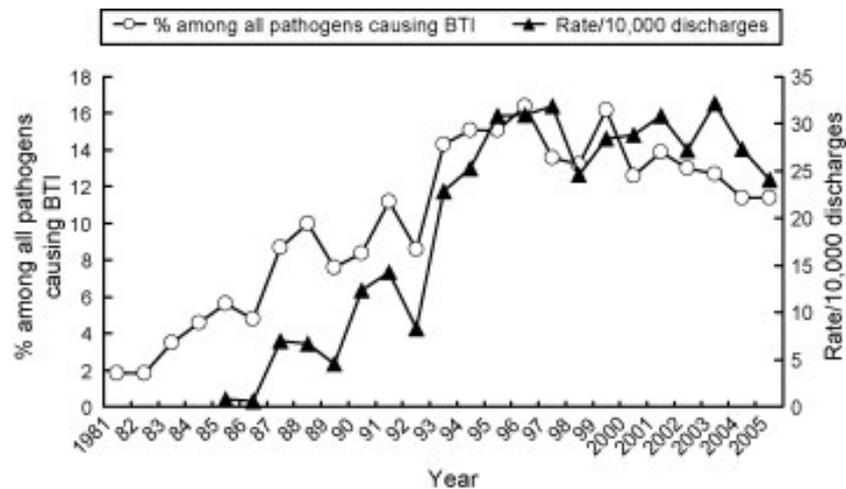
In a myeloid leukemia trial,<sup>20</sup> two-thirds of the 13.8% of treatment related mortality was due to fungal infections leading to 2.3% mortality rate. Candidaemia or bacteraemia occurred in two of the eight fatal SFI cases and aspergillus pneumonia occurred in six. During the second half of the study the treatment related death rate was halved, possibly related to increased clinical awareness, improved therapy of leukostasis, inpatient hospital management and the use of prophylactic azoles.

The Munster study<sup>21</sup> on 433 children with malignancy, identified AML as a high risk factor. The SFI rate in acute lymphoblastic leukaemia was 8.5% compared to 47% in AML. SFI was developed in 15% of patients with haematological malignancies compared to 0.9% of children with other malignancies. Finally for patients with long-term indwelling intravenous catheters the SFI rate was 39% compared with 8.5% in those without them. This risk factor does emphasize the great importance of strict aseptic management of such lines although is confounded by its greater use in higher risk patients.

*Candida* spp. are the most predominant causes of invasive fungal infections, pathogens.<sup>10</sup> In the USA, the annual incidence of *Candida* associated blood stream infections ranged from 6 to 23 per 100,000 persons<sup>22</sup> and in European countries from 2.5 to 11 per 100,000 persons.<sup>23</sup> The incidence of nosocomial blood stream infections due to *Candida* spp. from 1981 to 2005 at the National Taiwan University Hospital is shown in Figure 1.<sup>23, 24</sup> Despite advances in medical care, crude mortality rates remain, high ranging from 30% to 50%.<sup>23,24</sup> *Candida parapsilosis* occurs with high frequency in premature neonates, pediatric patients and in patients with vascular catheters<sup>23,25</sup> and *Candida tropicalis* in patients with hematological malignancy.<sup>23,26</sup> Nearly 20% of the isolates of *Candida parapsilosis* were resistant in vitro to amphotericin B, which may have an important implication in selection of an antifungal agent for this organism, which is commonly encountered in paediatric patients. In addition, persistent fungaemia in paediatric patients is associated with amphotericin B resistance.<sup>27</sup> Recently in a neonatal intensive care unit, *Candida tropicalis* had been observed as a cause of fungaemia.<sup>28</sup> Reports have shown that *Candida crusei* possesses decreased susceptibility to amphotericin B and intrinsic resistance to fluconazole has also been reported.<sup>29, 30</sup> Although cross resistance was noted within the azoles in some *Candida glabrata*, new triazoles such as voriconazole,

posaconazole and the echinocandins are active against *Candida tropicalis* and *Candida glabrata*.<sup>29,30,11</sup>

**Figure 1** Incidence of nosocomial bloodstream infections (BTI) due to *Candida* spp. among patients treated at National Taiwan University Hospital, Taiwan, 1981-2005<sup>23,24</sup>



*Aspergillus* species, chiefly *Aspergillus fumigatus* and *Aspergillus flavus* occurs predominantly in highly immunocompromised patients mainly in patients with haematological malignancies and/or those receiving haematopoietic stem cell transplantation. Environmental exposure, prolonged granulocytopenia and use of corticosteroids are the major risk factors. During the years 1999-2000 there had been an increase in the number of invasive aspergillus infections among patients with haematological malignancies while there had been a relative stability in yeast and non-aspergillus ‘mould’ infections.<sup>31</sup> In a large Italian multicentre study of invasive mould infections among patients with haematological malignancies, 65% of 14 cases of invasive aspergillosis and 69% of 310 cases of invasive aspergillosis were diagnosed in patients with AML. A significantly lower proportion of patients with haematological malignancies other than AML were affected by invasive aspergillosis, however fatality rates among other patient subgroups with haematological malignancy and invasive aspergillosis was not lower than in patients with AML.<sup>31</sup> Between 1998 and 2003, in a French survey of 88 cases of invasive aspergillosis diagnosed, patients with

haematological malignancies were the majority of the cases documented.<sup>32</sup> The majority of *Aspergillus* species were susceptible to amphotericin B, extended spectrum triazoles and the echinocandins, although *Aspergillus terreus* was considered particularly resistant to amphotericin B.<sup>29,32</sup> Reports from recent studies<sup>33,34</sup> suggested that the new triazoles, voriconazole and posaconazole were more effective than fluconazole for preventing invasive aspergillosis in patients receiving haematopoietic stem cell transplantation.

## *1.2 Amphotericin B*

A macrocyclic polyene, Amphotericin B deoxycholate (C-AmB), has been available for more than 40 years characterized in-vitro by a broad antifungal activity covering most of the fungal pathogens involved in human disease in clinical practice.<sup>35</sup> It has been the drug of choice for IFIs over other antifungal agents and it is licensed for the greatest number of indications.

During the treatment of most IFIs, resistance to amphotericin B remains uncommon. Intrinsic resistance to amphotericin B is rare in *Candida* species, however the results of a study showed a significant higher mortality in immunocompromised patients with candidaemia due to isolates with amphotericin B elevated mean inhibitory concentrations MIC > 0.8 mg/liter.<sup>36</sup> Resistance with *C. lusitana* strains and likely resistance with *C. guilliermondii* have been reported.<sup>37</sup> Elevated MIC values occur in other non-albican *Candida* species such as *C. glabrata* and *C. krusei*, but are usually still considered susceptible.<sup>38</sup> *Trichosporon* species are resistant to amphotericin B, but resistance of *Cryptococcus neoformans* to amphotericin B is rare.<sup>39</sup> Reports of clinical failure and in-vitro resistance with amphotericin B among the filamentous fungi can be seen in *Pseudoallescheria boydii*, *Fusarium* species, *Scedosporium* species, *Aspergillus terreus* and occasionally *Aspergillus flavus*.<sup>40</sup>

The conventional form of amphotericin B is well known for its acute and chronic toxicities like nephrotoxicity, hypokalaemia, elevated serum creatinine levels, fever, chills, vomiting and has consequently limited its potential use for systemic therapy.<sup>41</sup> The aim to reduce amphotericin toxicities and to improve its effectiveness during the last ten years involved several strategies including chemical modification of amphotericin B and changes in delivery systems. In this respect, three lipid formulations of amphotericin B

are currently available commercially as shown in Table 1. These lipid formulations differ in several aspects, in their lipid composition, shape, physiochemical properties<sup>42</sup> and pharmacokinetic and pharmacodynamic properties as demonstrated by several preclinical and clinical trials that reported them to be less toxic than amphotericin B (Fungizone).<sup>43</sup>

**Table 1 Lipid formulations of amphotericin B : general characteristics:<sup>42</sup> PK/PD properties<sup>42, 44,45</sup>**

Generic Name	Trade Name	FDA approval	Amphotericin B: lipid ratio	Dose (mg/kg)	Cmax (mg/l)	Vd (l/kg)	AUC (mg h/l)	Plasma Half Life(h)
AmBD	Fungizone	1958	-	0.6	1.1	5.1	17.1	27-39
ABL C	Abelect	1995	1:03	5	1.7	131	9.5	16
ABCD	Amphocil	1996	1:01	5	3.1	4.3	43	28
L-AmB	Ambisome	1997	1:09	5	83	0.11	555	8.6

Lipid formulations of amphotericin B have been licensed in many countries for the following indications.<sup>11</sup>

**ABCD (Amphocil):** for patients with aspergillosis in whom previous C-AmB therapy had failed and for invasive aspergillosis in patients in whom renal impairment or unacceptable toxicity precludes the use of C-AmB in effective doses. Approved dosage is 3-4 mg/kg per day.

**ABL C (Abelect):** for treatment of IFIs (Candidiasis included) in patients who are refractory or intolerant to C-AmB. Approved dosage is 5 mg/kg per day.

**L-AmB (Ambisome):** for treatment of systemic aspergillus and candida infections and of cryptococcal meningitis in patients positive for HIV infection, in patients in whom renal impairment or unacceptable toxicity precludes the use of C-AmB; for empirical therapy of presumed fungal infection in febrile neutropenic patients; treatment of visceral leishmaniasis. Dosage approved is 6 mg/kg per day for cryptococcal meningitis in patients with HIV infection, 3 mg/kg per day for empirical therapy in neutropenic patients and 3-5 mg/kg per day for systemic fungal infections.

Amphotericin B has been shown to be more effective for the treatment of a broad spectrum of mycoses and been extensively studied in adult patients. However data in children are more limited.<sup>46</sup> Due to the more rapid clearance in children, nephrotoxicity associated with amphotericin B is less severe in infants and children than in adults.<sup>2</sup> The advantages are increased daily doses of the parent drug, reduced toxicity and better delivery to primary reticuloendothelial organs offered by the lipid formulations of amphotericin B.<sup>46,47</sup> However, infusion related reactions and nephrotoxicity are variably reduced with L-AmB (ambisome) more than (ABLC) Abelect and more than (ABCD) Amphocil. There is little information from randomized trials other than for ambisome, and compared with Abelect and Amphocil, there is also much less need for premedication, including steroids for ambisome.<sup>19</sup> A multicentre L-AmB (ambisome) study demonstrated that nephrotoxicity was significantly less prevalent (at 10%) for 1 mg/kg ambisome and 12% for 3 mg/kg compared with a 24% incidence with C-Amb.<sup>48</sup> The results of a large review of patients who received ABLC suggested that children experienced less nephrotoxicity with the lipid formulation of amphotericin B. Elevation of serum creatinine level > 2.5 times baseline was experienced in 13% of patients aged > 18 years of age compared to only 6% in patients aged < 18 years.<sup>49</sup> The collaborative exchange of antifungal research assessed the safety and efficacy of amphotericin B lipid complex (ABLC) in 548 children who received at least four doses of ABLC. There were 54.5% (139/255) of patients that showed a complete or partial response with 39.1% for invasive aspergillosis and 58.1% for invasive candidiasis. Overall transplant patients showed a lower response rate with a complete or partial response of 47% in patients with a documented fungal infection.<sup>2</sup> A retrospective study of 46 children treated with ABLC reported a response rate of 89% against invasive candidiasis and 78% against invasive aspergillosis with an overall response rate of 83%.<sup>50</sup> Concerning infusion related reactions and nephrotoxicity, L-AmB has proven less toxic than C-AmB (19% vs. 34%).<sup>51</sup> A randomized comparative study<sup>52</sup> on L-AmB 5 mg/day with C-AmB 1mg/kg per day in patients with invasive fungal infection and neutropenia suggested an improved response with L-AmB compared with C-AmB. The overall response rate was 52% for L-AmB and 29% in C-AmB in patients with suspected or documented invasive aspergillosis. At completion of therapy a complete response of 64% was in seen in

patients receiving L-AmB and 17% in patients receiving C-AmB. A large randomized double blind trial<sup>53</sup> compared L-AmB at two doses 3 and 5 mg/kg per day with ABLC (Abelect) at 5 mg/kg per day. Infusion related reactions occurred more than three times as often with ABLC compared to L-AmB and the incidence of hypoxia was higher in ABLC than seen with C-AmB and also a doubling of creatinine occurred in 42% of Abelect cases compared with 14.1% for L-AmB 3 mg/kg and 14.8% for L-AmB 5mg/kg.

### *1.3 Echinocandins*

A new class of antifungals, the echinocandins has recently been developed. These are semi synthetic amphiphilic lipopeptides, products of cyclopentamine, formed during the fermentation of fungi such as *Aspergillus nidulans* var. *echinulatus* or *Zalerion arboricola*.<sup>54</sup> They exert selective antifungal activity by non-competitive inhibition of 1,3- $\beta$ -glucan synthase and thus interfering with the cell wall biosynthesis.<sup>55,56,57</sup> Thus glucans play a key role in cell division and cell growth and provide structural integrity to the fungal cell wall by forming a fibril of three helically-entwined linear polysachharides.<sup>58,59</sup> Selective inhibition of glucan synthesis enzyme complies results in fungicidal activity against candida and fungistatic against aspergillus.<sup>57,60</sup>

Echinocandins have variable activity against dematiaceous fungi and the endemic dimorphic pathogens in addition to activity against candida and aspergillus.<sup>56,57</sup> *Fusarium* and other hyalohyphomycetes, *Candida neoformans*, *Trichosporum* spp, and other Zygomycetes are inactive against echinocandins.<sup>57</sup> There are limited data on echinocandin resistance and this will need to be monitored with continued widespread use. Among *Candida* spp. and *Aspergillus* spp. primary resistance to echinocandins appears extremely uncommon.<sup>55</sup> In laboratory derived mutants of *sachromyces cerevisiae*, resistance has been shown to occur via mutations in the genes that encode for the  $\beta$ -glucan synthase complex.<sup>57</sup> Notable fluconazole resistant strains of *Candida* spp are active against echinocandins.<sup>61,62</sup>

The echinocandins currently in use are listed below.<sup>10</sup>

**Caspofungin:** approved in 2001 by the FDA for the treatment of patients with invasive aspergillosis who are refractory to other antifungal treatments. It was also approved subsequently for treatment of peritonitis, intra abdominal abscesses, oesophageal candidiasis, and pleural space infections caused by *Candida* spp., and for the treatment of fever in patients with neutropenia.

**Micafungin:** first available in 2005 when it was approved for the treatment of oesophageal candidiasis and prophylaxis in patients undergoing stem cell transplantation.

**Anidulafungin:** approved in 2006 for the use in the treatment of oesophageal candidaemia, peritonitis, oesophageal candidiasis and intra-abdominal abscesses due to *Candida* spp.

All the above agents are water soluble and are available only for IV use.<sup>63</sup> Echinocandins have dose-dependent linear pharmacokinetics and are highly protein bound.<sup>64</sup> Although the concentrations in cerebrospinal fluid are low, the echinocandins are broadly distributed to all major organs.<sup>65</sup> Metabolism occurs by a cytochrome p-450 independent mechanism in the liver and excretion of inactive metabolites is in the faeces and urine and excretion of the active form is less than 2%.<sup>65</sup> The new agents broaden the choice of agents and the decision to use them has to be developed on clinical and pharmacoeconomic benefits.

### 1.3.1 Caspofungin

Caspofungin has potent in-vitro inhibitory activity against *Aspergillus* spp. and moderate activity against other moulds such as *H. capsulatum*, *C. immitis* and *B. dermatidis* and also against *Pneumocystis jiroveci* and dematiaceous fungi. However, it has no activity against *C. neoformans*, *Trichosporon* spp., *Fusarium* spp., hyalohyphomycetes, zygomycetes and *Sporothrix schenckii*.<sup>62,66</sup> Caspofungin has linear pharmacokinetics, is not metabolized by the CYP isoenzyme system<sup>56</sup> and is primarily excreted by the liver.<sup>61</sup> Casopofungin is fungicidal and highly active in-vitro against most isolates of *Candida* Spp.<sup>67,68</sup> There is no known maximum tolerated dose and no toxicity defined maximum length of therapy at present.<sup>56</sup>

In a randomized double-blind study<sup>69</sup> comparing caspofungin and fluconazole in the treatment of oesophageal candidiasis the clinical response rate was 81% for caspofungin vs. 85% for fluconazole and for activity against *Candida glabrata* the response rate was 93% vs. 67% for caspofungin and fluconazole respectively. Another randomized double blinded study<sup>70</sup> compared caspofungin with amphotericin B for the treatment of oesophageal candidiasis and the clinical response rate for caspofungin was 74% (34 mg), 91% (50 mg), 82% (70 mg) and the clinical response for amphotericin B was 63%.

Two studies<sup>71,72</sup> on the efficacy of caspofungin as salvage therapy for the treatment of aspergillosis showed a favorable response of 45% in one study<sup>71</sup> and 44% partial or complete response in a second study.<sup>72</sup> Only in cases of advanced insufficiency (Child-Pugh scores 7-9) the dose should be adjusted, as caspofungin is not nephrotoxic.<sup>73</sup> It has very few serious side effects and those reported include headache, fever, nausea, rash, elevation of hepatic enzyme levels and phlebitis at the site of infusion.<sup>10</sup> No significant differences in adverse effects between caspofungin and fluconazole were found in a trial comparing caspofungin IV (50 mg daily) and fluconazole IV (200 mg daily) for esophageal candidiasis.<sup>69</sup> Caspofungin has few significant drug interactions.<sup>74</sup> It has been suggested that caspofungin with cyclosporine and tacrolimus caused elevated liver enzymes.<sup>75</sup> However, this claim has been disputed by recent studies.<sup>76</sup>

### 1.3.2 Micafungin

Micafungin is an FDA approved antifungal agent that acts by inhibiting 1,3- $\beta$ -D-glucan synthesis in the fungal cell wall.<sup>77</sup> Micafungin has the same spectrum of antifungal activity as caspofungin. A study by Erica et al. demonstrated that micafungin exhibited potent in-vitro activity against *C. glabrata* and was effective against azole-resistant strains.<sup>78</sup> It is metabolised in the liver with <1% of the intact drug unchanged in urine and is excreted in an inactive form in bile and faeces.<sup>79</sup> A multicentre open label dose comparison study<sup>80</sup> on micafungin in the treatment of deep-seated mycoses showed a clinical response rate of 60% in invasive pulmonary aspergillosis, 67% in chronic necrotising pulmonary aspergillosis, 55% in pulmonary aspergilloma and 100% in candidaemia. Another multicentre randomised double blind study,<sup>81</sup> compared

micafungin with fluconazole for the treatment of oesophageal candidiasis and the endoscopic cure rate was 87.7% vs. 88% respectively.

The results of a multicentre open label study<sup>82</sup> on micafungin showed a clinical response rate of 83.2% for the treatment of invasive candidiasis. Micafungin has few side effects including nausea, vomiting, headache, phlebitis, diarrhoea and leukopenia. In addition symptoms like rash, facial swelling, haemolysis and vasodilatation have been reported.

It interacts with nifedepine and sirolimus but it appears not to interact with cyclosporine or tacrolimus.<sup>74</sup> However, a recent study<sup>83</sup> has suggested that cyclosporine levels should be monitored because micafungin is a mild inhibitor of cyclosporine metabolism. No other interactions have been described for micafungin.

### 1.3.3 Anidulafungin

Anidulafungin is the newest echinocandin antifungal drug approved for use in the USA and is most active in invasive fungal infections.<sup>84</sup> It has a half life of 25 to 42 hours and no dose adjustment in renal failure or hepatic failure is required. The recommended daily dose is 200/100 loading dose/daily maintenance dose (in mg).<sup>85</sup> A wide range of *Candida* spp., including species resistant to Amphotericin B (*Candida lusitanae*), azoles (*Candida crusei*) and other echinocandins (*C. parapsilosis*) are sensitive to anidulafungin<sup>86,87</sup> and also is highly active against *Aspergillus* spp.<sup>87</sup>

An open label randomized study<sup>88</sup> for the treatment of oesophageal candidiasis, anidulafungin showed an endoscopic success rate of 85%. Another open label dose ranging study<sup>89</sup> on anidulafungin for the treatment of candidemia and invasive candidiasis showed a clinical response rate of 84% for 50 mg/day, 90% for 75 mg/day and 89% for 100 mg/day. Anidulafungin is a well tolerated drug with few side effects like hypotension, fever, constipation, nausea, vomiting, hypokalemia and elevated hepatic enzymes.<sup>90</sup> If anidulafungin is administered rapidly histamine like reactions (hypotension, dyspnoea, flushing ) arise.<sup>90,63</sup>

## 1.4 Azoles

The azole antifungals are categorized into two broad classes, imidazoles and triazoles which differ in terms of their chemical structure. Among the imidazoles only ketoconazole has systemic activity and all triazoles have systemic activity. Triazoles include fluconazole, itraconazole, voriconazole, posaconazole and ravuconazole.<sup>91</sup> The newer triazole antifungals (voriconazole, posaconazole and ravuconazole) have good activity against fluconazole resistant and itraconazole resistant *Candida* spp. and moulds.<sup>2</sup>

They inhibit fungal lanosterol 14- $\alpha$ -demethylase, which catalyses a late step in ergosterol biosynthesis leading to accumulation of methylated sterols in the fungal cell membrane and depletion of ergosterol.<sup>92</sup> Both groups have similar antifungal spectra and mechanism of action, but the triazoles are more slowly metabolized and have less effect on human sterol synthesis than the imidazoles. Intrinsic azole resistances such as *C. glabrata* and *C. krusei* have become more common with the increased use of fluconazole prophylaxis. In *Candida* spp., three mechanisms of azole resistance have been described: alteration of the target lanosterol 14- $\alpha$ -demethylase, reduced azole accumulation through active efflux and mutation in the ergosterol pathway allowing for the accumulation of less toxic sterols in the presence of azoles.<sup>93</sup> The introduction of ketoconazole in the early 1980s allowed outpatient therapy for several endemic mycoses, notably histoplasmosis, blastomycosis, and coccidioidomycosis. At higher doses, ketoconazole could have significant toxicity but overall it was a safer drug than amphotericin B.<sup>94</sup> In the 1990's outpatient therapy for most endemic mycoses with a low incidence of toxicity had been enabled by triazoles.<sup>95</sup> These drugs were more easily administered and less toxic but cross resistance in *Candida* spp. was possible as the mechanism of actions of all triazoles is similar and such resistance was observed from paediatric HIV infected patients in isolates of *C. albicans*.<sup>96</sup>

### 1.4.1 Fluconazole

Fluconazole is fungistatic and the activity of fluconazole is concentration-independent and does not increase once the maximum fungistatic concentration is attained.<sup>97</sup> It has a broad-spectrum antifungal activity and has proven efficacy against *Cryptococcus neoformans* and several *Candida* species and has been used with various levels of success

against blastomycosis, histoplasmosis, sporotrichosis, and coccidioidomycosis.<sup>98</sup> Fluconazole has been used to treat patients with cryptococcal meningitis, oesophageal candidiasis, oropharyngeal candidiasis and chronic disseminated candidiasis.<sup>99</sup> It has better bioavailability (90%) in oral form than in intravenous form. Studies on fluconazole treatment in children outside the neonatal period are very few and the majority of the data is derived from studies performed in adults. In an open, prospective randomized study<sup>100</sup> fluconazole was found to be safe and effective in preventing invasive *Candida* infections in 50 children undergoing chemotherapy for cancer. There was a significant difference in the pharmacokinetics of fluconazole between adults and children. Brammer et al.<sup>101</sup> reviewed five separate fluconazole pharmacokinetic studies which included 101 infants and children ranging from 2 weeks to 16 years. The results of this study demonstrated that fluconazole clearance was more rapid in children than adults. Compared to adults (30 hrs) the mean plasma half life of fluconazole was 20 hrs in children which suggested that the daily fluconazole dose needed to be approximately doubled for children over three months of age to 6-12 mg/kg/day. A recent study by Bodey et al.<sup>102</sup> demonstrated that fluconazole is equally effective but less toxic than amphotericin B for prophylaxis in inpatients with leukemia. The use of fluconazole has fewer side effects and is limited to nausea, vomiting, anorexia, rash and a mild elevation of hepatic enzyme levels.<sup>103</sup>

#### 1.4.2 Itraconazole

Itraconazole is widely used for a variety of serious fungal infections including *Aspergillus*, *Cryptococcus*, *Candida*, *Blastomyces*, disseminated *Penicillium mameffei* and *Histoplasma capsulatum*.<sup>104</sup> The mechanism of action is described as the impairment of the synthesis of ergosterol, an essential component of the fungal cell membrane.<sup>105</sup> The major metabolite, hydroxyl-itraconazole is assumed to be equivalent to that of itraconazole in its antifungal activity.<sup>106</sup> Because itraconazole is insoluble in aqueous media,<sup>107</sup> it is orally administered and there is an urgent need for an intravenous formulation. The oral suspension is better absorbed on an empty stomach but administration of a capsular formulation with food increases absorption.<sup>108</sup> There is no need for dosage adjustment in the presence of renal function impairment because elimination of itraconazole is primarily hepatic.<sup>109</sup> Itraconazole has less nephrotoxicity

than amphotericin B and compared to other conventional antifungal agents it has a broader spectrum of activity than fluconazole.<sup>110</sup> It is well tolerated and a recent study reported that 10% of the subjects had nausea, vomiting and elevated transaminases occurred in 5% of the subjects.<sup>111</sup> Important interactions occur with itraconazole and concomitant use with cyclophosphamide should be discouraged and prior or concurrent use of rifampin, carbamazepine, phenytoin and phenobarbital should be avoided.<sup>112</sup> Compared to adults, children need twice daily dosing of itraconazole. This is supported by a study of 26 children < 12 years of age which reported that 5 mg/kg once daily dosing led to substantially lower serum levels in children (especially in children < 2 years of age).<sup>113</sup> A recent randomized trial which compared fluconazole and itraconazole reported similar overall clinical and mycological results and more importantly there were no serious side effects with either antifungal.<sup>114</sup>

### *1.5 Extended spectrum triazoles*

The mechanism of action of second generation triazoles is by inhibition of cytochrome P450(CYP450) dependent conversion of lanosterol to ergosterol which leads to an accumulation of toxic 14- $\alpha$ -methylsterols and a depletion of membrane associated ergosterol which results in inhibition of cell growth or cell death.<sup>2</sup> Voriconazole which was approved for the treatment of fungal infections in 2002 and posaconazole which received US Food and Drug Administration (FDA) approval in September 2006 are the antifungal agents included in this class. Clinical trials of ravuconazole have not yet been completed.<sup>115</sup>

#### 1.5.1 Voriconazole

Voriconazole (V Fend;Pfizer Inc) is a newer extended spectrum triazole available in both oral and intravenous formulations.<sup>116,117</sup> Voriconazole combines the increased bioavailability of fluconazole with the broad spectrum antifungal activity of itraconazole. It has a very broad spectrum antifungal activity that includes *Candida* spp. *C. neoformans*, *Aspergillus* spp. *Trichosporon* spp. *Fusarium* spp. and other hyaline moulds, the endemic dimorphic fungi and dematiaceous fungi.<sup>118</sup> It is fungistatic against *Candida* species and fungicidal against *Aspergillus*.<sup>119,120</sup> Voriconazole encompasses anticandidal activity of

strains of *C. albicans* and *C. glabrata* and *C. Krusei* and most, but not all with decreased susceptibility to fluconazole.<sup>30</sup> Voriconazole is also active against fungi that are resistant to amphotericin B, including *A. terreus* and *P. boydii*.<sup>121</sup> The drug is not active against Zygomycetes and in patients receiving VCZ as prophylaxis, it has been reported that an increased number of breakthrough infections due to Zygomycetes are seen.<sup>122</sup>

Voriconazole is well absorbed orally and has an excellent bioavailability of more than 90%.<sup>123, 124</sup> The IV preparation is solubilized in sulfobutyl ether  $\beta$ -cyclodextrin sodium which is secreted by the kidneys, necessitating dose adaptation in cases of renal impairment<sup>125</sup> and is administered twice a day at a dose of 3 to 6 mg/kg.<sup>126</sup> Following oral administration steady state plasma levels range from 2 to 3  $\mu$ g/ml and 3 to 6  $\mu$ g/ml after intravenous infusion.<sup>126</sup> VCZ has excellent penetration into the central nervous system as well as other tissues and is 58% protein-bound.<sup>64</sup> It is extensively metabolized in the liver via the cytochrome p-450 enzyme family and less than 5% of a dose is excreted unchanged in urine.<sup>64, 123</sup> Some of the population are poor metabolizers and some are extensive metabolizers due to point mutation in the gene encoding CYP2C19.<sup>127</sup> About 20% of non-indian Asians and 5-7% of Caucasians have a deficiency in expressing this enzyme. As a result in these subjects voriconazole levels are as much as 4-fold greater than for homozygous subjects who metabolize the drug more extensively.<sup>128</sup>

For primary therapy of invasive aspergillosis VCZ has added a new and improved therapeutic option and has become the drug of choice for this entity.<sup>129</sup> In febrile neutropenic patients VCZ is often used as empirical treatment of fever, although it failed to gain approval for this indication by the US Food and Drug Administration (FDA).<sup>130</sup> With no apparent post antifungal effect VCZ exhibits concentration-independent fungistatic activity against *Candida* spp. and *C. neoformans*.<sup>131</sup> An AUC: MIC ratio of 20-25:1 was indicated by recent in-vivo studies of disseminated *C. albicans* infection for treatment success.<sup>132</sup> In contrast, based on both time-kill studies VCZ appears to exert a dose-dependent fungicidal effect on *Aspergillus*<sup>120,119</sup> and clearance of fungal burden in target organs of animal models of invasive aspergillosis.<sup>133</sup>

In patients intolerant of, or with infections refractory to other antifungal agents,<sup>123</sup> VCZ is approved for the primary treatment of invasive aspergillosis and for treatment of infections due to *P. boydii* and *Fusarium* Spp.<sup>134</sup> For the primary treatment of aspergillosis VCZ is superior than amphotericin B deoxycholate<sup>134</sup> and in an open label multicenter study<sup>129</sup> of 116 patients with invasive aspergillosis a similar positive experience of VCZ was noted (at week 12 of treatment a complete or partial response of 53% versus 32% and a survival rate of 71% versus 58%). Likewise, approximately 40% of patients were successfully treated with VCZ as reported in a study of 422 patients with invasive aspergillosis.<sup>135</sup>

Despite documented efficacy in the treatment of invasive aspergillosis and the prevention of breakthrough fungal infection in the same patient population, VCZ has not been approved anywhere for empirical treatment of febrile neutropenic patients.<sup>123, 134</sup> VCZ is generally well tolerated and has few side effects, the most common of which are visual disturbances, mild elevation of transaminases and gastrointestinal symptoms.<sup>126</sup> Other adverse effects include skin reactions which are less than 10% prevalent. Vomiting, diarrhea, abdominal pain and headache are also reported.<sup>64,134</sup> Reversible disturbance of vision (photophobia), which occurs in 30% of patients is the most common side effect but is transient. A 50% reduction in VCZ dose was recommended for patients with mild to moderate hepatic dysfunction, whilst in patients with severe hepatic failure its use is contraindicated.<sup>10</sup>

Discontinuation of the drug is rarely necessary as these side effects are reversible.<sup>122</sup> However, in a very small number of patients, severe reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported.<sup>117,123</sup> Five patients who developed facial erythema and cheilitis have been described; one of these patients also developed lesions similar to those characteristic of discoid lupus erythematosus.<sup>136</sup> With increased serum voriconazole levels the risk of developing hepatitis appears to increase.<sup>137</sup>

### 1.5.2 Posaconazole

Posaconazole (PCZ) is a hydroxylated analogue of itraconazole.<sup>10</sup> It first became available in Europe in 2005 and was approved by the FDA in September 2006 for the

treatment of oropharyngeal candidiasis in HIV-positive patients.<sup>115</sup> In addition, to these indications, The European Commission also approved PCZ as first line therapy for the treatment of invasive aspergillosis, fusariosis, chromoblastomycosis, mycetoma and coccidioidomycosis infections in patients who are intolerant of certain commonly used antifungal agents.<sup>115</sup> As indicated by the findings of time-kill studies,<sup>138</sup> PCZ exhibits fungicidal activity against specific species of yeasts.<sup>138,139</sup> It has a fungicidal activity against *Aspergillus* spp and is also fungicidal against *C. inconspicua*, *C. kefyr*, *C. Krusei*, *C. lusitaniae* and *C. neoformans*. But it is fungistatic against *C albicans*, *C guillermondi*, *C glabrata*, *C parapsilosis* and *C tropicalis*.<sup>138,140</sup> The activity of PCZ against Zygomycetes is the major difference between PCZ and voriconazole and PCZ is the only antifungal agent besides AMB that is active against these fungi.<sup>10</sup> PCZ has a prolonged post-antifungal effect against *C albicans* (20-30 hours) in-vivo.<sup>141</sup> PCZ is available only in an oral formulation (400-800 mg/day in divided doses). Its oral availability is increased by administering PCZ with a meal, in a suspension rather than a tablet and in divided doses and is excreted mainly in the faeces and a minor portion is metabolized in the liver through glucoronidation.<sup>142</sup> Dependent on the number of daily doses, the bioavailability of PCZ is high but variable.<sup>143</sup> An intravenous form of PCZ has been developed as a prodrug, but because of its poor aqueous solubility, it has not yet been evaluated in human clinical trials.<sup>144,145</sup> Drug interactions can occur due to the ability of PCZ to inhibit the CYP3A4 isoenzyme and its function as a substrate for P-glycoprotein.<sup>146</sup> Coadministration of tacrolimus with posaconazole has been found to significantly increase exposure to tacrolimus.<sup>147</sup> In heart transplant recipients, a cyclosporine dose reduction of up to 28.6% was required due to the interaction between cyclosporine and PCZ.<sup>148</sup> Coadministration of PCZ with cimetidine, phenytoin and rifabutin is not recommended as PCZ concentrations are lowered by the above drugs.<sup>142</sup>

A multicentred, randomized study<sup>33</sup> for prophylaxis in neutropenia in 602 patients compared a dose of 200 mg three times a day of PCZ for 12 weeks with fluconazole and itraconazole and the results suggested that PCZ was superior to fluconazole and itraconazole in prevention and improved overall survival. Another multicentred, randomized study<sup>34</sup> on prophylaxis in graft-versus-host disease, demonstrated that PCZ was similar to fluconazole in all fungal infections and also superior to fluconazole in

preventing proven or probable aspergillosis (2.3% vs.7.0%). Overall success rate of 42% and a survival rate of 79% were shown in two salvage studies.<sup>149,150</sup>

The acquisition cost of PCZ based on the 2007 average wholesale price in US dollars, was found to be (200 mg three times a day) \$82.30 per day for prophylaxis of IFIs which is higher than the acquisition cost of fluconazole (400 mg four times a day; \$28.80 per day) or itraconazole (200 mg twice a day; \$39.80 per day).<sup>151</sup> At the dosages commonly used in the treatment of fungal infections, the acquisition costs of PCZ 200 mg three times a day and voriconazole 200-300 mg twice a day were \$82.30 per day and \$74.30 to \$111.50 per day respectively.<sup>151</sup> Further pharmacoeconomic studies are needed to determine which agent is cost effective in these infections.

### 1.5.3 Ravuconazole

Ravuconazole is an investigational triazole currently undergoing phase 2 clinical trials as an oral agent, but to optimize its therapeutic potential, development of an intravenous formulation was deemed necessary. An approach using a water-soluble prodrug was employed to develop an IV formulation, since the development of intravenous administration of ravuconazole was precluded by its poor solubility.

Ravuconazole is a potent and broad spectrum antifungal agent with an excellent antifungal activity against fungal pathogens such as *C. albicans*, *Cryptococcus neoformans*. However several species of Mucorales, *Fusarium* and *Scedosporium prolificans* are not sensitive to ravuconazole. The drug is highly active against *Aspergillus* spp. and has inhibitory activity for other species of hyaline filamentous fungi, black moulds and zygomycetes as indicated by an in-vitro study.<sup>152</sup> Evaluating the activity of ravuconazole against 923 clinical isolates of non-dermatophyte filamentous fungi ravuconazole was active against 56.2% of mucorales tested whereas only one third were sensitive to itraconazole and almost the whole collection of mucorales was not sensitive to voriconazole. To date, no trials in humans using ravuconazole as treatment for IFIs have been published.<sup>10</sup>

## 1.6 Drug Audit

According to World Health Organisation (WHO), drugs are frequently not used according to usually accepted criteria, nor used to their full potential.<sup>153</sup> It has been recognised long ago that there is a need for drug audit to assess and improve the quality of medical care.<sup>154,155</sup> When considering the appropriateness of drug usage, the prescribing habits of physicians are important as they regulate drug consumption. Differences in drug consumption patterns between similar populations in developed countries and the mortality and/or morbidity following inappropriate use of drug/s, adverse reactions and antimicrobial resistance have often been attributed to physicians. An important service of drug usage review/evaluation (DUR/DUE) is being provided by Pharmacists. The outcomes of these assessments often lead to improvements in cost-effective prescribing and better utilisation of limited resources. As organisations are searching for methods of reducing their costs, this service is high in demand. A typical drug evaluation process generally involves a Pharmacist screening the literature and clinical data, developing and gaining agreement on practice guidelines in conjunction with other related departments and evaluating the collected data against it. The results of the review will be presented to the prescribers and methods to modify prescribing behaviour sought and then evaluated.<sup>156</sup>

Using a Pharmacy based review, Folli et al<sup>157</sup> identified physician ordering errors in two paediatric hospitals. They found that paediatric intensive care unit patients and paediatric patients younger than two years were particularly susceptible to errors, most of them were dosing errors.<sup>158</sup> Of 10788 medication orders written for 1020 patients, 616 (5.7%) orders involved an error of drug ordering, transcribing, dispensing, administering or monitoring. There were five (0.8%) preventable adverse effects, 115 (18.6%) potential adverse drug events and 486 (80.5%) errors with relatively little potential for harm. A total of 320 (31%) patients experienced a medication error; 118 (12%) patients experienced two or more errors. The majority of errors occurred at the ordering stage (77.8%), followed by administering (12.8%) and transcribing (5.8%). The most frequent type of medication errors were dosing errors (28.4%).<sup>159</sup>

Adverse drug events and medication errors are serious problems in paediatrics. Compared with adults the relatively higher rates of potentially harmful errors in hospitalised children are more complex in paediatrics and underscore the need for safer systems in this setting. However, until recently the incidence of paediatric medication errors has received relatively little scrutiny compared with adults and even less has been done to assess their preventability.<sup>159</sup>

### *1.7 Drug utilisation review*

Drug utilisation review is a quality assurance approach for the facility per se, and it involves the setting of criteria and standards, an assessment phase using a set of screening criteria and a follow-up correctional phase with the prescriber. It comprises of all aspects of drug treatment from the time a patient presents to a prescriber, to the final outcome of the therapy.<sup>160</sup>

#### Objectives of quality assurance activities

The objectives of this activity are to ensure appropriate, safe and cost-effective drug therapy by achieving quality drug use and patient care. The outcomes of drug use are improved by<sup>161</sup>

- determining drug usage and prescribing patterns
- developing criteria and standards which explain optimal drug use
- promoting rational therapy through education and by the provision of drug information and advice
- carrying out regular drug use audits to evaluate the appropriateness of drug use and characterise inappropriateness
- minimising the risk of adverse drug events caused by inappropriate drug use
- promoting economical drug use by reducing wastage and unnecessary drug and drug related expenditure
- providing feedback of DUE results to prescribers, managers and other relevant groups

Data sources commonly available within the hospitals are patient demographics, clinical and administrative data. The demographic data available such as age, sex, disease, average length of stay etc; clinical data such as patient charts, admission records, adverse drug reaction reports, microbiology/infection control data etc and finally administrative data such as drug purchasing, drug utilisation, equipment purchasing, utilisation and cost per adjusted hospital bed day data etc.<sup>162</sup>

### 1.7.1 Benefits of DUE programs<sup>163</sup>

Area of practice	Perceived benefits
Hospital and government administrators	<ul style="list-style-type: none"> <li>Cost savings</li> <li>Potential to justify expenditure/identify efficiencies</li> <li>Embraces the concept of Total Quality Management</li> <li>In some countries, hospitals require a formal DUE program in place to achieve accreditation</li> </ul>
Hospital pharmacists	<ul style="list-style-type: none"> <li>Extends opportunities for pharmaceutical care</li> <li>Provides a leadership role within a multidisciplinary team</li> <li>Contributes to cost justification of clinical pharmacy services</li> </ul>
Other health professionals	<ul style="list-style-type: none"> <li>Increase potential to prevent adverse drug reactions or iatrogenic disease</li> <li>Recognizes the 'added value' applied by pharmacists to the drug use process</li> <li>Education</li> </ul>
Patients	<ul style="list-style-type: none"> <li>Improved quality care</li> </ul>

## *1.8 Study Objectives*

To retrospectively evaluate Intravenous antifungal medications in paediatric patients in a public hospital for children. This will be achieved by retrospectively evaluating

- Dose and the duration of antifungals prescribed
- Infusion related reactions and adverse effects
- Potassium level, serum creatinine and urea levels, liver function tests
- Fever management
- Adherence to hospital guidelines
- Cost of antifungal treatment

where appropriate recommendations will be made to improve patient outcomes and minimise hospital costs.

## 2 METHODOLOGY

A retrospective study was conducted at Princess Margaret Hospital for Children (PMH), Subiaco, Western Australia a 250-bed paediatric hospital.

### 2.1 *Sample selection*

All paediatric patients prescribed intravenous antifungal treatment over one year period (July 2006 to 30<sup>th</sup> June 2007) at PMH were evaluated retrospectively.

### 2.2 *Data collection*

The data related to antifungal prescribing was collected from the medical records into a coded prepared form. The drug charts and nursing notes were reviewed for each day in the records. The following data were collected for each patient prescribed IV antifungal drugs. Gender, age, weight, basic diagnosis, fungal infection (aspergillosis, candidiasis etc), dosing information, dose changes, duration of antifungal treatment, creatinine level, liver function tests, potassium levels, temperature, length of stay, recommencement of dosage of oral fluconazole and L-AmB, infusion related reactions and adverse effects. Antifungal treatment costs and estimated daily cost per patient were calculated. Details of drug expenditure were obtained from the purchasing records of the Department of Pharmacy. Costs did not include hospitalisation costs.

### 2.3 *Costs of Pharmacy prepared and ward prepared IV antifungals*

The hospital pharmacy Central Intravenous Additive Service (CIVAS) and the ward preparation costs of antifungal infusions were determined by including the labour costs of pharmacists, pharmacy technicians or nurses (includes checking by a second nurse) for the preparation of each antifungal dose and the cost of consumables for the pharmacy. A 2% waste of vial contents on reconstitution was also included for L-AmB. The weekend cost included an additional 75% Saturday and 100% Sunday loading to the normal labour cost calculated for the preparation. An additional estimated cost of \$4 was included for consumables such as plastic syringes and needles. As there were only four patients on C-AmB on different days of the year, the cost of the required vials was included.

Reconstituted vials must not be retained, so the cost of one vial was included for the doses of caspofungin and voriconazole in the pharmacy and ward setting. Costs are presented in Australian dollars.

#### *2.4 Data Analysis*

The data collected was evaluated against the Australian Therapeutic Guidelines Antibiotics Version 13<sup>164</sup> and hospital in-house guidelines for antifungal therapy obtained from the Microbiology Department at PMH.

#### *2.5 Statistical Analysis*

Statistical analysis of the data was performed using the SPSS 15 statistical software package for windows.

#### *2.6 Data Storage*

Each patient was identified by a code number hence their identity remained anonymous. The code was maintained by the Chief Pharmacist of the Pharmacy Department at PMH.

#### *2.7 Ethical issues*

The study involved the collection and analysis of patient data, therefore ethical approval was obtained from Curtin University of Technology Human Research Ethics Committee and an approval on the GEKO system (Governance Evidence Knowledge Outcome) from PMH which covers audit activity. As this study involved the analysis of patient records, ethical issues arise in relation to confidentiality and release of data. A unique non-patient identifiable code was allocated to each record to enable re-identification of the record if necessary. The key to the code was held at all times by the Chief Pharmacist of PMH. Any coded data to leave the hospital was kept secure in accord with National Health and Medical Research Council guidelines and only group data will be released from the research.

### 3.1 Demographic data

The baseline characteristics of the 59 patients included in the study are presented in Table 2. The majority of patients were male (40) and 19 female patients. All patients who were  $\leq 16$  years of age were included in the study; the median age was four years (Table 3), the minimum age was three months and the maximum was 16 years. The mean age of the patients was 5.88 years, being somewhat above the median value. The median weight of the patients included in this study was 16.8 kg., where the weight varied from a minimum weight of 750 grams to a maximum of 63.6 kg. The mean weight was found to be 22.9 kg. The doses of the antifungals were calculated according to the actual weight of the patients.

**Table 2** Patient gender

Gender	Number of patients(%)
Male	40 (67.8)
Female	19 (32.2)
Total	59

**Table 3** Age and weight of the patient cohort

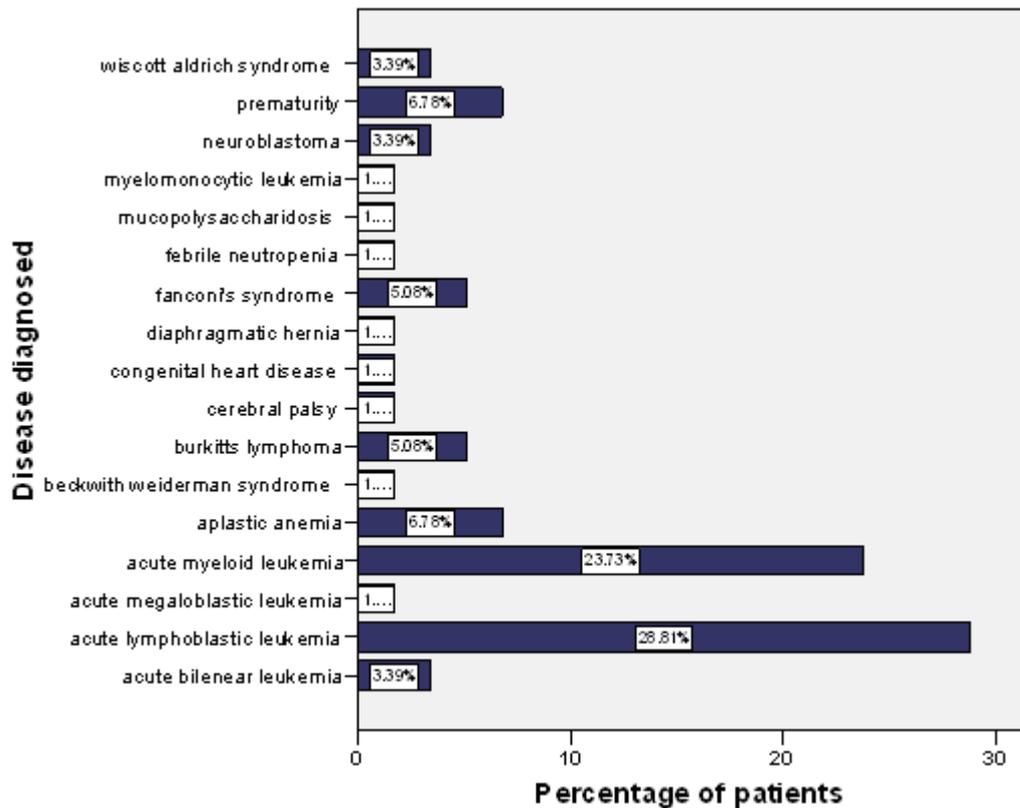
Descriptive	Age ( years)	Weight (kg)
Minimum	0.03	0.75
Maximum	16	63.6
Mean	5.88	22.9
Median	4	16.8
Std.deviation	5.02	16.7

### 3.2 Disease diagnosed

The principal diagnosis of the patients is summarized in the Figure 2. The most frequent disease diagnosed was leukaemia which constituted 28.8% of patients with acute

lymphoblastic leukaemia and 23.7% with acute myeloid leukaemia 6.76% of the patients were premature. In addition, 6.76% of patients had aplastic anaemia. Burkitts lymphoma and Fanconis syndrome was diagnosed in 5.08% of patients. Other diseases diagnosed in patients who were included in this study were myelomonocytic leukemia, febrile neutropenia, diaphragmatic hernia, cerebral palsy, Beckwith-Weiderman syndrome and congenital heart disease.

**Figure 2 Basic diagnosis of disease in patients who were prescribed IV antifungal medication n=59**



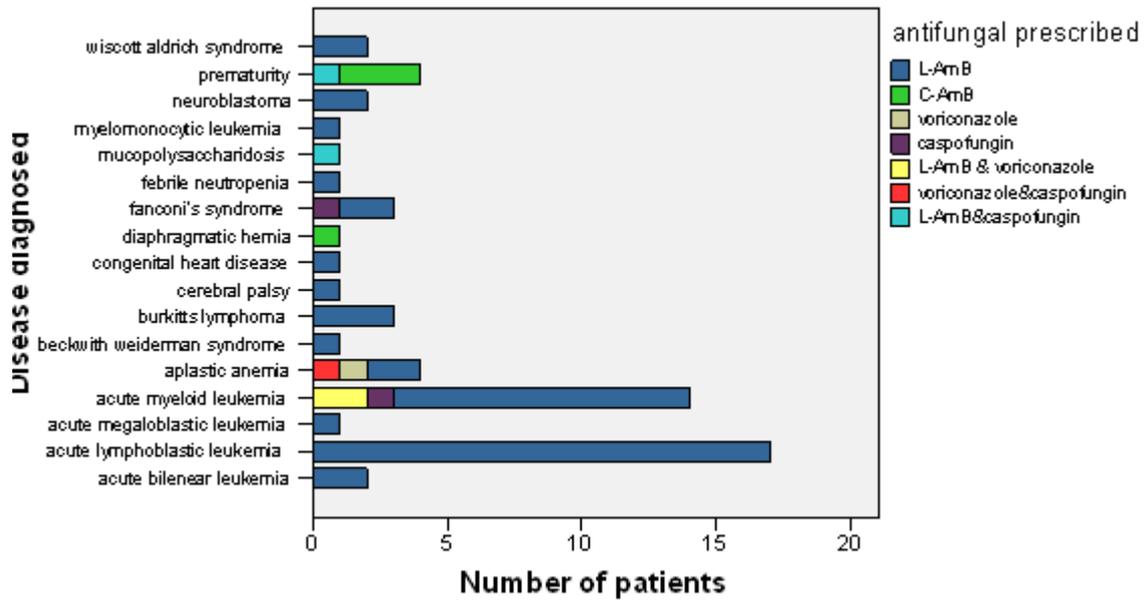
**Table 4** Antifungals prescribed for all patients included in the study

<b>Antifungal prescribed</b>	<b>Number of patients</b>	<b>Percentage of patients</b>
L-AmB	47	79.7
C-AmB	4	6.8
Voriconazole	1	1.7
Caspofungin	2	3.4
L-AmB +voriconazole	2	3.4
L-AmB +caspofungin	2	3.4
Voriconazole+c aspo fungin	1	1.7

### *3.3 Antifungal medications prescribed for principal diagnosis*

As discussed earlier, the findings of this study have indicated that L-AmB was the most frequently prescribed antifungal. Caspofungin, combination of L-AmB and voriconazole along with L-AmB were the drugs used in patients with acute myeloid leukaemia. Voriconazole and combination of voriconazole and caspofungin was used in the treatment of a patient with aplastic anaemia. Caspofungin was used in the treatment of a patient with acute myeloid leukaemia and fanconis syndrome and as a combination product. L-AmB and caspofungin was prescribed for patients with mucopolysaccharidosis and in prematurity. Prematurity and mucopolysaccharidosis was the basic diagnosis for the four patients who were prescribed C-AmB (Figure 3). Overall the data suggests that according to the hospital oncology ward protocol a dose of 3 mg/kg/day of L-AmB was the dose recommended for all treatment.

**Figure 3 Antifungal medication prescribed for the basic diagnosed disease**



### 3.4 Gender and duration of IV antifungal treatment

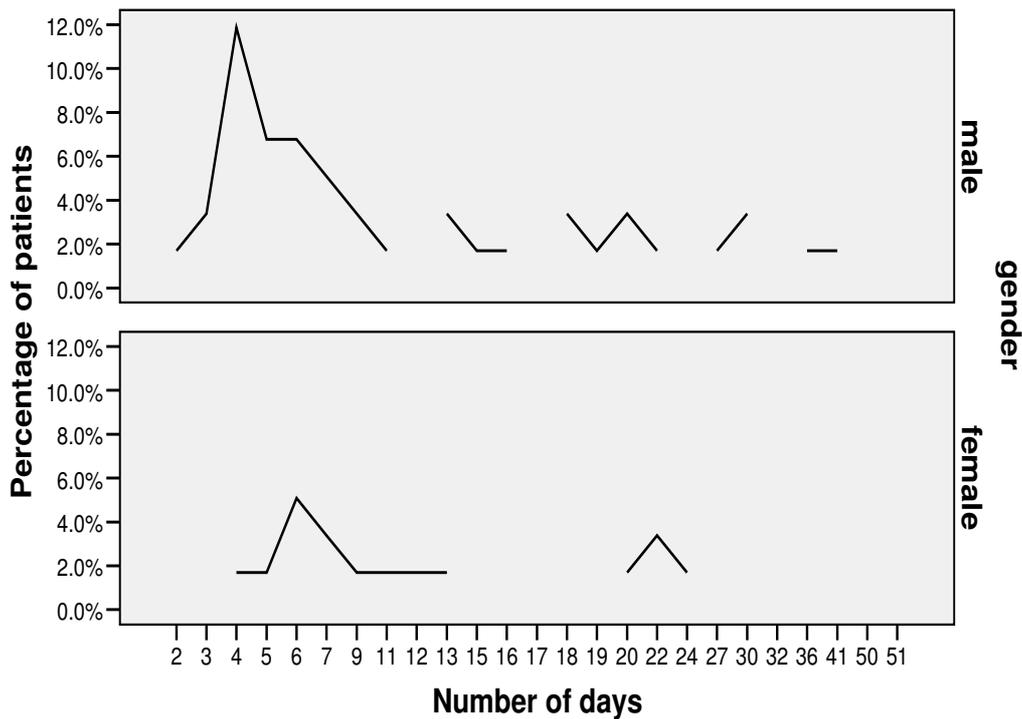
The difference in the duration of treatment of antifungal medication prescribed for all patients included in the study as seen in Table 5 and Figure 4. It was found that overall female patients had a longer duration of treatment than male patients. The median period of treatment was found to be 12 days for female patients and seven days for male. It was also seen that the minimum number of days of antifungal treatment for female patients was four days and two days for male patients.

**Table 5 Gender and duration of days of treatment of antifungal**

Gender (%)	Minimum*	Maximum*	Median*
Male (65.6%)	2	51	7
Female (31.1%)	4	50	12

\* Number of days

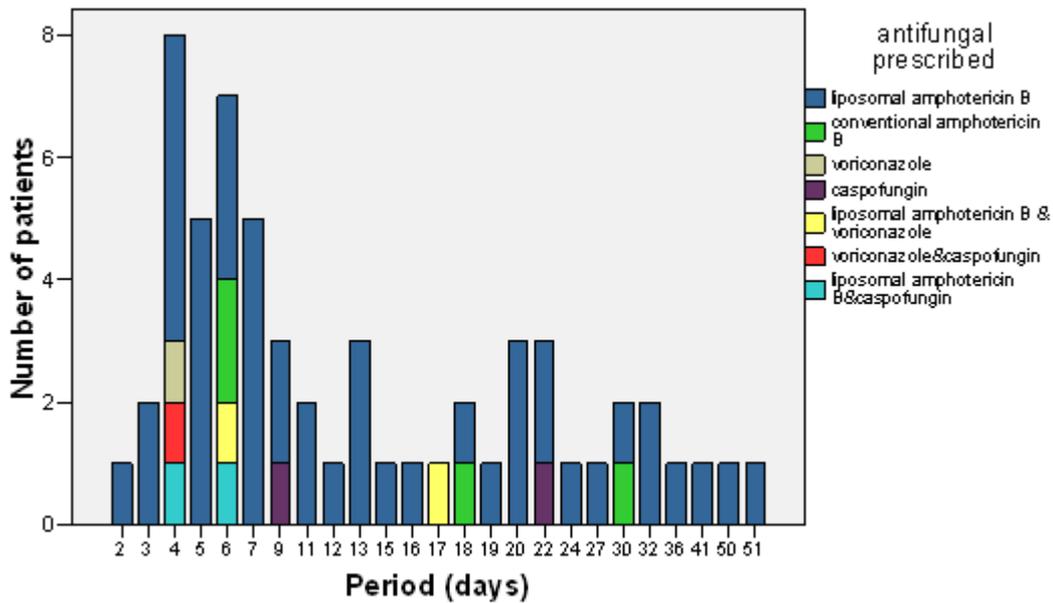
**Figure 4 Gender of the patients and the duration of treatment**



### 3.5 Antifungal prescribed and the duration of treatment

L-AmB was found to have longest treatment duration and the maximum period of treatment was 51 days. C-AmB was prescribed for 30, 18 and six days whereas caspofungin had treatment days recorded as 22 and nine days. There was only one patient on voriconazole and the duration of treatment was four days. The combination antifungal of L-AmB and voriconazole was prescribed for 17 and six days and combination of L-AmB and caspofungin for six and four days. There was limited data on a combination of voriconazole and caspofungin.

**Figure 5 Antifungal prescribed and the duration of days of treatment**



As shown in the above Figure 5, patients who were prescribed L-AmB had a longer duration of treatment which was found to be up to 51 days. It is also seen that C-AmB was prescribed for a longer period of time which was 30 days. Voriconazole was given for 4 days. All the antifungal treatments which exceeded 3 weeks were L-AmB and one case of C-AmB.

### 3.6 Liposomal amphotericin B (L-AmB)

Of the 59 patients who were included in this study, 47 patients were prescribed L-AmB. The dose of L-AmB prescribed is shown in Table 6. The mean dose was calculated for patients who were prescribed more than one dose of L-AmB. From the results obtained it can be seen that the maximum L-AmB dose prescribed was 5 mg/kg/day and the minimum dose was 1 mg/kg/day which was prescribed for two patients. Interestingly, 34 patients out of 47 were prescribed 3mg/kg/day of L-AmB.

**Table 6** Dosages of L-AmB prescribed

<b>Antifungal prescribed</b>	<b>Number of patients</b>	<b>Dose of L-AmB prescribed (mg/kg/day)</b>
L-AmB	2	1
	1	1
		3
		1
	1	3
		1
	1	3
		1
	2	1
		3
	1	3
	34	3
	2	3
		5
	1	3
		5
		5
	3	
2	3	
	5	
Total	47	

### 3.6.1 Duration of L-AmB treatment

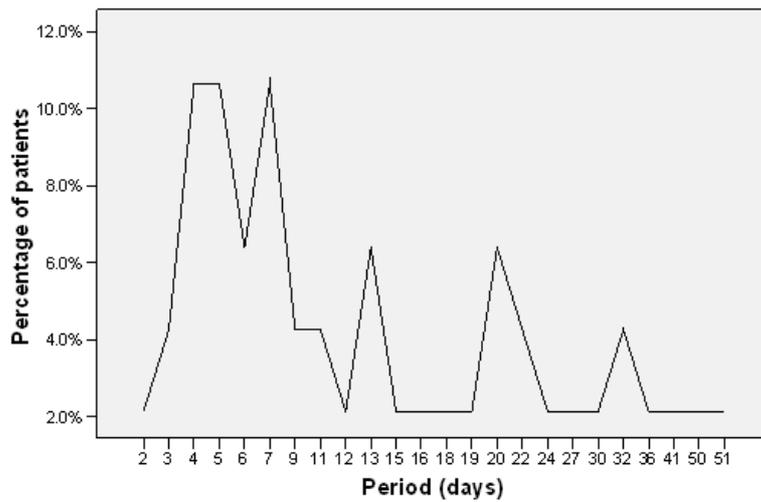
The median number of days for L-AmB treatment was found to be 11 days and the maximum was 51 days (Table 7). A majority of patients were treated for a period between two and 11 days (Figure 6).

**Table 7** Duration of L-AmB treatment

<b>Minimum*</b>	<b>Maximum*</b>	<b>Median*</b>
2	51	11

\* Number of days

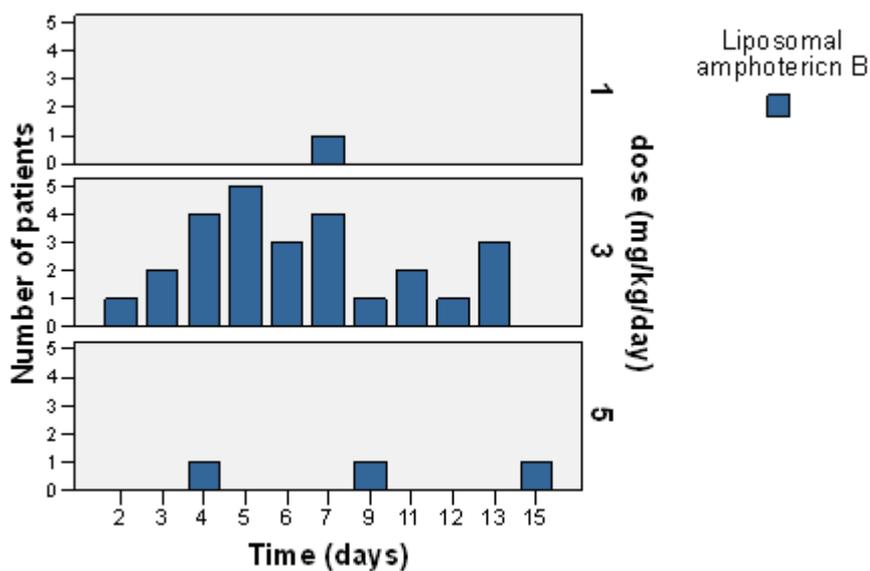
**Figure 6 Mean duration of L-AmB treatment**



### 3.6.2 Mean dose and duration of treatment of L-AmB below 15 days

The dose and the duration of treatment of L-AmB are summarized in Figure 7. It suggests that a significantly higher proportion of patients received 3 mg/kg/day of L-AmB and the duration of treatment varied from two days to 15 days with a maximum of five patients on treatment for five days. However, there was only one patient on 1 mg/kg/day of L-AmB given for seven days. Three of the patients received a dose of 5mg/kg/day of L-AmB for four, nine and 15 days.

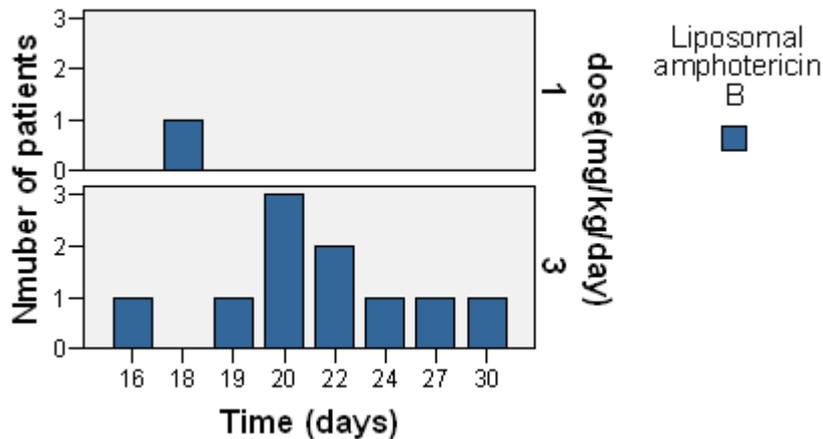
**Figure 7 Mean dose and duration of L-AmB treatment below 15 days**



### 3.6.3 Mean dose and duration of L-AmB treatment above 15 days and below 30 days

The results from the study (Figure 8) show that one patient received a dose of 1 mg/kg/day of the drug for 18 days. L-AmB dosage of 3 mg/kg/day was prescribed to a higher proportion of patients for a period of 16 to 30 days.

**Figure 8** Mean dose and duration of L-AmB treatment above 15 days and below 30 days



### 3.6.4 Mean dose and duration of L-AmB treatment above 30 days

The mean dose and duration of L-AmB received by three patients is shown in Table.8. Two patients were prescribed 3 mg/kg/day for 32 days and the other patient on 41 days

**Table 8** Dose and duration of L-AmB above 30 days

Number of patients	Dose(mg/kg/day)	Number of days
2	3	32
1	3	41

The following Figures 9 (a-d) shows the relationship between the doses of L-AmB prescribed and duration of days of treatment for four patients whose mean duration was found to be above 30 days. There was one patient (no: 4) in this study group who was prescribed 7mg/kg/day of L-AmB for a period of 43 days.

**Figure 9 Dose and duration of liposomal amphotericin B (Figure (a-d)).**

Figure a. Patient no: 1

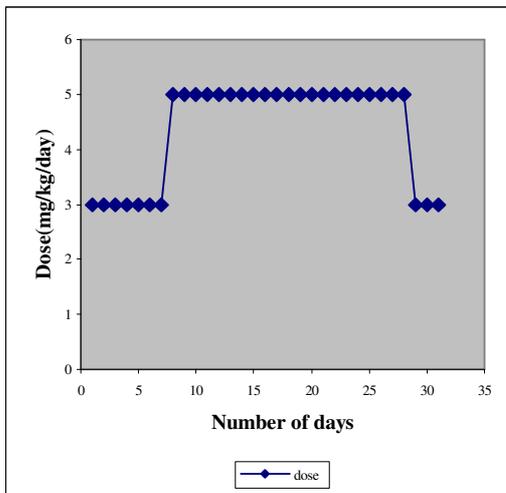


Figure b. Patient no: 2

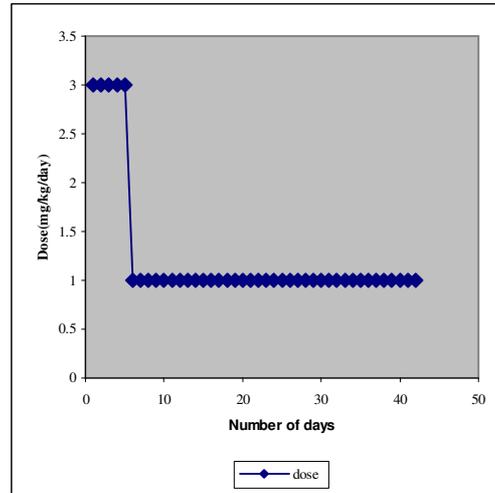


Figure c. Patient no: 3

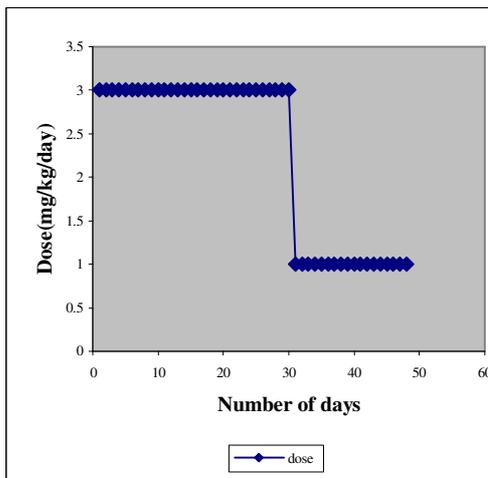
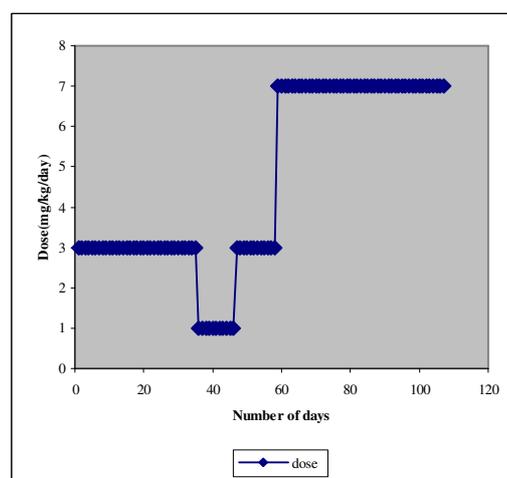


Figure d. Patient no: 4



### 3.6.5 Infusion related reactions reported in patients who were prescribed L-AmB

In evaluating the overall infusion related reactions (Table 9), of the total 47 patients who were prescribed L-AmB, 32 (68.1%) patients were reported to have had vomiting and tachycardia accounted for 23 (48.9%) of the patients. Nausea was observed in 22 (48.9%) patients and nine (19.1%) patients were recorded with hypotension. It must be stated that

these patients were being treated with cancer chemotherapies. It would have been difficult to isolate the reactions only from the IV L-AmB.

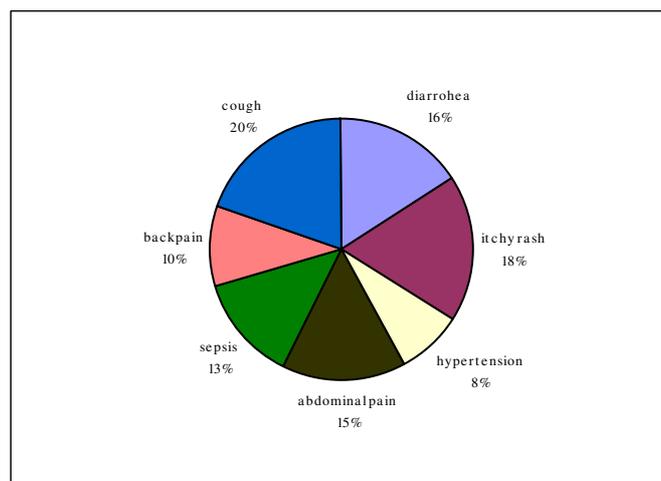
**Table 9** Infusion related reactions reported in patients who were prescribed L-AmB

<b>Infusion related symptoms in patients prescribed L-AmB</b>	<b>Symptoms observed number of patients (%)</b>	<b>Symptoms absent Number of patients (%)</b>	<b>Total number of patients</b>
Vomiting	32 (68.1)	15 (31.9)	47
Nausea	22 (46.8)	25 (53.2)	47
Tachycardia	23 (48.9)	21 (51.1)	47
Hypotension	9 (19.1)	38 (80.9)	47

### 3.6.6 Adverse effects observed in patients who were prescribed L-AmB

The overall adverse effects reported for patients receiving L-AmB is shown in Figure 10. All patients in this study were also on other medications. A higher proportion of patients developed cough (20%) followed by itchy rash (18%). Diarrhoea was observed in 16% of patients and 15% of patients developed abdominal pain. Additionally 13% of patients were reported to have sepsis and back pain was observed in 10% of patient group. Hypertension was less frequent and was observed in 8% of patients.

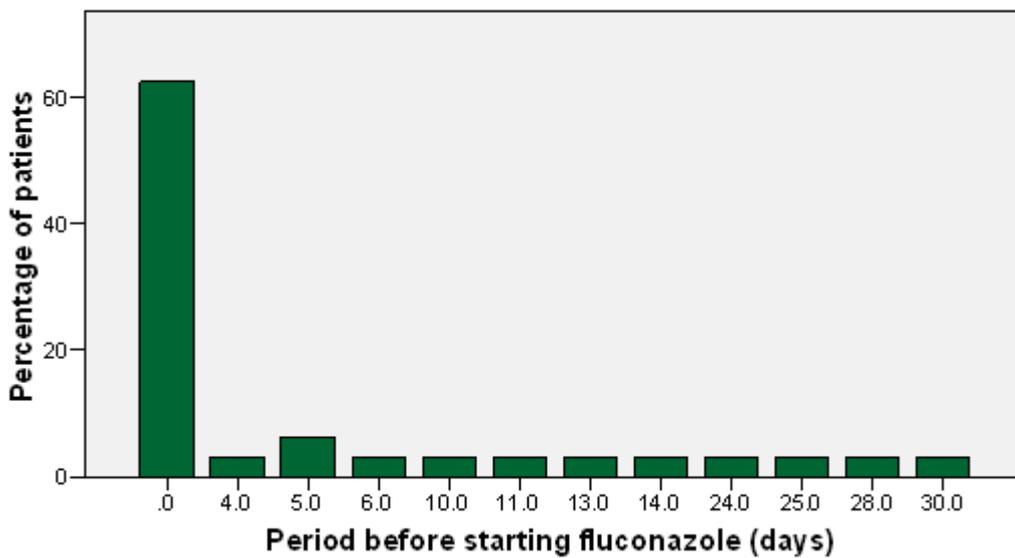
**Figure 10** Symptoms of adverse effects reported in patients concurrently on L-AmB therapy



### 3.6.7 Assessment of subsequent fluconazole commencement in patients receiving L-AmB.

The overall outcome of the analysis shows that 62% of patients were restarted on fluconazole the day L-AmB was ceased. However, 6% of patients receiving L-AmB had fluconazole started after five days of cessation of L-AmB. From the data obtained from the records (Figure 11), it was indicated that one patient had their fluconazole dose started each after 24, 25, 28 and 30 days following the cessation of L-AmB.

**Figure 11 Commencement of fluconazole after cessation of L-AmB**



### 3.7 Conventional amphotericin B

Out of 59 patients included in the study who received antifungal medication, only four of the patients were given C-AmB and all the patients were neonates whose ages are shown in Table 10.

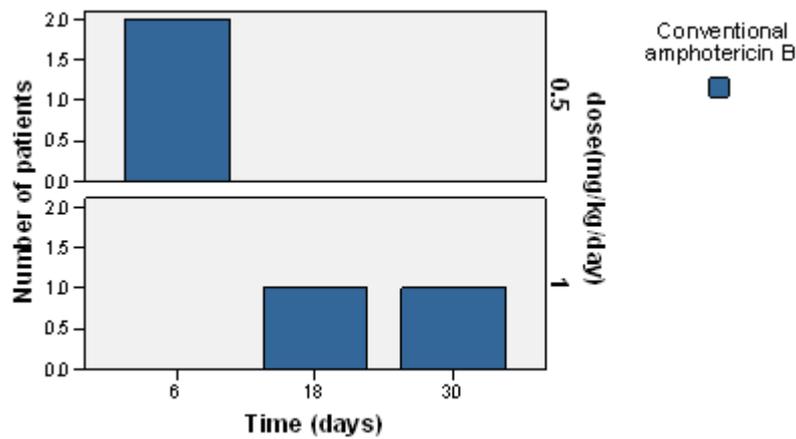
**Table 10 Number of patients receiving C-AmB**

C-AmB	Age		Total
18 days	37 days	11 weeks	26 weeks
Number of 1 patients	1	1	1
			4

### 3.7.1 Dose and duration of treatment of C-AmB

From the data in Figure 12, it can be seen that 1 mg/kg/day of C-AmB was administered to two of the patients for a period of 18 and 30 days respectively. There was one patient who was given 0.5 mg/kg/day of C-AmB for six days.

**Figure 12 Dose and duration of treatment of C-AmB**



### 3.7.2 Infusion related reactions observed in patients who were prescribed C-AmB

Of the four patients who received C-AmB during the study, there was no significant infusion related reactions reported as shown in Table 11. However, tachycardia occurred in all patients.

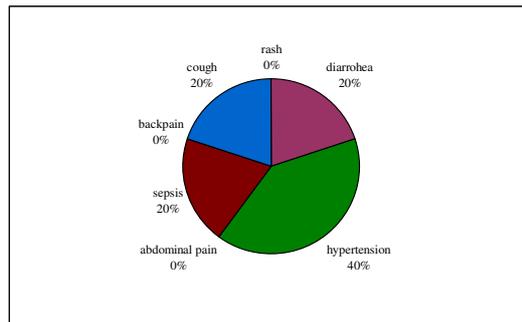
**Table 11 Infusion related reactions reported in patients who were prescribed C-AmB**

Infusion related reactions	Reactions observed (number of patients)	Total
Vomiting	0	4
Nausea	0	
Tachycardia	4	
Hypotension	0	

### 3.7.3 Adverse effects in patients who were prescribed C-AmB

Adverse effects associated with C-AmB included hypertension, sepsis, cough and diarrhoea. The most frequent was that 40% of the patients had hypertension and cough. Sepsis and diarrhoea accounted for 20% of the patients. Symptoms of abdominal pain, rash and back pain were not reported in any of the four patients. These could have been complicated by other medications being used.

**Figure 13** Adverse effects reported in patients who were prescribed C-AmB



### 3.8 Voriconazole

Limited data was available for voriconazole as only one patient of the 59 was prescribed voriconazole (Table 12). The fungal infection was identified as aspergillosis and the microorganism was aspergillus fumigatus. A dose of 5 mg/kg/ day of voriconazole were given for a period of four days.

There were three infusion related reactions reported to be related to voriconazole. The most common side effect of photophobia was observed in the patient. In addition tachycardia and increased respiratory rate occurred. Diarrhoea, hypertension and itchy rashes were also reported in this patient as adverse effects. Of note, this patient was on other medications and the adverse effects could be associated with them.

**Table 12 Summary of patient data for voriconazole**

Antifungal prescribed	Number of patients	Fungal infection	Dose(mg/kg/day)	Duration of treatment (days)	Infusion related reactions	Adverse effects
Voriconazole	1	Aspergillosis	5	4	Photophobia Tachycardia Increased respiratory rate	Diarrhea Hypertension Itchy rash

### 3.9 Caspofungin

Of the 59 patients two patients received caspofungin for antifungal treatment and the data is shown in Table 13. The fungal infection was identified as invasive pulmonary aspergillosis. One patient received 1.2mg/kg/day of caspofungin for 22 days and the other patient 1.8 mg/kg/day for nine days. Infusion related reactions reported were nausea, vomiting, and hypotension. Identified as an adverse effect related to caspofungin, cough occurred in both patients. Other adverse effects reported related were sepsis, itchy rash, abdominal pain, respiratory distress and diarrhoea.

**Table 13 Summary of caspofungin data**

Antifungal prescribed	Number of patients	Fungal infection	Dose(mg/kg/day)	Duration of treatment(days)	Infusion related reaction	Adverse effects
Caspofungin	2	Invasive pulmonary aspergillosis	1.2	22	Nausea Vomiting Hypotension	Cough Sepsis Respiratory distress Itchy rash Cough
			1	18	Nausea vomiting	Abdominal pain Diarrhoea

### 3.10 Combination antifungals

Details of antifungal combination treatment are summarized in Table 14. It was found that L-AmB was combined with caspofungin and voriconazole as combination antifungals. Of the 59 patients included in the study, five received combination antifungals. Two patients were prescribed a combination of L-AmB and caspofungin and

the infusion related reactions reported were tachycardia, nausea, vomiting and hypotension. Adverse effects such as diarrhoea, hypertension, sepsis and cough was observed in the patients. A combination of L-AmB and voriconazole was prescribed for three patients and the infusion related reaction related to voriconazole, photophobia occurred in these patients along with vomiting, nausea, hypotension, sepsis, severe cough and respiratory distress. Itchy rashes and abdominal pain occurred in these patients. There was one patient who received a combination of caspofungin and voriconazole 2.5 mg/kg/day for duration of four days. No significant infusion related reactions were reported except vomiting. Cough and sepsis occurred in the patient as side effects. Of note, all the patients were on other medications as well as the antifungals.

**Table 14 Summary of combination antifungal treatments**

<b>Antifungal prescribed</b>	<b>Number of patients</b>	<b>Infusion related reaction</b>	<b>Adverse effects</b>
L-AmB + Caspofungin	1	Tachycardia	Diarrhoea
L-AmB + Voriconazole	3	Vomiting Nausea Hypotension Photophobia	Sepsis Severe cough Respiratory distress Itchy rashes Abdominal pain
Caspofungin+ voriconazole	1	Vomiting	Cough sepsis

Figure 14 Dose and duration of combination antifungal treatment (fig e-i)

Figure e: Patient 7

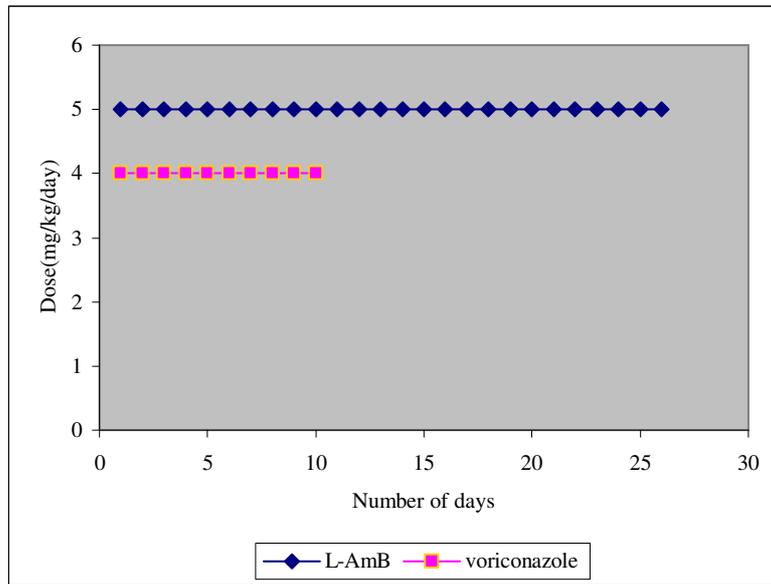


Figure f: Patient 8

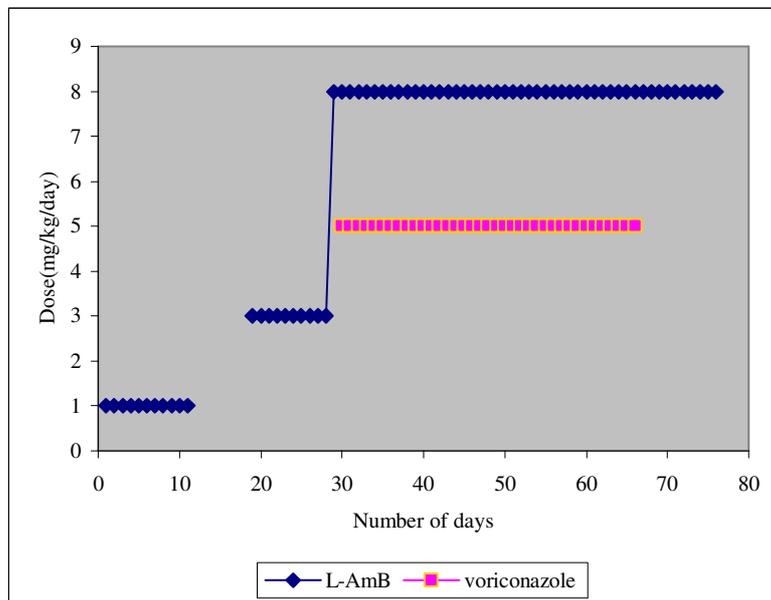


Figure g: Patient 9

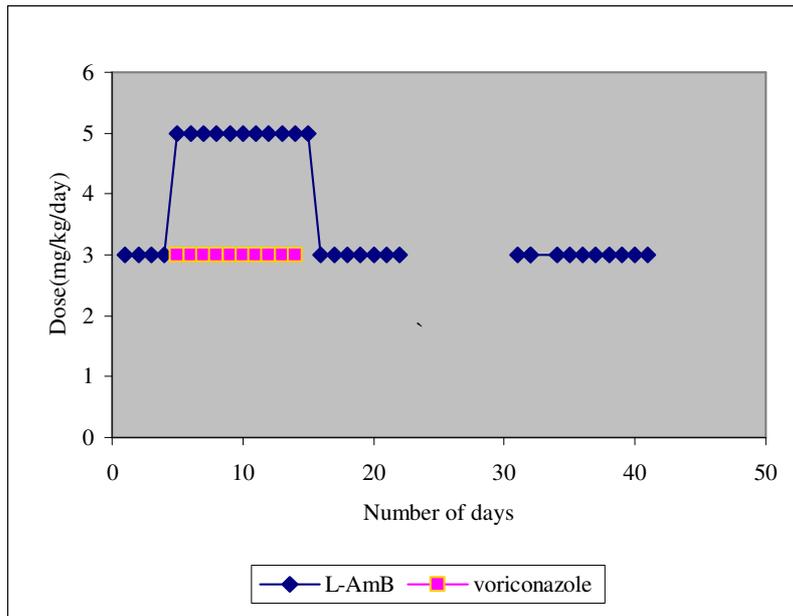


Figure h: Patient 10

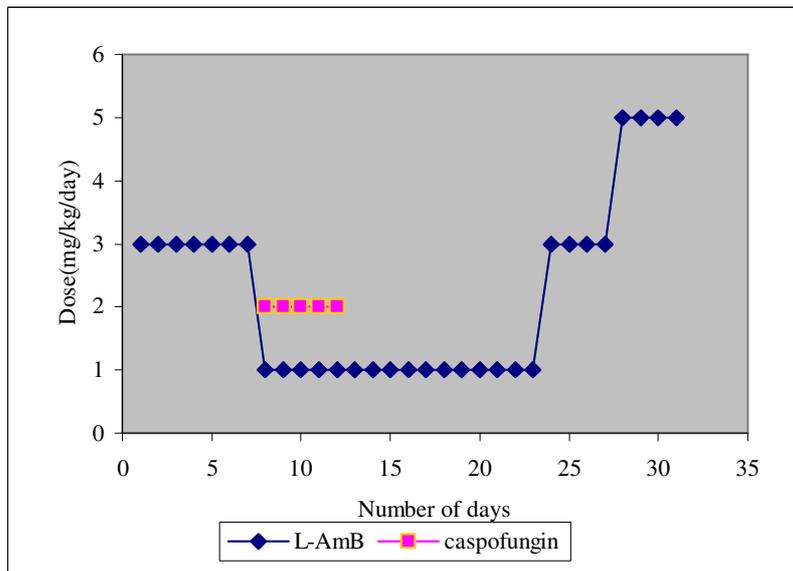


Figure i: Patient 11

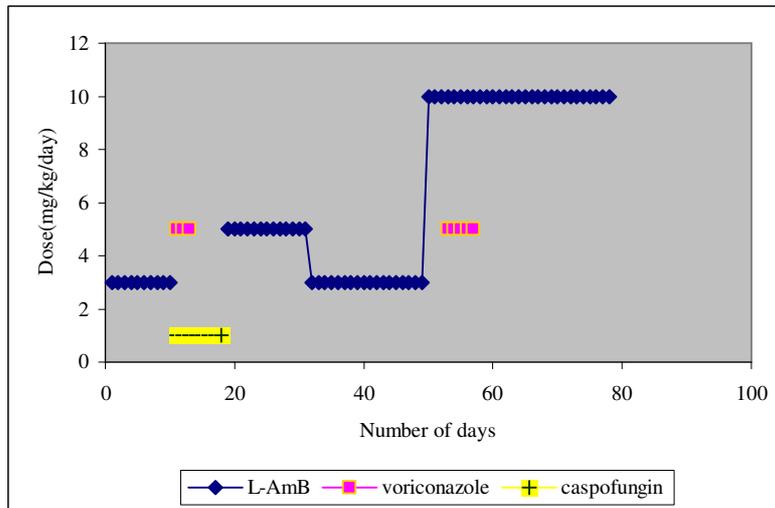
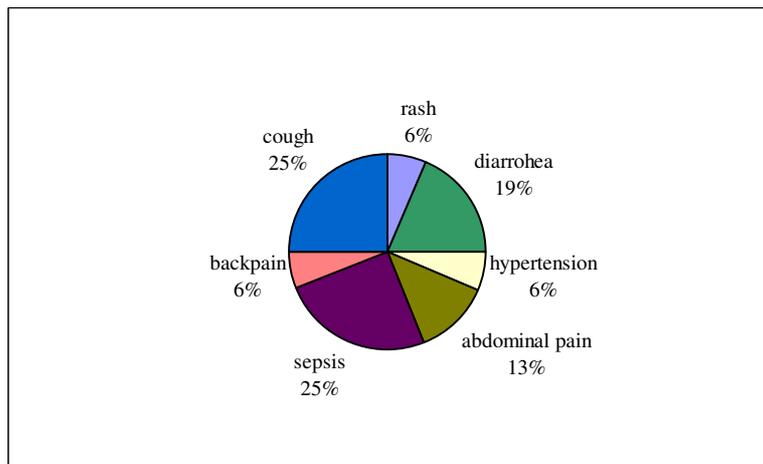


Figure 15 Adverse effects reported in patients who were prescribed combination antifungal treatment.



Overall the results suggest that nausea and vomiting occurred more frequently in patients who received combination antifungals. And also, a significantly higher proportion of patients developed cough followed by sepsis (Figure 15). This may have arisen from the severity of the infections.

### 3.11 Antifungal medication prescribed for neonates

Of the 59 patients included in the study who were prescribed antifungal medication, nine were neonates. As discussed earlier, four patients were given C-AmB (Table 15). Two patients received L-AmB 3mg/kg/day for 22 days for one patient and the other patient for 14 days. A combination of L-AmB with caspofungin was received by one patient with a dose of 0.5 mg/kg/day.

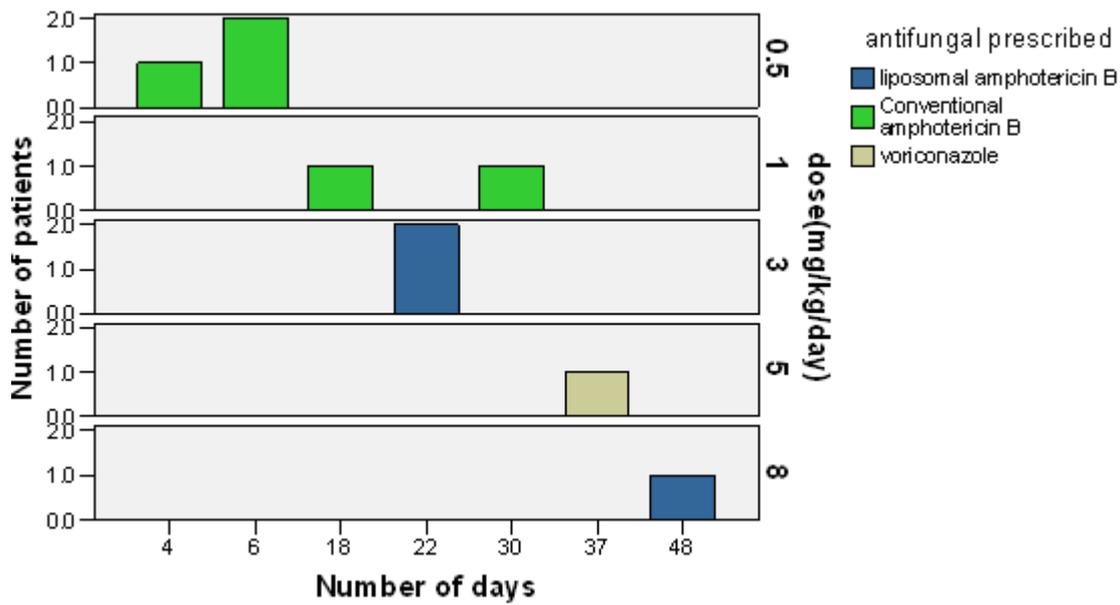
**Table 15** Dose and duration of antifungals prescribed for neonates

Number of neonates	Antifungal prescribed	Dose (mg/kg/day)	Duration of treatment(days)
2	L-AmB	3	22
		3	14
4	C-AmB	0.5	6
		0.5	6
		1	18
		1	30
1	Combination of L-AmB + voriconazole	L-AmB	9
		3	18
		8	48
		Voriconazole	3
		5	3

### 3.12 Infusion related reactions and adverse effects

Tachycardia occurred in two patients and one patient had vomiting as infusion related reactions. No other infusion related reactions were reported. Hypertension and cough occurred in two patients and no other adverse reactions were observed.

**Figure 16 Mean dose and duration of antifungal prescribed for neonates**

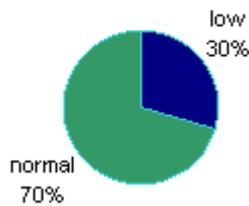


### 3.13 Potassium, liver function, creatinine and temperature data

#### 3.13.1 Potassium levels in patients who received L-AmB

The overall potassium level data for all patients included in this study who received L-AmB are shown in Figure 17. The result suggests that 73% of the patients had a normal potassium level and that 27% of patients had a low potassium level. Normal potassium level for each patient varied according to the patients.

**Figure 17 Potassium level data for all patients who were prescribed L-AmB**



#### 3.13.2 Liver function tests (n = 59)

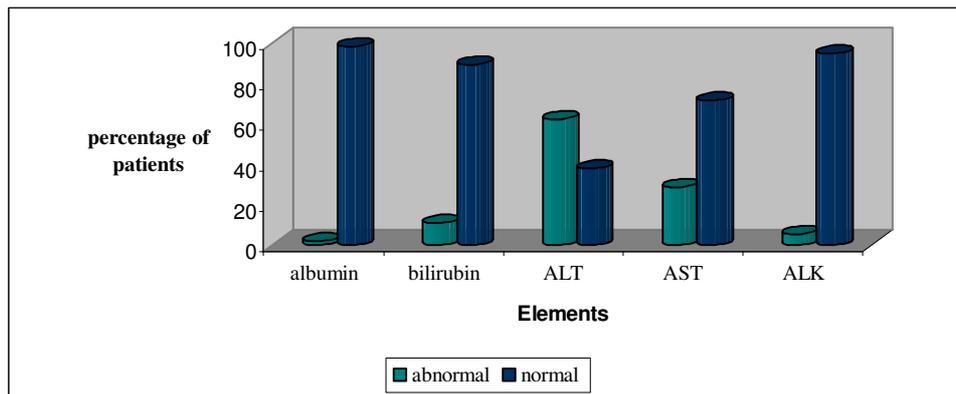
Data for liver function tests for all the patients included in the study are summarized in Figure 18. The normal levels of all the elements are shown in the Table 16. A

significantly higher proportion of patients receiving antifungal were found to have abnormal ALT and abnormal AST. Overall the albumin levels were found to be normal.

**Table 16** Normal level data for liver function tests

Element	Normal level
Albumin (g/L)	32-48
Bilirubin ( $\mu\text{mol/L}$ )	<20
ALT ( $\mu\text{L}$ )	<30
AST ( $\mu\text{L}$ )	<60
ALK ( $\mu\text{L}$ )	100-350

**Figure 18** Results of liver function tests for the patient cohort



### 3.13.3 Creatinine and urea level

In evaluating the data for serum creatinine and urea, listed in Table 17, it was found that 11(18.6%) out of the 59 patients had abnormal serum creatinine levels. In addition the antifungal used in patients with abnormal creatinine levels were found to be six patients on L-AmB and four patients receiving combination drug of L-AmB with caspofungin and voriconazole. There was also one patient on voriconazole. 16 (28.6%) of 59 patients were found to have high urea levels and the antifungals recieved were L-AmB (n=15) and a combination of L-AmB and caspofungin.

**Table 17** Summary of serum creatinine and urea level

<b>Elements</b>	<b>Normal level (number of patients (%))</b>	<b>Abnormal (high) level (number of patients (%))</b>	<b>Antifungal used in patients with abnormal levels*</b>	<b>total</b>
Serum Creatinine ( $\mu\text{mol/L}$ )	48 (81.4)	11 (18.6)	L-AmB - 6  Combination of L-AmB +casposfungin - 2  Combination of L-AmB +voriconazole-2  Voriconazole-1	59
Urea ( $\text{mmol/L}$ )	40 (71.4)	16 (28.6)	L-AmB -15 Combination of L-AmB +casposfungin - 1	59

### 3.13.4 Creatinine clearance data

Creatinine clearance for all the patients whose serum creatinine level was high was calculated and is summarised in Table 18. All patients who had lower creatinine clearance levels were also on other medications which could increase serum creatinine clearance. Cyclosporin and diphenhydramine which affects creatinine clearance were found to be the most frequently prescribed drugs among the patients whose serum creatinine level was high. The second most frequent drug was cyclosporin followed by other drugs.

### 3.14 Temperature data of patients during antifungal treatment

During the period of antifungal treatment there was a reduction in the temperature level of patients from the day the antifungal was commenced until the cessation of antifungal treatment. The mean temperature of the patients is summarized in the Table 19. It was found that the mean temperature at the start of antifungal treatment was  $38.3^{\circ}\text{C}$  and at the cessation of antifungal treatment the temperature has reduced to  $37.0^{\circ}\text{C}$ .

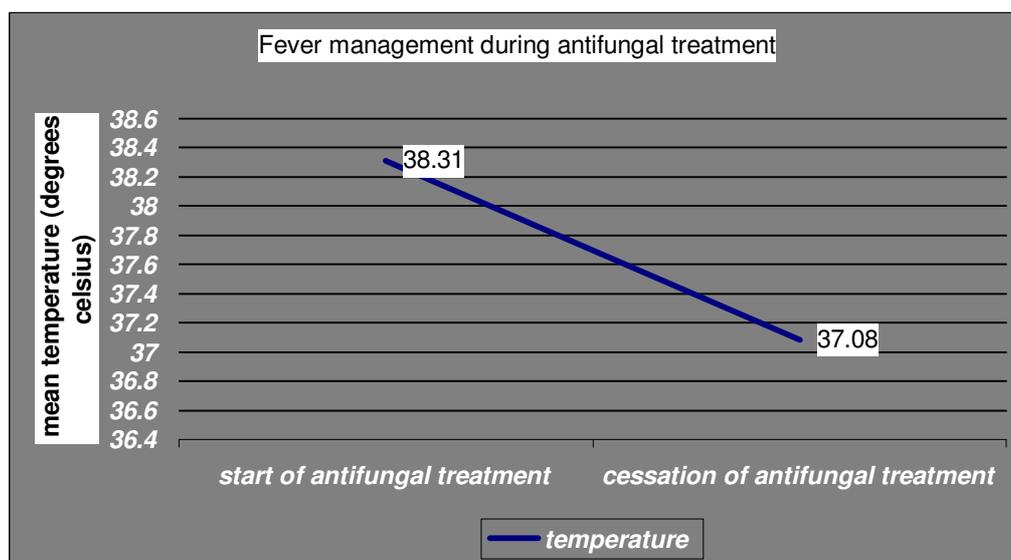
**Table 18 Creatinine clearance and the other medications which increases serum creatinine level**

Patient	Age (years)	Height (cm)	Serum creatinine ( $\mu\text{mol/L}$ )	Creatinine clearance (mL/min)	Antifungal prescribed	Dose(mg/kg /day)	Other medications which increase serum creatinine level while
1	16	152.0	225	33.1	L-AmB	3	cyclosporin diphenhydramine acyclovir fluconazole
2	7.5	110.5	114	47.4	L-AmB	3	cyclosporin diphenhydramine acyclovir fluconazole
3	16	163.5	143	56.0	L-AmB	3	cyclosporin diazepam ciprofloxacin
4	3	98.0	56	85.7	L-AmB	3	Vancomycin Loratidine
5	9	127.5	89	70.1	LAmB+ voriconazole	3 5 3 5	lorazepam oxycodine fluconazole acyclovir diphenhydramine cyclosporin methylprednisolone
6	11	156.5	149	51.4	LAmB+ voriconazole	3 8 3 5	ciprofloxacin fluconazole vancomycin acyclovir

**Table 19 Mean temperature of patients at the start and at the cessation of antifungal treatment**

Measurement	Minimum ( <sup>0</sup> C)	Maximum ( <sup>0</sup> C)	Mean ( <sup>0</sup> C)
Start of antifungal treatment	35.5	39.8	38.3
Cessation of antifungal treatment	35	38.5	37

**Figure 19 Mean temperature data at commencement and cessation of antifungal treatment**



### 3.15 Days of the week when the IV antifungal treatment were changed or ceased

The major ward rounds are scheduled for a Tuesday and Thursday. Decisions on the change of antifungal dose or the timing of cessation of the antifungal are made at the rounds. Changes can be made by physicians in the ward. It is seen from the results in Table 19, that the majority of the changes made in antifungal dose in the ward were on Thursdays (43.5%) followed by on Tuesdays (21.7%). On the other hand cessation of antifungal treatment was found to occur on Wednesdays (22.7%) and Fridays (21.3%) and also it was noted that 17.3% and 16% of patients had their antifungal course stopped on Tuesdays and Thursdays respectively. Notably few patients had their antifungal treatment changed or ceased on Saturdays, Sundays or Mondays.

### 3.16 Cost of antifungal treatment in the hospital

The costs of the antifungals were obtained from the Pharmacy Department. For L-AmB, amounts above 100 mg used in the preparation, the time involved included the cost of an extra two minutes for addition of each vial to the labour cost of Pharmacist, Pharmacy technician and the nurse (Table 21 & 22).

**Table 20** Days of the week when the antifungal dose was changed and ceased.

<b>Days of treatment</b>	<b>Change of antifungal dose(n=23) (%)</b>	<b>Cessation of antifungal treatment (n=59) (%)</b>
Monday	4.3	12.0
Tuesday	21.7	17.3
Wednesday	8.7	22.7
Thursday	43.5	16.0
Friday	13.0	21.3
Saturday	4.3	8.0
Sunday	4.3	2.7

**Table 21** Cost of antifungal drugs in AUD

<b>Antifungal</b>	<b>Cost(\$)</b>	<b>1 mg(including 2% wastage on reconstitution)(\$)</b>
Liposomal amphotericin B (50 mg vial)	268.5	5.5
Conventional amphotericin B 50 mg vial	24	Per vial cost
Voriconazole 200 mg vial	190.84	Per vial cost
Caspofungin 50 mg vial	729.4	Per vial cost

**Table 22 Total labour and consumable costs for preparing L-AmB**

<b>Days</b>	<b>1-100(mg)</b>		<b>101-150(mg)</b>	
	<b>Pharmacy prepared cost (\$)</b>	<b>Ward prepared cost (\$)</b>	<b>Pharmacy prepared cost (\$)</b>	<b>Ward prepared cost (\$)</b>
Weekdays	11.74	14.5	13.14	15.9
Saturday	16.58	21.1	19.02	23.54
Sunday	18.19	23.25	20.99	26.05

Days	151-200 (mg)		201-250(mg)		251-300(mg)	
	Pharmacy prepared cost (\$)	Ward prepared cost (\$)	Pharmacy prepared cost (\$)	Ward prepared cost (\$)	Pharmacy prepared cost (\$)	Ward prepared cost (\$)
Weekday	14.54	17.3	15.94	18.7	17.34	20.1
Saturday	21.46	25.98	23.9	28.42	26.34	30.86
Sunday	23.79	28.85	26.59	31.65	29.39	34.45

**Table 23** Examples of treatment costs of L-AmB received by the patients

Pt No:	Age (years)	Wt (kg)	Dose (mg)	Mg/kg/day	Cost (\$)							
					Number of days							
					1(weekday) Pharmacy prepared cost(\$)	Ward prepared cost (\$)	7 Pharmacy prepared cost(\$)	Ward prepared cost (\$)	14 Pharmacy prepared cost(\$)	Ward prepared cost (\$)	21 Pharmacy prepared cost(\$)	Ward prepared cost (\$)
1	4	21.2	63	3	358	553	2,601	4,009	5,202	8,019	7,803	12,029
2	4	25.5	75	3	424	553	3,063	4,009	6,126	8,019	9,189	12,090
			128	5	717	823	5,118	5,904	10,327	11,808	15,377	17,733
3	16	59.1	178	3	993	1,093	7,072	7,812	14,145	15,625	21,218	23,438
			296	5	1,645	1,633	11,659	11,615	23,319	23,231	34,979	34,847
4	16	53.5	160	3	894	1,093	6,379	7,812	12,759	15,625	19,139	23,438

### 3.17 Treatment costs of L-AmB received by the patients

Costs per patient were calculated by taking into account costs per mg (based on the 2008 prices provided by the hospital pharmacy) multiplied by the number of prescribed doses and the number of days of treatment and adding the labour cost in pharmacy and in the ward setting. Random patients were selected for calculation of costs as shown in the above (Table 23) in calculating a general average total treatment cost on a weekly basis. Overall the treatment cost in the ward setting was higher. It is clearly demonstrated that treatment cost of the antifungal depends on the body weight and therefore the size of the dose administered to the patients. For a patient (no: 4), of 16 years with a body weight of 53.5 kg, the estimated pharmacy prepared and ward prepared cost were found to be \$19,139 and \$23,438 respectively for antifungal treatment for 21 days. The difference is

mainly due to the required cost of four vials for a 160 mg of L-AmB in the ward setting whereas in the pharmacy setting the cost was calculated on a per mg basis.

**Table 24 Total treatment cost for patients who received L-AmB for more than 30 days**

Patient number	Age (years)	Weight (kg)	Dose (mg)	Mg/kg	Number of days	Treatment cost (\$)		Total number of days
						Pharmacy prepared	Ward prepared	
40	2	14.74	45	3	3	812	905	40
			15	1	37	3,977	11,254	
21	4	20.7	60	3	30	10,649	17,179	48
			20	1	18	2,425	5,467	
99	1.5	11.8	35	3	33	7,172	9,960	102
			12	1	11	906	3,014	
			45	3	10	2,992	3,313	
			80	8	18	7,913	10,316	
			85	8	30	14,774	17,179	
43	11	57.7	180	3	7	7,149	7,812	31
			290	54	21	34,286	34,847	
			174	3	3	2,958	3,338	

**Table 25 Total treatment cost for patients receiving L-AmB for more than 30 days**

Pt:no	Total treatment cost (\$)		Total cost/day (\$)		Treatment cost in excess of 21 days (\$)	
	Pharmacy prepared	Ward prepared	Pharmacy prepared	Ward prepared	Pharmacy prepared	Ward prepared
40	4,790	12,159	119	303	2,275	5,775
21	13,074	22,646	272	471	7,626	13,210
99	34,222	43,784	335	429	27,106	34,770
43	44,394	45,998	1,432	1,483	14,320	14,838

**Table 26** Cost estimates for patients receiving L-AmB for more than 30 days

<b>Description</b>	<b>Pharmacy prepared cost(\$)</b>	<b>Ward prepared cost (\$)</b>	<b>Difference in ward and pharmacy prepared cost (\$)</b>
Mean cost/ day	539	672	132
Total treatment cost for 4 patients on L-AmB for more than 30 days	96,482	124,702	28,220
Cost for > 21 days	51,329	68,594	17,265
Savings	45,152	56,107	10,955

### *3.18 Cost estimates for patients receiving L-AmB for more than 30 days*

The estimated cost of the four patients (4/59) who received L-AmB where it was prescribed for a period of more than 30 days is shown in Table 25. Patient (no:99) received L-AmB for a period of 102 days which was the longest duration of antifungal treatment in this study period. The estimated cost for the treatment was found to be \$34,222 if pharmacy prepared and \$43,784 if prepared in the ward setting. The treatment cost for more than 21 days which was 81 days, \$27,106 or \$34,770 for pharmacy and ward preparation respectively. When compared with patient number 43 who received antifungal treatment for 31 days provided higher estimated total costs of \$44,394 and \$45,998 for the pharmacy and ward settings respectively. This could be explained by the body weight of this patient with an estimated cost per day of \$1,432 and \$1,483 in pharmacy and ward settings respectively. On calculating the mean cost, table 24 clearly depicts that on an average cost per day for each patient was found to be \$539 and \$672 in pharmacy and ward setting and that a mean cost of \$132 could be saved each day if the antifungals were prepared in pharmacy CIVAS. Overall a total cost of \$28,220 could be saved for all the four patients included in this study who received L-AmB for more than

four weeks. In addition, if the antifungal treatment was ceased at an optimum duration of three weeks \$45,152 and \$56,107 could have been saved in pharmacy and ward setting and also an additional \$10,995 could be saved if prepared in pharmacy setting.

**Table 27 Treatment cost of C-AmB received by the patients**

Pt. no:	Age (weeks)	Weight (kg)	Dose (mg)	Mg/kg	Number of days	Treatment Cost (\$)	
						Pharmacy prepared	Ward prepared
40	2.5	1.3	0.5	0.5	6	289	351
42	11	3.4	3.5	1	18	877	1,066
43	26	3.8	3.8	1	30	1,469	1,789

**Table 28 Treatment cost of voriconazole received by the patient**

Pt no:	Age (years)	Weight (kg)	Dose (mg)	Mg/kg	Number of days	Total Cost (\$)	
						Pharmacy prepared	Ward prepared
21	4	21.3	106	5	4	810	829

**Table 29 Treatment cost of caspofungin received by the patients**

Pt no:	Age (years)	Weight (kg)	Dose (mg)	Mg/kg	Number of days	Treatment Cost (\$)		Total number of days	Total treatment cost(\$)	
						Pharmacy prepared	Ward prepared		Pharmacy prepared	Ward prepared
79	14	45.1	45	1	10	7,422	7,478	19	14,104	14,262
			50	1	9	6,681	6,783			
55	16	40.2	50	0.8	22	16,338	16,466	22	16,338	16,466

### 3.19 Treatment cost of Voriconazole and Caspofungin

Of the 59 patients included in this study four, one and two patients received C-AmB, voriconazole and caspofungin respectively. Among all the antifungal medication prescribed in this study, caspofungin was the most expensive drug. From Table 28, it can

be seen that the total treatment cost for patient 55 was \$16,338 and \$16,466 in the pharmacy and ward setting. The cost of one vial was calculated in both pharmacy and ward setting and the difference between the costs was the labour cost in pharmacy and ward setting. Unfortunately voriconazole was prescribed to only one patient during the study period and the cost of one vial was calculated for both ward and pharmacy setting and the total treatment cost for 5 days was found to be \$810 and \$819 in the pharmacy and ward setting respectively.

During the study period 4/59 patients received combination antifungals as a part of the antifungal regimen and the treatment cost for each of the antifungals is summarised in Table 28. The highest cost estimated was for patient 85 with a body weight of 40.2 kg on 200 mg of L-AmB for a period of 26 days was found to be \$29,404 and \$35,983 for pharmacy and ward setting respectively. For 290 mg of L-AmB prescribed for patient five with a body weight 58.4 kg, the treatment cost for 11 days was the next highest cost which was estimated to be \$17,885 or \$18,175 in pharmacy and ward setting preparation. Caspofungin with an amount of 35mg was prescribed for a period of four days and the estimated cost was \$3,011 and \$3,030 for the pharmacy and ward setting respectively.

**Table 30** Cost for antifungal treatment when a combination was included as a part of the antifungal regimen

Patient no:	Age (years)	Weight (kg)	Antifungal prescribed	Dose (mg)	Mg /kg	Number of days	Treatment cost (\$)	
							Pharmacy prepared	Ward prepared
5	13	58.4	L-AmB	180	3	3	3,040	3,321
			L-AmB	290	5	11	17,885	18,175
			voriconazole	175	3	10	2,069	2,125
			L-AmB	165	3	7	6,552	7,793
			L-AmB	160	3	11	9,970	12,213
80	4	16.2	L-AmB	50	3	7	2,055	2,130
			L-AmB	15	1	16	1,718	4,863
			L-AmB	45	3	4	1,083	1,206
			Caspofungin	35	2	4	3,011	3,030
			L-AmB	80	5	4	1,853	2,280
85	16	40.2	L-AmB	200	5	26	29,404	35,983
			voriconazole	190	4	10	2,069	2,125
99	1.5	11.8	L-AmB	12	1	11	995	3,337
			L-AmB	45	3	10	2,721	3,035
			L-AmB	80	8	17	8,365	10,300
			Voriconazole	45	4	38	10,353	11,556
			L-AmB	85	7	30	14,774	17,179

**Table 31 Total cost for antifungal treatment when a combination was included as a part of the antifungal regimen**

Patient number	Total number of days	Total treatment cost (\$)		Treatment cost/day (\$)	
		Pharmacy prepared	Ward prepared	Pharmacy prepared	Ward prepared
5	42	39,519	43,630	940	1,038
80	35	9,722	13,512	277	386
85	36	31,474	38,108	874	1,058
90	107	37,210	45,407	347	424

**Table 32** Cost estimates for antifungal treatment when a combination was included as a part of the antifungal regimen

<b>Description</b>	<b>Pharmacy prepared</b>	<b>Ward prepared cost(\$)</b>	<b>Difference in ward and pharmacy prepared cost (\$)</b>
Mean cost/day	610	726	116
Total cost for 4 patients on combination antifungal	117,927	140,659	28,220

*3.20 Cost estimates for antifungal treatment when a combination was included as a part of the antifungal regimen*

Total cost for antifungal treatment when a combination was included as a part of the antifungal regimen for all four patients who received antifungal treatment is shown in Table 30. The mean cost per day for antifungal treatment in the pharmacy prepared setting was estimated to be \$610 and at the same time in the ward setting the treatment cost per day was found to be \$726 (Table 31). In addition, a daily treatment cost of \$116 could be saved if the antifungals were prepared in the pharmacy CIVAS. In calculating an estimated total cost for the four patients, \$117,927 accounted for the pharmacy prepared setting and \$140,659 for the ward prepared setting. A total treatment cost of \$28,220 could be saved when prepared in the pharmacy CIVAS.

## 4 GENERAL DISCUSSION

Many advances in the development of antifungal agents have been made in the past decade. Whilst remarkable advances in the treatment of IFIs have been reported with the availability of extended-spectrum triazoles and echinocandins, the mortality rate from infections remains high.<sup>115</sup>

The currently available antifungal therapies exhibit limited effectiveness and a complete response depends on correction of the underlying disease.<sup>165</sup> Based upon both large prospective clinical studies, the intensification of transplant procedures and antineoplastic therapy has been enabled by stringent guidelines for the early diagnosis of infections and systematically escalated antifungal treatment.<sup>166</sup>

### 4.1 *Study population*

The current study population included mainly patients diagnosed with acute leukaemia. Despite the lengthy study period, the overall number of patients, which was a census population, was rather small. It was interesting to note that, as at Duke university Hospital where L-AmB was used in 70% of the cases in the treatment of documented infections, in this study L-AmB was given more often and accounted for 79.7% of study population.<sup>167</sup> This was not entirely unexpected since L-AmB remains the gold standard for the treatment of many invasive fungal infections in adults and in children as well as the comparative agent for all newer antifungal agents.<sup>2</sup>

### 4.2 *Treatment with L-AmB*

In a retrospective audit of L-AmB use carried out in the USA, because of problems associated with a lack of consensus on dose and duration of treatment for certain infections and the clinical diagnosis of fungal infections, no attempt was made to determine whether antifungal drugs has been used correctly.<sup>167</sup> Consequently, the current study attempted to assess whether IV antifungal drugs were used according to current accepted clinical practice in a paediatric setting.

For the current study, drawing firm conclusions for all antifungals was impossible due to an insufficient sample size for the patients who received antifungals other than L-AmB. These were voriconazole, caspofungin and C-AmB. During the current study period it was noted that a single dose of 3 mg/kg/day of L-AmB were received by 34 patients out of the 47 patients who were prescribed L-AMB which is the standard dose recommended by the Antibiotic Therapeutic Guidelines.<sup>164</sup> Some investigators have examined the use of low-dose of IV L-AmB (ranging from 0.5 mg/kg/day to <0.1 mg/kg/day) for prophylaxis. In a retrospective analysis, both the incidence of transplant related mortality and invasive aspergillosis was decreased. However due to the presence of confounding environmental and prognostic factors and the use of historical controls, these results were inconclusive.<sup>168, 169</sup> There was an encouraging trend towards a reduced incidence of IFIs in patients receiving chemotherapy and in haematopoietic stem cell transplantation recipients observed in two double-blind placebo controlled studies using L-AmB at 1 mg/kg/day or 2 mg/kg/day three times weekly for prophylaxis.<sup>170, 171</sup>

#### *4.3 Duration of L-AmB treatment*

In the current study, the results demonstrated that the median duration of therapy with L-AMB were 11 days and the median dose was 3 mg/kg/day unlike the results from a study conducted by Wiley et al.,<sup>172</sup> where the median duration was 15 days and the median dose was 5 mg/kg/day. No firm recommendation regarding the optimal duration of antifungal prophylaxis can be given in the absence of adequate trials.<sup>173</sup>

#### *4.4 L-AmB for prophylaxis*

The findings from the current study demonstrated that 1 mg/kg/day of L-AmB were given more often in the hospital for prophylaxis or empirical therapy. This was not entirely unexpected since management of neutropenic and febrile patients prophylaxis has become conventional practice.<sup>174</sup> The use of antifungal prophylaxis results in the selection of naively resistant organisms as it has the potential for induction of resistance potentially leading to a change in the epidemiology of fungal infections, which has been pointed out by several reports.<sup>173</sup>

With the use of prophylactic L-AmB in children undergoing intensive chemotherapy for AML, using historical controls the preliminary study of Ritter<sup>175</sup> demonstrated an apparent dramatic reduction in the incidence of SFI. A blinded and randomised study from Sweden<sup>171</sup> compared L-AmB dosage of 1 mg/kg/day with placebo. Of the 36 patients who received L-AmB and 40 placebos in well balanced groups, the fungal colonisation increased in follow up in the placebo group (41-62%) and decreased in the L-AmB group (55-33%). In one patient receiving L-AMB and three receiving placebo proven fungal infection occurred. This trial demonstrated that prophylactic L-AMB was well tolerated and effective.

#### *4.5 Dosage of L-AmB*

The maximum dose of L-AmB treatment received by the patients in the current study group was 10 mg/kg/day followed by 8 and 7 mg/kg/day. In another study, a randomised trial of two doses (1 vs. 4 mg/kg/day) of L-AmB was carried out by the EORTC antifungal group in the treatment of probable and proven aspergillosis.<sup>176</sup> There were eight proven SFI on L-AmB 1 mg/kg/day and 12 on 4 mg/kg/day and 33 probable cases versus 34 probable on the 1 and 4 mg/kg/day doses respectively. The outcome of the trial showed no advantages for the higher dose of L-AmB and in addition, there were more proven cases on the 4 mg arm. But the chances of missing an advantage with these numbers were high. Thus, optimal dosage for various clinical situations must remain an open question.<sup>19</sup>

No dose related trends in adverse effects were observed in a pharmacokinetic study of L-AmB conducted in 39 children ranging in age from one to 17 years and also a maximally tolerated dose of 10 mg/kg/day.<sup>177</sup> A prospective study evaluated the safety and efficacy of L-AmB administered to 260 adults, 242 children (<15 years) and 43 infants (< 2 months of age). The largest doses of L-AmB administered for the longest period of time were well tolerated by the infants and children, again suggesting that L-AmB is well tolerated in paediatric patients and better generally than the older patients.<sup>178</sup>

In children undergoing chemotherapy, the safety of weekly high doses of L-AmB has been confirmed recently.<sup>179</sup> The relevance of high dose regimens of L-AmB in the prophylaxis of fungal infections suggested by the pre-clinical and pharmacokinetic

studies supported this new therapeutic approach. This approach could decrease the expenditure on antifungal agents.<sup>180</sup> In patients with IFI, dosages of L-AmB as high as 15 mg/kg/day were well tolerated (despite a relatively high rate of hypokalemia) with an AUC maximised at 10 mg/kg/day.<sup>181</sup> The occurrence of adverse effects could have been favoured by factors specific to the SCT patients. The recommendations for antifungal treatment issued by the European Agency for Evaluation of Medicinal Products have underlined the difficulties related to safety evaluation of antifungal treatments. Indeed owing to the numerous concomitant medications and serious underlying conditions, it is difficult to establish the drug-relatedness of adverse effects in such patients.<sup>182</sup> In a recent pilot study,<sup>183</sup> 21 SCT recipients who received 7.5 mg/kg/day of L-AMB, side effects were not observed. A clinical study in young children by Mehta et al.<sup>184</sup> investigated the pharmacokinetics of once weekly high dose of L-AmB therapy. It was found that L-AmB was well tolerated and was measurable in plasma seven days after a high dose infusion and was near the minimum inhibitory concentration for susceptible strains.

In the UK, a trial<sup>170</sup> in patients undergoing chemotherapy was carried out. 74 patients received L-AmB 2 mg/kg three times weekly and 87 patients had placebo. None of the patients on L-AmB had proven systemic fungal infection after the treatment however, three (3.4%) on placebo had. In 40% of patients on placebo and 20% on L-AmB, fungal colonisation occurred. Compared to placebo, no excess toxicity was reported with L-AmB.

#### *4.6 Adverse effects observed with the use of L-AmB*

For dose escalation or prophylactic therapy, L-AmB is probably the only antifungal agent which can reasonably be considered because of the reduced toxicity.<sup>19</sup> The results from the current study demonstrated that 32 out of 49 patients (68.1%) during the study period were reported to have had vomiting during infusion followed by tachycardia 23 (48.9%) and nausea 22 (46.8%). It is more difficult to establish adverse effects in patients receiving numerous concomitant medications. The Walsh study<sup>177</sup> demonstrated that there was a clear advantage for L-AmB with a highly significant reduction in the incidence of chills rigors, fevers and other reactions including hypotension, tachycardia, hypertension, dyspnoea compared to other antifungal agents.<sup>19</sup> Infusion related and

adverse reactions in this study were recorded from the nurse's daily notes. However, the symptoms were not described under any category whether it was infusion related or adverse effects.

#### *4.7 Limitations of C-AmB*

Conventional amphotericin (C-AmB) was received only by four out of 59 patients during the current study period. It was also interesting to note that all four patients were below one year of age. Clinical use of C-AmB is limited by a number of factors. (a) Serum drug concentrations are comparatively low at standard doses (1.0 mg/kg/day) of C-AmB<sup>185</sup> (b) Since the drug extensively binds to cholesterol containing cell membranes the bioavailability of C-AMB in organ tissue is small.<sup>186,187</sup> (c) Considerable acute and chronic toxicity limits the tolerability of C-AmB, which may necessitate dose reduction or cessation of treatment. In fact, C-AmB dose escalation is limited to a daily dose of 1.5 mg/kg/day.<sup>188</sup>

#### *4.8 Adverse effects of C-AmB*

Compared to L-AmB, the use of C-AmB however, is complicated by a high incidence of potentially serious side effects.<sup>189, 190</sup> As discussed earlier, all the four patients receiving C-AmB were neonates which could be the reason no infusion related reactions were recorded. However, it was noted that tachycardia occurred in all four patients. Hypertension was observed in 40 % of the patients as an adverse effect and it was important to note that all patients in this study group were on other concurrent medications. It is particularly important to note from the results from a comparative study between L-AmB and C-AmB by Walsh et al.<sup>177</sup> the values for hypertension (L-AmB 2.3%, C-AmB 11.3%) tachycardia (L-AmB 2.3%, C-AmB 12.5%), hypotension (L-AmB 3.5%, C-AMB 8.1%) and hypoxia (L-AmB 0.3%, C-AmB 6.4%). There were significantly less prevalence of adverse effects with L-AMB and of note is a 5.8% evidence of dyspnoea with L-AmB compared with 10.8% with C-AmB.

#### *4.9 Comparison of L-AmB and C-AmB*

The pharmacokinetics of amphotericin B have been greatly altered by the lipid formulation. However, it remains unclear to what extent there is a relationship between the clinical efficacy and pharmacokinetics of L-AmB. Increasing the dosage will result in greater concentrations of amphotericin B in tissue as indicated by the preclinical data obtained with mice<sup>191</sup> as well as data obtained from L-AmB treated patients. It still remains to be shown if an equivalently greater antifungal activity can be translated by the significantly greater  $C_{max}$  and AUC values of L-AmB. It may be concluded from preclinical experience that a dose increase from 1 to 3 mg/kg does not significantly increase treatment associated side effects of L-AmB. An L-AmB dose of 3mg/kg is presently recommended.<sup>192</sup>

#### *4.10 Treatment with voriconazole*

In the current study, a voriconazole dose of 5 mg/kg/day was received by only one patient for a period of four days and the infusion related reactions of photophobia, tachycardia and dyspnoea were reported. Diarrhoea, hypertension and itchy rashes were also reported as adverse effects in these patients who received voriconazole. The fungal infection was identified as aspergillus. It was difficult to establish any conclusions from this study for voriconazole as only limited data were available since the sample size was just one patient.

Because the pharmacokinetics in paediatric patients are linear, children require higher doses of voriconazole than adults to attain similar serum concentrations over time.<sup>2</sup> The results from limited pharmacokinetic analyses<sup>92</sup> have demonstrated that a paediatric dose of approximately 11 mg/kg administered every 12 hours was approximately bioequivalent to an adult dosage of 4 mg/kg/day given every 12 hours. The authors recommended a higher doses of voriconazole though unproven in large controlled clinical settings.<sup>92</sup>

For the treatment of invasive aspergillosis, voriconazole has become the drug of choice and the change for primary therapy of aspergillosis from amphotericin B to voriconazole followed the publication of a large multinational randomised trial that compared

amphotericin B with voriconazole in 277 patients with probable or proven aspergillosis.<sup>134</sup> It was found that 53% of the voriconazole group and 32% of the amphotericin B group had complete or partial responses at week 12. Patient survival was 71% in the voriconazole group and 58% in the amphotericin B group. These results supported the fact that for initial therapy for patients with invasive aspergillosis, voriconazole was more effective than amphotericin B.

Voriconazole also was an effective therapy for candidiasis. Approximately 40% of patients treated with voriconazole in a study of 422 patients with invasive candidiasis.<sup>135</sup> Reversible dose dependent visual disturbances (increased brightness, blurred vision) were the most frequent side effect of voriconazole in as many as one third of treated patients.<sup>193</sup> Liver function abnormalities, skin reactions likely due to photosensitisation, fever and digestive track events were the other side effects reported.<sup>194</sup>

#### *4.11 Treatment with caspofungin*

Reports from the current study demonstrated that caspofungin dosage of 1.2 mg/kg/day and 1.8 mg/kg/day was prescribed to a patient who was diagnosed with invasive pulmonary aspergillosis. Unfortunately, information regarding caspofungin was limited as well as there were only two patients out of the 59 patients in this study period who received caspofungin. However, these results were similar in many aspects to other reports on caspofungin.

An FDA approved clinical study on 56 patients with acute invasive aspergillosis used caspofungin as salvage therapy and it was found that more than 40% of the patients had a favourable response to therapy.<sup>71</sup> A pharmacokinetic study was conducted in children on a basis of weight (1 mg/kg/day) and body surface area (50 or 70 mg/m<sup>2</sup>/dy) in 39 patients between the ages two and 17 years. The results suggested that the weight based approach resulted in sub-optimal plasma concentrations, whereas the body surface area approach yielded similar plasma concentrations when compared to plasma concentrations attained in adults treated with 50 mg/day.<sup>195</sup>

To date, the use of caspofungin in patients with severe hepatic insufficiency has no clinical experience. The maximum tolerated daily dose of caspofungin in patients is not

known. In healthy subjects, caspofungin continues to be well tolerated at single doses up to 210 mg/day and multiple doses up to 100 mg/day.<sup>196</sup>

A randomised double blind, comparative study for the empirical use of caspofungin in febrile neutropenic patients showed it was as efficacious as L-AmB in preventing breakthrough fungal infections and in treating baseline fungal infections. Caspofungin was superior to L-AmB and also was better tolerated with fewer side effects.<sup>197</sup> Another randomised double blinded study compared caspofungin with amphotericin B deoxycholate and demonstrated that the efficacy of caspofungin was similar to amphotericin B deoxycholate for the primary treatment of invasive candidiasis.<sup>198</sup> Patients treated with caspofungin had fewer drug related adverse events than those treated with C-AmB (20.2% vs. 48.8%)<sup>198</sup> and L-AmB (35.1% vs. 51.6%).<sup>197</sup> Data on the range of usefulness and efficacy of caspofungin in children with IFIs is limited to case series data and case reports, though there is pharmacokinetic data to show the importance of an increased (higher) dose of caspofungin in a child vs. adult patient.<sup>2</sup>

#### *4.12 L-AmB and fluconazole*

From the results obtained from the current study, it could be seen that the oral administration of fluconazole was stopped during the treatment with L-AmB and L-AmB and fluconazole was not given concomitantly, a practice which is considered both unorthodox and controversial.<sup>188,199</sup> However, it was found that 38% of the patients who received L-AmB did not have their fluconazole drug started the day L-AmB was ceased. The combination of antifungal agents may lead to antagonism or increased toxicity by decreasing the ability of agents to exert their competitive action on the same target (proposed for amphotericin B and azoles).<sup>200</sup> Lewis et al.<sup>201</sup> suggested that there was no interaction on simultaneous administration of amphotericin B and fluconazole, whereas sequential administration (fluconazole exposure before amphotericin B) resulted in a substantial decrease in amphotericin B fungicidal activity.

#### *4.13 Combination antifungal treatment*

The combination drugs given in this study were L-AmB with caspofungin and voriconazole, and caspofungin and voriconazole. The two largest studies on the

combination of L-AmB and caspofungin comes from the Sloan-Ketering Cancer Centre and M.D Anderson Cancer Centre.<sup>202,40</sup> In the Sloan-Ketering study<sup>202</sup> a combination of caspofungin and L-AmB was received by a total of 30 patients with acute or chronic leukaemia, (67%) who had pulmonary aspergillosis. A favourable clinical and radiographic response was manifested in 60% of the patients to the combination regimen. In the M.D Anderson study<sup>40</sup> a total of 48 evaluable patients, 23 with proven or probable aspergillosis and 25 with possible aspergillosis received a combination of caspofungin and L-AMB. The overall favourable response was higher in patients with possible infections (42%), but the response rate for patients with proven or probable infections was dramatically lower. No significant toxicity was associated in this combination regimen in both the above analyses.<sup>40, 202</sup> This was supported by findings from smaller case series (each < 10 patients) that no worsening toxicity was associated with the combination of caspofungin and a polyene.<sup>203,204</sup> It was concluded that the dual-therapy with caspofungin and L-AmB was safe and well tolerated.<sup>205</sup>

The findings of the side effects reported from this study on patients on a combination of L-AmB and caspofungin showed that the patient did not have any major toxicities, though the sample size was insufficient, they supported the above findings.

Voriconazole has a greater potential to alter the pharmacokinetics of co-administered drugs. Though several interactions have been reported, numerous others are suspected, as mentioned in the official labelling, these remain unpublished leading in some cases to contraindications. Thus it appears premature to compare the frequencies of drug-drug interactions compared with other azole agents.<sup>206</sup>

In the current study one patient who had invasive aspergillosis identified, received a combination of caspofungin and voriconazole for a period of four days, however this patient was on long term treatment with L-AmB. For invasive aspergillosis the use of concomitant therapy with voriconazole and caspofungin has been less frequently evaluated.

In one series, two patients with leukaemia responded favourably to a regimen of caspofungin and voriconazole for pulmonary aspergillosis and one patient received the same regimen to treat disseminated infection.<sup>207</sup> A recent study has reported a synergistic

effect of voriconazole and caspofungin against itraconazole-resistant strains of *A.fumigatus*.<sup>208</sup> An animal model study for treating aspergillus infection reported caspofungin in combination with voriconazole reduced the kidney burden in 60% of the animals.<sup>209</sup>

#### *4.14 Antifungal treatment for neonates*

The findings of this study demonstrated that L-AmB, C-AmB and a combination of L-AmB and caspofungin were the drugs used for neonates during the study period. There are few controlled studies, despite a 45 year history of amphotericin use, that address pharmacokinetics and efficacy in newborns, especially in premature infants. In neonates, treatment of *Candida* infection is based largely on extrapolation of data gathered from older patients, which has been reported only as uncontrolled, retrospective analyses of amphotericin B outcomes in preterm neonates.<sup>210</sup> With doses ranging from 0.5 to 1.5 mg/kg treatment success in this population has been reported.<sup>211,212,213</sup> If no response is apparent after several days at the lower dose, a usual approach is to initiate therapy at a dose of 0.5 mg/kg and escalate to 1.0 mg/kg.<sup>210</sup> Reports of immediate reactions to drug administration as seen in adults are absent in neonates and correspondingly do not appear to limit therapy with this agent.<sup>210</sup>

The largest study<sup>214</sup> in neonates used L-AmB with doses ranging from 1mg/kg/day to a maximum of 5 mg/kg/day to treat 40 preterm and four term neonates with severe fungal infections. Of the population 72.7% had the infection eradicated, including all the full term and 28 of the preterm infants; however 12 preterm infants died as a result of infection. Fungal eradication was demonstrated in 92% of patients in another prospective study<sup>215</sup> of L-AmB where 24 premature infants received doses of 2.5 to 7 mg/kg/day. An open label multicentre trial<sup>216</sup> which included 11 premature infants, nine of whom completed therapy at a dose of 5 mg/kg/day showed an efficacy rate of 75% with the only toxicity reported was a mild rise in serum creatinine. Final reports from study conducted by Weitkamp et al.<sup>217</sup> showed the experience of 21 premature infants who received L-AmB at doses ranging from 1 to 5 mg/kg/day, had 100% eradication of fungal infection and recovered clinically.

Although randomized controlled trials of comparisons between L-AmB and C-AmB in neonates are lacking, the available information suggests that these formulations are safe and effective. However, in neonates C-AmB is well tolerated and significantly cost effective.<sup>210</sup>

#### *4.15 Resolution of fever in patients undergoing antifungal treatment*

During the current study period it was also interesting to note there was a significant improvement in the temperature level of the patients from the day antifungal treatment was administered to the cessation of antifungal treatment. The most important factors limiting the planned intensity of antineoplastic chemotherapy in cancer patients are neutropenia, fever and infection, sometimes causing delays in treatment or reduced dosages with obvious potential implications for effectiveness. In addition, side effects and cost need to be considered.<sup>218</sup> Risk of severe infectious complications and fungal infections may be increased by intensive neoplastic treatments, such as those used in remission induction of acute leukaemia.<sup>219</sup>

Guidelines for the use of antimicrobial agents in neutropenic patients with cancer<sup>5</sup> emphasize that, no specific drug or combination of drugs, and no specific period of treatment, no specific scheme can be unequivocally applied to all febrile neutropenic patients. Because the definitions of infectious diseases and criteria used to assess the response to therapy vary considerably, the results from study to study are often not comparable.<sup>5</sup>

In one study L-AmB was more efficacious (63%) than C-AmB (32%) for resolution of fever ( $p=0.03$ ).<sup>48</sup> Using resolution of fever as an endpoint in a recent study<sup>130</sup> showed equivalent success rates of voriconazole and L-AmB (82% vs. 85%). Differences in overall survival were reported in two studies. 86% with C-AmB vs. 97% with L-AmB and 89% with L-AmB vs. 93% with caspofungin.<sup>177,197</sup> In one trial, the overall response of itraconazole was superior to that of C-AmB.

Resolution of fever is influenced by many factors other than IFI and is therefore a matter of debate. Inclusion of patients with different risk profiles such as duration of persistent fever, variable use of antifungal prophylaxis, differences in haemato-oncological

conditions, different durations of antifungal therapy and factors such as open design, sample sizes make the comparison of the study results difficult. In summary, there was no clear cut superiority of one antifungal agent.<sup>12</sup>

#### *4.16 Nephrotoxicity*

The findings from the current study showed that 18.6% of patients had a high serum creatinine level hence a low creatinine clearance. It should be mentioned that all patients who had a lower creatinine clearance were also on other medications which increase serum creatinine such as cyclosporine, diphenhydramine and acyclovir. As a majority of the patients were on L-AmB the incidence of nephrotoxicity was low compared to C-AmB as reported from other studies. An insufficient sample size was available for C-AmB in this study.

A retrospective review by Wingard et al.<sup>221</sup> of C-AmB in the treatment of fungal infections in bone-marrow transplant demonstrated that the incidence of nephrotoxicity was found to be 29% and in 53% of the patients doubling of the serum creatinine level occurred. In a safety and efficacy analysis salvage therapy,<sup>222</sup> L-AmB was given to 556 patients who were intolerant or refractory to C-AmB and 160 of this population had developed renal toxicity (serum creatinine>2.5mg/dL). On treatment with L-AmB a significant decrease in serum creatinine levels of these patients was noted and also 71% of all L-AmB treated patients had a stable creatinine level. Compared with C-AmB,<sup>223</sup> patients treated first-line with L-AmB<sup>177,197,130</sup> showed lower rates of nephrotoxicity. Moreover the dosage of L-AmB and the degree of reduced nephrotoxicity are only weakly correlated.<sup>181,49</sup>

Within the limitations of our retrospective study, having a small sample size from various clinical settings, the number of increased serum creatinine levels suggested that use of L-AmB associated nephrotoxicity was uncommon, as reported by Wingard et al.<sup>221</sup> The rate of nephrotoxicity may be partially explained by the increased concomitant use of cyclosporine observed in this study, this is supported by a report from a study which suggested that there was an increased nephrotoxicity when the two drugs were used together.<sup>224</sup> Accordingly the patients in this study group with an increased serum creatinine level received concomitant nephrotoxic drugs.

An article by Cannon et al.<sup>225</sup> suggested that L-AmB associated nephrotoxicity was not as frequent as that reported by Wingard et al.<sup>221</sup> A nephrotoxicity rate of 4.3% (2/46) was reported by Cannon et al.<sup>225</sup> in their observational study whereas, in this study a nephrotoxicity rate of 20% (11/59) was reported.

A randomised controlled trial<sup>226</sup> which included 105 patients with haematologic malignancies and with fever of unknown origin after receiving chemotherapy. The patients were randomly allocated to receive L-AmB 1mg/kg/day or C-AmB at 0.6 mg/kg/day for empirical antifungal therapy. The results demonstrated that compared with C-AmB group, the incidence of renal toxicity was significantly lower in the L-AmB group, 32% vs. 8% respectively (p=0.003). Infusion related reactions were similar in both groups (77% for c-AmB vs.73% L-AmB). This trial suggested that compared to C-AmB, L-AmB at 1 mg/kg/day produced less nephrotoxicity, with a similar frequency of infusion related adverse effects.

#### *4.17 Cost evaluation*

The economic impact of fungal infection is substantial, with an estimated cost per adult of USD 48,732 for candidiasis in hospital costs beyond the cost of care for transplant recipients in hospital in 1998. Although less frequent, aspergillosis was even more costly to treat with an estimated incremental cost of USD 86,635 in transplant recipients in 1998.<sup>227</sup>

The estimated antifungal cost data for the current study showed that for a patient (no: 43) (Table 24) of 11 years of age with a body weight of 57.7 kg who received L-AmB for a duration of 31 days, the drug treatment cost was AUD 44,394.00 in the pharmacy setting prepared by CIVAS and AUD 45,998.00 in the ward setting prepared by nurses. A total antifungal treatment cost of AUD 14,320.00 or AUD 14,838.00 for pharmacy and ward settings respectively could have been saved if the L-AmB treatment was ceased at 21 days. The cost of IV antifungal treatment is markedly dependent on the age and weight of the patients and the duration of treatment. For example, a patient of low body weight on

the same dose per kilogram treatment for long duration and a patient of higher body weight on a dose per kilogram for a short course of antifungal treatment could end up in similar treatment cost. This also applies to patients on combination treatment as the basic decision of the dose and the duration of treatment depends on the high or low risk profile of patients.

The results from a study<sup>228</sup> which examined the cost burden of hospitalization of patients with aspergillus and candida infections in Australia from 1995-1999 showed that the hospitalisation of 4,583 patients with aspergillosis and 57,758 with candidiasis were associated with a hospital cost of AUD 563 million. The mean length of stay in hospital was 12 days for aspergillosis diagnosis and the hospital cost was AUD 9,334. For disseminated, invasive and non-invasive candidiasis, the respective mean lengths of stays were 31, 17 and 12 days and the respective hospital costs were AUD 33,274, AUD 12,954 and AUD 7,694.

In the USA, for antifungal prophylaxis, an estimated total hospital cost of US \$72,706 was calculated in a study conducted by Wilson et al.<sup>227</sup> from the Maryland Hospital Discharge Data Set in 1997. On the other hand the hospital cost of treating proven fungal infections was US \$119,926 for transplant recipients with candidiasis and US \$157,929 for those with aspergillosis. Adjusted for inflation, in 2006 this yields a hospital cost of US \$200,087 and US \$263,798 respectively.

Successful antifungal prophylaxis has the potential to lower the overall costs of care because it can reduce the incidence of infection. Different regimens may not be equally cost effective as the costs of using various types of prophylaxis vary as do their effectiveness. However no suggestion can be made that any prophylaxis reduces the additional cost of empiric therapy or treatment of breakthrough infections to zero.<sup>229</sup>

With regard to antifungal cost, the dosage should be considered. Without question the most effective dosage is basic for this decision; however there is no need to exceed the optimal dosage. The dose escalation study of Walsh et al.<sup>181</sup> showed that with L-AmB doses up to 15 mg/kg in patients with fungal infections, for doses above 10 mg/kg  $C_{max}$  and area AUC did not further increase. This unique pharmacokinetics is thought to be explained by the fact that uptake of L-AmB by the reticuloendothelial system occurs with

accumulation of AmB in tissues. Before a practice standard is established, confirmation of such dosage schemes is needed.

Duration of antibiotic treatment beyond reasonable periods mentioned in the current study adds to the treatment cost. For example, for a randomly selected four patients from this study who received L-AmB for more than 30 days, the total treatment costs for antifungals prepared in the pharmacy and ward settings were AUD 96,482 and AUD 124,702 respectively.

When the additional cost over the optimum period of treatment of 21 days was calculated the total cost was found to be AUD 51,329 and AUD 68,594 for pharmacy and ward setting preparation respectively (Table 24). If AUD 51,329 could have been saved for four patients large savings could be expected for all patients who received prolonged antifungal treatment. Adherence to decisions made at the pharmacist-microbiologist meeting should be implemented when decisions are made at ward level, because cost savings on antifungal treatment can be made if a daily ceasing schedule was followed rather than only two or three days per week. From the results it could be seen that 12% of patients had their antifungal treatment ceased on Mondays which could have probably be done on previous Thursdays and the cost for treatment for four days from the day it should have been ceased to the actual day it was stopped could be saved. Treatment cost of AUD 1,083 for pharmacy setting and AUD 1,206 for the ward setting preparation could probably be saved for four days for a patient of four years of age with 16.2 kg body weight (patient number 80) who received an extra 3 mg/kg/day of L-AmB for four days (Table 28)

The current study also suggests an important factor that a reasonable saving can be made in pharmacy prepared antifungal by CIVAS than a nurse prepared antifungal in the ward setting. As the reconstituted vials cannot be retained in a ward setting, for doses where residual drug in the ward setting was discarded, increased the total treatment cost dependent on the duration of treatment. A particular dosage regimen controls the amount of residual drug and therefore the cost differential. Hospitals often depend on nurses for preparation of reconstituted drugs and having a CIVAS at the hospital can generate savings in the total drug cost. For example for four patients receiving L-AmB, selected

randomly from the study, a total of AUD 28,220 could be saved, if L-AmB was prepared in CIVAS and a total of AUD 22,732 could be saved in four patients for antifungal treatment when a combination was included as a part of the antifungal regimen.

The cost data used in the current study have included drug, staff and consumables cost. The capital and maintenance cost of the CIVAS unit was not included. This would be amortised over numerous preparations. Similarly the cost of the area used by the nursing staff was not included.

Other costs such as diagnostic procedures, laboratory testing, cost of treating side effects of the drug, and monitoring for drug side-effects were not considered. The determined cost data relates to a supply cost rather than a total cost. Some of the other hospital costs are difficult to apportion to the cost per infusion.

Results with current antifungal therapies in cancer patients with fungal infections have prompted exploration of other methods of improving survival rates. Failure of antifungal therapy is not solely a function of the efficacy of a given drug: the ultimate treatment outcome is influenced by factors such as underlying disease state, the site of fungal infection, multiple organ or organ failure, drug pharmacokinetics and patient compliance.<sup>230</sup> By the time invasive fungal infections become apparent, many of these factors are beyond the scope of medical intervention and therefore the focus has shifted to earlier interventional strategies.<sup>231</sup>

A thorough study of the epidemiology of fungal infections in cancer patients and criteria such as safety, efficacy, cost, consequence of doing so, potential for development of resistant strains of fungi and prevalence of fungal infections in a given population should be considered before instituting prophylaxis in all patients.<sup>232</sup> Development of new pre-emptive strategies aimed at distinguishing patients who need antifungal prophylaxis or empirical treatment should be investigated. The new antifungal agents may provide exciting options for combination antifungal therapy being active against some fungi resistant to L-AmB and may have a role in the management of fever and neutropenia.<sup>233</sup>

Reduced nephrotoxicity with L-AMB and other antifungal agents are important improvements. However antifungal efficacy remains the most important consideration in choosing the most appropriate agent in the face of fungal infections. If cost were of no

consequence L-AmB would probably still be the accepted standard of care for empirical therapy. The dose of 3 mg/kg/day although commonly accepted is based on clinical usage rather than a strong evidence base in children.<sup>19</sup> However, when toxicity and efficacy are taken into consideration L-AmB may not be as expensive as it appears.

In cases of mycoses that are refractory to treatment or for which no established treatment exists, it appears that combination of antifungal drugs is a logical step.<sup>10</sup> However, since few clinical data are available combinations are used on an empirical basis in most cases. However, prospective clinical trials to evaluate various combinations of antifungal are supported by some data obtained from in-vitro animal model and clinical studies.<sup>234</sup>

The current study was a treatment audit. The value of carrying out such studies includes an insight into how the hospital guidelines are followed. Such a study provides important information and demonstrates an increased understanding of the most effective means antifungal treatment, adverse effects. Audits help hospitals identify barriers to guideline adherence. In this case, overall IV antifungal treatment followed acceptable guidelines and no specific intervention could be proposed from the findings. Lengthy treatments however require regular reviews. Some savings could be made by ceasing the drug on any day rather than mainly at two ward rounds each week.

## 5 CONCLUSION

The cost of patient care will increase with the inappropriate use of antifungal agents and may diminish its quality. Moreover, with the ever increasing budgetary constraints and arrival of competitive market in health care, the direct cost of prescribing inappropriate antifungal therapy may mean that any further opportunity for employing more useful alternatives may be fortified.<sup>235</sup> This could be prevented by improving prescribing practices. However, significant questions remain, including the efficacy of the new antifungal agents against less common fungi and the management of breakthrough infections and treatment failures.<sup>233</sup>

At present understanding of newer antifungal agents in children is limited. In future children should be included in the studies of new antifungal drugs and combination therapy and stratify the results by age, given the potential differences in pharmacokinetics, pharmacodynamics, efficacy and safety.<sup>2</sup> Further studies are needed to judge the use of antifungals to allow empirical antifungal therapy or antifungal prophylaxis.

The understanding of the most effective means of treating disseminated fungal disease in the immunocompromised cancer patients could be greatly increased by the information gained from rigorously controlled and statistically valid studies.<sup>231</sup> In patients with difficult to treat infections or infections due to suspected resistant strains, the use of combination therapy remains an important empirical strategy and the decision of what treatment to use in each cases should be individualised.<sup>236</sup> Finally, further evolution of treatment and prevention strategies together with surgical intervention and timely diagnosis are urgently required.<sup>115</sup>

In summary, the data from this study indicated a satisfactory concordance of IV antifungal treatment with guidelines. However, the remaining requirements for appropriate use required additional education. It was concluded from this study that L-AmB still remains the antifungal agent of choice for the majority of cases which were reported to be acute myeloid leukaemia. The use of newer antifungal agents (voriconazole, caspofungin and posaconazole) should be taken into consideration as very

few patients in this study population were prescribed any of the newer antifungal drugs. This study also showed that combination antifungal therapy were prescribed to five out of 59 patients included in this study and this limited evidence supports a need for further studies of combination therapy and the combination choice and individual dosages. Majority of the patients received 3 and 5 mg/kg/day of L-AmB which is the recommended paediatric dosage in the Australian Therapeutic Guidelines. It was also noted that the mean temperature of the patients undergoing antifungal treatment was reduced by the end of the therapy. Nephrotoxicity was reported only in 18% of the patient. The total drug cost is reduced if the drug was prepared in the Pharmacy CIVAS. The days on which IV treatment is ceased should be reviewed to identify if cost savings can be achieved.

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