

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

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

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

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

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

Keywords: economic, model, empirical antifungal

### Introduction

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

Liposomal amphotericin B (LAMB) (Ambisome<sup>®</sup>, Gilead Sciences) and voriconazole (Vfend<sup>®</sup>, Pfizer) are two antifungals that have been used successfully in empirical therapy.<sup>3</sup> In

an open-labelled randomized trial by Walsh *et al.*,<sup>4</sup> which compared LAMB with voriconazole for empirical therapy in neutropenic patients, voriconazole appeared to be inferior in preventing the composite endpoint of survival, breakthrough fungal infections, premature discontinuations, persistence of baseline fungal infections and fever persistence. Nevertheless, the authors concluded that voriconazole is a suitable alternative to amphotericin B preparations. This conclusion was driven by the fewer breakthrough fungal infections observed among voriconazole-treated patients (1.9% versus 5.0%). However, this is controversial, given that all the other endpoints favoured

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LAMB. Data analysed by the US Food and Drug Administration (FDA) suggest that voriconazole was inferior to LAMB with respect to overall success rates (23.7% versus 30.1%, respectively).<sup>5</sup> As a consequence, the FDA's Antifungal Drugs Advisory Committee voted unanimously against accepting the empirical use of voriconazole in neutropenic patients with fever.

An advantage voriconazole maintains over LAMB, however, is its significantly lower acquisition costs. Indeed, since voriconazole became available, it has been accepted as an effective alternative to LAMB for use as a first-line empirical therapy in Australian hospitals as well as in many practices worldwide.<sup>6,7</sup> In a recent study by Collins *et al.*,<sup>8</sup> voriconazole was suggested to be more cost-effective than LAMB for empirical use in febrile neutropenia. The study was from the US perspective, and represented practice at the authors' local institution only. Surprisingly, apart from the study by Collins *et al.*, there are no pharmacoeconomic data regarding the empirical use of voriconazole versus LAMB. Indeed, from the Australian hospital perspective, no economic evaluations have been performed yet on voriconazole and/or LAMB, and thus, their financial impact as empirical therapy remains unresolved.

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

**Materials and methods**

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

fever during the period of neutropenia and was successfully treated for any baseline fungal infection.

*Perspective*

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

*Model structure*

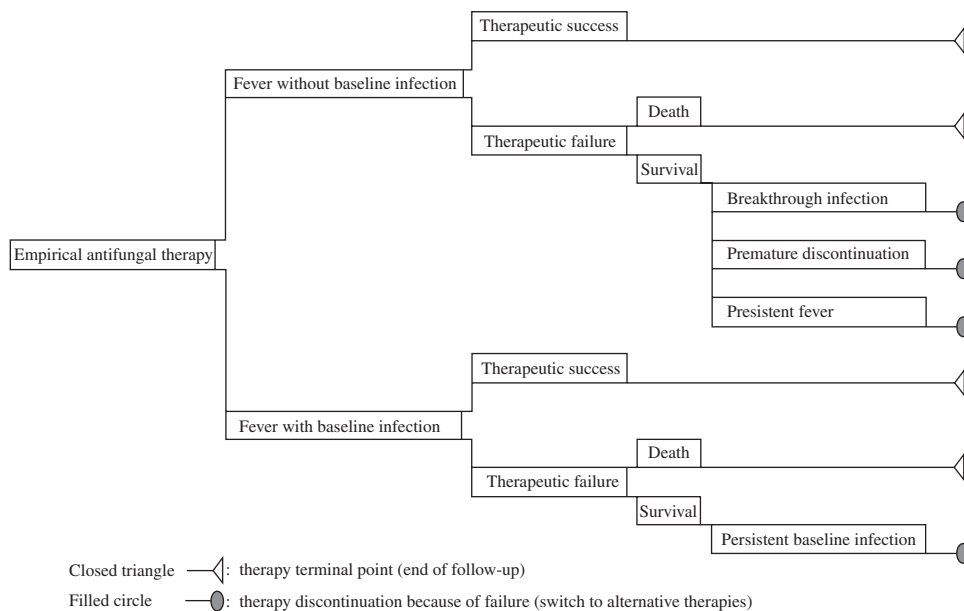
Decision analysis<sup>9</sup> was applied to the comparison of voriconazole and LAMB, the structure of which is illustrated in Figure 1.

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

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

*Model inputs*

The model was populated with data derived primarily from the trial. These included clinical outcomes rates, morbidity and mortality,



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

## Economics of empirical antifungal therapy

**Table 1.** Outcomes and probabilities of voriconazole and LAMB<sup>4</sup> used in the model

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

<sup>a</sup>Number of patients with persistent fever = number of patients who failed therapy – number of patients who failed therapy for reasons other than persistent fever.

duration of initial therapy and reasons for treatment failure. The clinical outcomes and their probabilities as per Walsh *et al.*<sup>4</sup> are summarized in Table 1.

An independent expert panel was convened, comprising four clinicians from Australia with clinical expertise in systemic antifungal therapy and specialist knowledge in oncology, haematology and infectious diseases. The panel advised on additional analyses of the data by Walsh *et al.* where appropriate. The panel also provided information on the economic consequences of the treatment pathway, which was not available from the literature. This included concomitant antibiotics, screening tests for fungal infections, monitoring tests for side effects and intensive care management [intensive care unit (ICU) data related to changing intravenous (iv) tubes and procedures that are not related to IFI were not included in the study]. In addition, the panel was used to advise on the alternative therapies used after initial therapy discontinuations. These were as per the Australian hospital setting, and included the name, dose and duration of administration of the alternative antifungals. The choice of alternative therapy was dependent on the reason for treatment discontinuation. Where breakthrough infections and baseline infections resulted in therapy discontinuations, the site of infection and the type of the infection's causative fungi reported by Walsh *et al.*<sup>4</sup> influenced the choice of the alternative antifungal. The expert panel also validated the decision tree model used in this study. An expert panel meeting was used to obtain consensus among panel members.

As per Walsh *et al.*,<sup>4</sup> patients on voriconazole received a loading dose of iv 6 mg/kg twice on the first day, followed by daily maintenance iv dose of 3 mg/kg twice a day (or 200 mg tablet taken twice daily). Patients prescribed oral voriconazole received 3 days of iv therapy before commencing oral therapy. LAMB was administered as iv 3 mg/kg/day throughout the treatment duration. For patients with baseline fungal infections, the maintenance voriconazole regimen was a twice daily iv 4 mg/kg or oral 300 mg, and the LAMB iv dose was 6 mg/kg/day. The oral voriconazole formulation was received by 22% of all patients on voriconazole. A reduction of LAMB dose to 1.5 mg/kg/day was permitted for some patients experiencing side effects.

According to the clinical study, baseline fungal infections are those diagnosed within 24 h after the initiation of therapy. Breakthrough fungal infections were defined as those diagnosed after 24 h of receiving antifungal therapy. For the purpose of the current study, patients with premature discontinuations were further classified as premature discontinuations because of severe side

effects (i.e. infusion-related reaction, hepatotoxicity and nephrotoxicity) and premature discontinuation because of lack of efficacy against suspected fungal infection or persistent fever.

### Data provided by expert panel

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

### Documentation of costs

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

- (i) In the case of successful treatment, the cost was a result of the duration of hospitalization caused by febrile neutropenia.

**Table 2.** Alternatives to voriconazole and LAMB after premature discontinuations

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

<sup>a</sup>70 mg/day (loading dose), 50 mg/day (maintenance dose).

<sup>b</sup>6 mg/kg twice daily (loading dose), 3 mg/kg twice daily (maintenance dose).

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

Cause of therapy failure	Alternative	Details
<b>Voriconazole (breakthrough fungal infection)</b>		
<i>Aspergillus</i> species	LAMB	5 mg/kg/day
<i>Candida</i> species	Caspofungin	Standard <sup>a</sup>
<i>Zygomycetes</i>	LAMB	5 mg/kg/day
<b>Voriconazole (non-responding baseline fungal infection)</b>		
<i>Aspergillus</i> species	LAMB	5 mg/kg/day
<i>Candida</i> species	Caspofungin	Standard <sup>a</sup>
<i>Zygomycetes</i>	LAMB	5 mg/kg/day
Voriconazole (persistent fever)	LAMB	5 mg/kg/day
<b>LAMB (breakthrough fungal infection)</b>		
<i>Aspergillus</i> species	Posaconazole/LAMB	Combination <sup>b</sup>
<i>Candida</i> species	Caspofungin/fluconazole	Combination <sup>c</sup>
dematiaceous moulds <sup>d</sup>	Voriconazole/terbinafine	Combination <sup>e</sup>
<b>LAMB (non-responding baseline fungal infection)</b>		
<i>Aspergillus</i> species	Posaconazole	800 mg/day
<i>Candida</i> species	Caspofungin	Standard <sup>a</sup>
<i>Trichoderma</i> fungaemia	Voriconazole	Standard <sup>f</sup>
LAMB (persistent fever)	Voriconazole	Standard <sup>f</sup>

<sup>a</sup>70 mg/day (loading dose), 50 mg/day (maintenance dose).

<sup>b</sup>800 mg/day posaconazole with 3 mg/kg/day LAMB. LAMB will cease when posaconazole steady-state is reached.

<sup>c</sup>70 mg/day (loading dose) and 50 mg/day (maintenance dose) caspofungin with 200 mg/day fluconazole.

<sup>d</sup>Dematiaceous moulds were of *Alternaria* species and unidentified species.

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

<sup>f</sup>6 mg/kg twice daily (loading dose), 3 mg/kg twice daily (maintenance dose).

(ii) In the case of therapeutic failure, two possible results were obtained:

a. For surviving patients who did not respond to initial treatment, the cost included additional costs resulting from changing

treatment procedures and giving alternatives that were associated with prolonged hospitalization and drug administration.

b. In cases where patients died, as with the successful treatment, the cost was a result of duration of hospitalization caused by febrile neutropenia.

## Economics of empirical antifungal therapy

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

- (i) The average patient does not pay for treatment and is covered by Medicare.
- (ii) Patients are inpatients throughout the study period.
- (iii) The number of hospitalization days due to febrile neutropenia can be established by the duration of antifungal therapy.
- (iv) Antifungal therapy can fail only once. If patients switch therapy after failing the initial therapy, their alternative therapy will be successful.
- (v) No specifications were made about durations for alternative therapies. Any alternative therapy was assumed to have duration similar to that of the discontinued initial therapy.

All assumptions were validated by the expert panel.

### Cost calculations

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

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

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

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

The cost inputs used in the modelling analysis are summarized in Table 4. Apart from medication and hospitalization costs, all resource costs involved in the study were obtained from the Australian Medicare Benefits Schedule Book (2007).<sup>11</sup> Medication costs involved in this study were obtained as drug wholesale prices, which are paid by Australian public hospitals, as per Health Purchasing Victoria tender (2007–2009).<sup>12</sup> The cost of hospitalization for febrile neutropenia was obtained from the Australian Refined Diagnosis-related Groups (2006–07),<sup>13</sup> and the cost of an ICU bed was as per Rechner and Lipman.<sup>14</sup> Hospitalization costs were adjusted for the financial year 2007–08 as per the Australian Consumer Price Index (2008).<sup>15</sup>

**Table 4.** Resource costs<sup>11–14</sup>

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

### Sensitivity analysis

Different scenarios produced by modifications of the values of several key variables and assumptions, in relation to costs and probabilities, were analysed to evaluate the robustness of the study conclusion. For any variable, the highest and lowest values within a reasonable range of values were used as substitutes for the baseline value. Where the highest or lowest substitution changes the study conclusion, more values within the range were used to replace the baseline value. This was repeated until the exact variable value (or range of values) that changes the study conclusion was determined.

As wholesale prices are at the discretion of the pharmaceutical companies, the effect of changing the voriconazole and LAMB prices was evaluated. The effect of variations in the hospitalization cost was investigated as well. The sensitivity analysis also evaluated the impact of estimations made by the expert panel. These included the duration of therapy, duration in ICU, ratio of patients with doses reduced because of side effects, dosage form of LAMB as alternative and dosage form of voriconazole as alternative. The effect of excluding the cost of antibiotics and G-CSF, and the increase in dose with baseline infections, and the effect of the voriconazole dosage form given before discontinuation were also evaluated. The ranges over which key variables were varied are shown in Table 5. The model's sensitivity to the probability of patient distribution in the decision tree was investigated by applying the probability data in the LAMB arm to the voriconazole arm, applying the probability data in the voriconazole arm to the LAMB arm and switching the probability data between the voriconazole and the LAMB arms. Another scenario analysed was the replacement of the probability of

**Table 5.** Variation range for variables in sensitivity analysis

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

patient distribution in the LAMB arm with that reported in another clinical study on the empirical use of LAMB.<sup>16</sup>

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

**Results**

*Cost of empirical therapy*

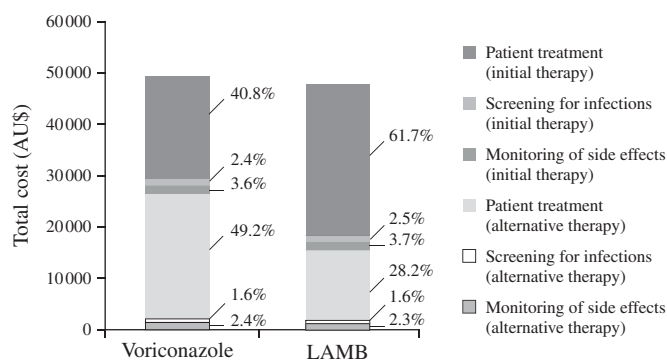
The weighted average cost of empirical therapy per patient for voriconazole (AU\$49 237) was higher than that for LAMB (AU\$47 815). This represents an economic advantage of LAMB over voriconazole in the order of AU\$1422 (2.9%) per patient. The contribution of different components in the overall cost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

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

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

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

## Economics of empirical antifungal therapy



**Figure 2.** Contribution of different cost components in overall therapy.

that with the voriconazole (AU\$189 228 and AU\$53 489, respectively).

### Sensitivity analysis

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

voriconazole and LAMB to AU\$63 964 and AU\$62 318, respectively, which is an increase in the overall cost difference to AU\$1646.

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

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

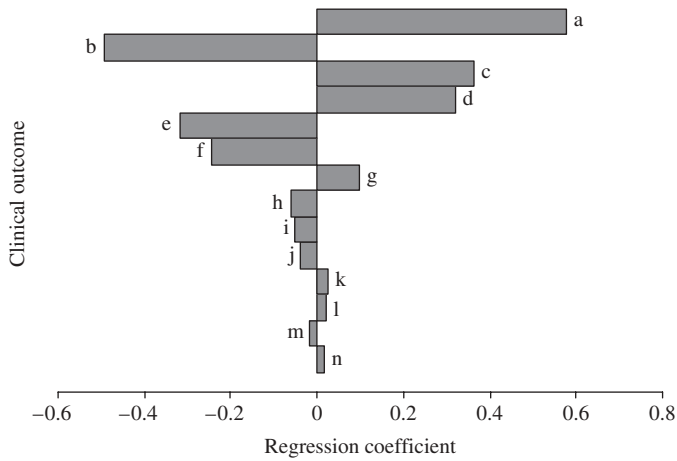
Two-way exchange in probability data between the voriconazole and the LAMB arms in the decision tree resulted in a cost saving of AU\$14 associated with voriconazole. The one-way

**Table 7.** The proportional cost of empirical voriconazole and LAMB

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

<sup>a</sup>All shown cost values were shortened to the nearest no-decimal digits status.

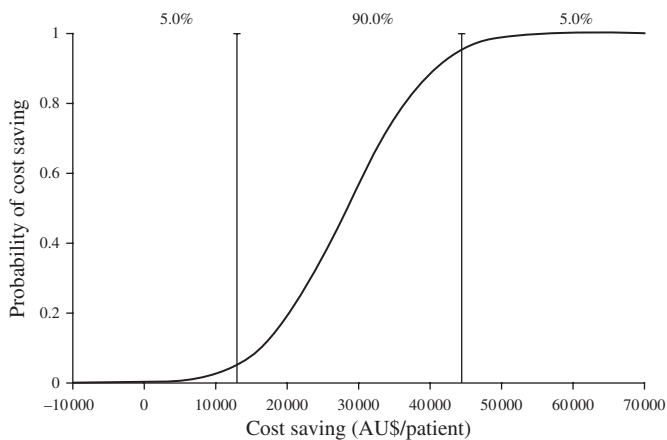
<sup>b</sup>Calculations involving cost values took in consideration two decimal digits (data not shown) associated with each of the cost values.



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

exchange in probability data, however, had no impact on the cost differentials. Even with replacing the LAMB probability data in this study with empirical LAMB data reported elsewhere in the literature,<sup>16</sup> the resulting cost saving (AU\$2873) still remained associated with LAMB.

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



**Figure 4.** ‘Cost saving’ probability curve.

**Discussion**

The present study is the first to investigate the pharmacoeconomics of using voriconazole and LAMB from an Australian perspective. The study compared the cost of voriconazole with that of LAMB as first-line empirical therapies for treating patients with febrile neutropenia. According to the analysis, LAMB demonstrated a total cost saving of AU\$1422 per patient (Table 7). The cost per patient successfully treated with LAMB was AU\$32 816 lower than that with the use of voriconazole. The cost of survival was also lower with the use of LAMB (difference of AU\$2665). On the basis of the data, LAMB appears to be a dominant empirical medication over voriconazole. It has higher efficacy (i.e. higher success rate and lower death rate) as well as lower total cost. Therefore, in terms of the overall economic evaluation in the present study, the incremental cost-effectiveness ratio would not be as good an indicator as the total difference in the medications’ costs.

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

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

The construction of the decision tree in the current study was based on data collected prospectively by Walsh *et al.*<sup>4</sup> in a randomized double-blind controlled trial. This makes the study findings considerably more reliable than findings based on the model used by Collins *et al.*, where data collection is retrospective in nature. A main limitation of the Collins *et al.* study is its retrospective nature that may lead to a selection bias.<sup>20</sup> While Collins *et al.*<sup>8</sup> argued that models based on day-to-day clinical practice, and not randomized clinical trials (RCTs), provide more accurate estimation of care, they only evaluated 63 patients in their study. The current study used data from the trial by Walsh *et al.*,<sup>4</sup> involving 837 patients.

RCTs are accepted as the most powerful tool for assessing the effectiveness of medications, interventions and procedures. By design, the blind and random assignment of adequate numbers of subjects in studies and the blind assessment of outcomes minimize bias due to observer and confounding factors from known and unknown variables.<sup>21</sup> In the context of economic evaluations, as an ideal, evaluation would be based on the best available clinical evidence, and an RCT would provide the most reliable source of data.<sup>22</sup> Indeed, conducting economic evaluation based on a clinical trial is an efficient way of getting valid and reliable information with minimum assumptions made

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during data collection.<sup>23</sup> Since 1994, more than 30% of the economic evaluations published on the United Kingdom's NHS Economic Evaluation Database, for instance, have been based on data from a single RCT.<sup>24</sup> However, while randomization minimizes the risk of selection bias, it does not insure the generalizability of results.<sup>24</sup> Thus, for the economic results of the current study to be applicable to the Australian setting, it is important for the results reported by the Walsh *et al.* trial to be generalizable (externally valid) to the Australian setting also. As per the expert panel, the clinical data by Walsh *et al.*<sup>4</sup> are in fact generalizable to Australia. The trial is a multicentre study where patients were recruited from a large number of study sites in several countries and continents. This reflected a variation in healthcare provisions within and among different systems, and increased the efficiency of trial-wide estimates. Also, the criteria for the inclusion and exclusion of patients were specified in the trial, where the patients included reflected the normal Australian clinical caseload, and the fact that these inclusion criteria were unified for the wide range of study sites has reduced the threat to the trial generalizability. In addition, the administration of both voriconazole and LAMB in the trial is generally similar to that currently recommended in the Australian guidelines. A main indicator of the relevance of the outcomes of the Walsh *et al.* trial to real practice in Australia is the fact that the Walsh *et al.* study is being used as a reference in the current Australian guidelines in relation to the empirical use of voriconazole and LAMB in practice.<sup>6,25</sup>

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

Therefore, LAMB having a higher rate for breakthrough infections does not routinely translate into it having a higher overall cost. This emphasizes the need to examine each of the treatment pathways that are associated with the use of medications individually and fully.

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

The sensitivity analysis conducted on the dataset demonstrated that the overall economic conclusion of the study was not sensitive to changes in the acquisition costs of either or both voriconazole and LAMB. This goes against what one may expect as result of the significantly lower acquisition cost of voriconazole when compared with LAMB (approximately AU\$332/day versus AU\$1475/day, respectively), and is reflective of the role of voriconazole and LAMB as alternative antifungals. LAMB is a common alternative to voriconazole and will increase the total cost of patients treated initially with voriconazole. In contrast, voriconazole is a common alternative to LAMB, which will reduce the total cost associated with patients treated initially with LAMB. This observation highlights the need for clinicians to consider all costs related to treating patients, including both acquisition cost and secondary cost (cost of therapy failure), when making a decision in regard to prescribing a medication. The hospitalization cost, with a value of AU\$1113/day, constitutes a major component in the inpatients' cost of treatment. As one would anticipate, the elimination or the 2-fold increase in the daily cost for hospital stay, as per the sensitivity analysis, considerably affected the overall cost for

both voriconazole and LAMB. Nonetheless, the overall economic conclusion made in the study was demonstrated to be insensitive to wide variations in hospitalization cost. This is to be expected given the similarity in patients' length of stay between the two arms of the study.

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

In the study by Walsh *et al.*,<sup>4</sup> dose reduction of LAMB to 1.5 mg/kg/day was permitted with the presence of side effects, which potentially decreases the total cost of LAMB. Nevertheless, applying the scenario where LAMB dose reduction was not allowed did not affect the economic outcome of the current study. This could be because only 1.5% of patients (estimated by the expert panel) receiving LAMB required dose reduction. Importantly, the sensitivity analysis illustrated that prescribing oral voriconazole instead of iv voriconazole as initial therapy would reduce the total cost associated with voriconazole. However, the use of oral formulations of voriconazole is not always possible, especially in cases where patients have impaired gastrointestinal functions (i.e. mucositis).

The only switch in the overall probability of distribution for variables that affected the study conclusion is the two-way switch made between the two study arms. Nonetheless, the resulting cost saving with voriconazole was only AU\$14. It appears that, in the current study, the difference in the overall probability of distribution for variables between both arms is not a key factor behind any wide cost differentials measured between the two antifungals. However, according to the uncertainty analysis (Figure 3), some individual variables can potentially affect the study outcomes. The individual variables that affected the model the most were persistent fever, therapeutic failure of febrile patients without baseline infections and/or

fever without baseline infections. This is expected as these variables have the highest ratios of patient distribution among all variables, which translates into longer overall hospital stay, and ultimately, higher overall cost, especially where the costs of hospitalization is a major component in the cost of patients' treatment. Added to this is the consideration that the treatment of patients under these conditions involves additional costs associated with using alternative antifungals. The economic advantage associated with LAMB increased most sharply if the rate of either or both persistent fever and therapeutic failure in fever without baseline infections associated with voriconazole increased. Conversely, the advantage of LAMB declined fastest if the rate of either or both of persistent fever and therapeutic failure in fever without baseline infections associated with its use increased. Importantly, the Monte Carlo simulation demonstrated a clear economic advantage for LAMB over voriconazole. On the basis of the uncertainty analysis, LAMB empirical therapy is expected to be associated with cost savings over voriconazole empirical therapy in 99.8% of cases. It is important to recognize this, in addition to the fact that the mean cost saving with LAMB, out of 10 000 simulations, was as high as AU\$28 494, given that the measured economic advantage of LAMB over voriconazole, in this study, is only AU\$1422, which is low enough to make one mistakenly consider that the two antifungals have similar overall costs and, therefore, are equally cost effective.

The limitations of the present study are mainly related to the assumptions made in the analysis. The fact that the decision tree structure only allowed for a single switch to alternatives is a limitation that may underestimate the cost of patients with multiple discontinuations. Nevertheless, the fact that therapy discontinuations were more with voriconazole when compared with LAMB (Table 1) indicates that the additional costs associated with secondary alternatives will be higher for voriconazole as opposed to LAMB, which will further increase the dominance of LAMB. The assumption that any alternative medication had a duration of administration that was similar to that for the discontinued initial medication is another limitation in the study. No data are available on the duration of empirical therapy in the Australian setting. However, according to the expert panel in this study, the duration appears to be similar for the different empirical antifungal agents, which is consistent with the result from the study by Walsh *et al.*,<sup>4</sup> where both voriconazole and LAMB had a median duration of 7 days. Realizing that the assumptions are limitations in the study, all assumptions were validated by the expert panel before they were applied. The use of an expert panel to estimate data is also recognized as a limitation in the current study. According to the hierarchy of evidence, for evaluating outcome values, expert opinion is the least favourable.<sup>21</sup> Various biases may affect experts' estimates.<sup>21</sup> Nevertheless, expert judgement is often referred to in situations where no other data sources are available,<sup>19,21</sup> which is the case in the present study. The panel opinions were elicited with consensus, where the panel represented a variety of expertise and hospitals to minimize bias and increase generalizability (external validity) of results, as was previously discussed. An additional limitation is that, ideally, an economic study should be a prospective analysis of a prospective randomized trial. This study, however, was a retrospective analysis of a prospective randomized trial. Indeed, future studies of empirical therapies that prospectively collect economic data will be valuable, and will address the limitations reported in the

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current available studies. Importantly, future studies should also investigate the long-term costs and quality of life associated with the empirical use of voriconazole and LAMB.

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

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

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### Transparency declarations

None to declare.

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