

# Economic considerations in the treatment of invasive aspergillosis: a review of voriconazole pharmacoeconomic studies

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**Abstract:** Invasive aspergillosis is a life-threatening fungal infection predominately affecting immunocompromised individuals. The incidence of inpatient-treated aspergillosis cases in the US is estimated to be between 3.02 and 3.80 per 10,000 hospitalized patients. The estimated difference in hospital costs of patients with an aspergillosis infection is US\$36,867 to US\$59,356 higher than those of patients without the infection. Voriconazole is a synthetic, broad spectrum triazole antifungal agent, with FDA-approved indications for the treatment of invasive aspergillosis, esophageal candidiasis, candidemia in nonneutropenic patients, invasive candidiasis, and infections due to *Scedosporium apiospermum* and *Fusarium* species in patients refractory to or intolerant of other therapy. Eight cost-effectiveness analyses, one cost-minimization analysis, and one cost analysis were identified from a Medline search. The 10 pharmacoeconomic analyses were conducted in six different countries comparing voriconazole to conventional amphotericin B, liposomal amphotericin B, itraconazole, and caspofungin. All the cost-effectiveness and cost-minimization analyses identified voriconazole as the most cost-effective therapy. The cost analysis demonstrated voriconazole cost-savings. While the acquisition costs of voriconazole are higher than those of conventional amphotericin B, the toxicity profile and rate of treatment success associated with voriconazole result in lower total treatment costs per successfully treated patient.

**Keywords:** voriconazole, antifungal agents, invasive aspergillosis, pharmacoeconomics

## Overview and management of invasive aspergillosis

Invasive aspergillosis is a life-threatening fungal infection predominately affecting immunocompromised individuals. The infection is most commonly caused by *Aspergillus fumigatus*, with *Aspergillus flavus*, *Aspergillus niger*, and *Aspergillus terreus* less often implicated.<sup>1</sup> Profound and prolonged neutropenia is the most common risk factor associated with development of disease. As such, hematopoietic stem cell transplant (HSCT) recipients and patients receiving aggressive chemotherapy for hematologic cancers are at particular risk.<sup>2,3</sup>

Invasive aspergillosis most frequently begins in the lungs after inhalation of *Aspergillus* conidia. Initial, nonspecific manifestations include fever, cough, and dyspnea.<sup>4</sup> Without treatment, invasive pulmonary aspergillosis is almost always fatal.<sup>1,4,5</sup>

Definitive diagnosis of invasive aspergillosis requires culture confirmation of *Aspergillus* species after biopsy of a sterile specimen. However, culture results lack sensitivity, may take as long as 4 weeks, and be confounded by contamination.<sup>1,4</sup> Prompt treatment is essential to improve survival. In the high-risk host, treatment is generally initiated based on signs and symptoms consistent with the disease. These may

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include fever despite the use of broad-spectrum antimicrobial agents, pulmonary infiltrates on CT scan (particularly with the presence of the halo or air-crescent sign), and/or detection of galactomannan antigen in the serum.<sup>1</sup>

Several antifungal agents are indicated for the treatment of invasive aspergillosis, including amphotericin B and its lipid formulations, itraconazole, voriconazole and caspofungin. Voriconazole, however, is the drug of choice for the primary treatment of invasive aspergillosis.<sup>1</sup> Voriconazole is initiated with a loading dose of 6 mg/kg intravenously (iv) every 12 hours for two doses and followed by 4 mg/kg every 12 hours. Parenteral administration is recommended in seriously ill patients, but clinically stable patients may be converted to oral tablets (with weight-based dosing rounded up to convenient pill sizes). A minimum of 6 to 12 weeks of therapy is required to adequately treat invasive pulmonary aspergillosis. Longer durations are necessary when prolonged periods of immune suppression are present and in cases where infected lesions are slow to resolve.<sup>1</sup> Voriconazole levels have been correlated with antifungal efficacy and toxicity in several small studies.<sup>6,7</sup> Though not yet routinely advocated, therapeutic drug monitoring is reasonable when drug toxicity or refractory fungal disease is suspected.<sup>4</sup>

The incidence of inpatient-treated aspergillosis cases in the US in the late 1990s was between 3.02 and 3.80 per 10,000 hospital patients, representing over 10,000 aspergillosis-related discharges from community hospitals.<sup>8,9</sup> The total US community hospital-related cost of aspergillosis in 1996 was estimated to be US\$633.1 million.<sup>8</sup> The estimated difference in hospital costs of patients with aspergillosis in the late 1990s were US\$36,867 to US\$59,356 higher than those of patients without the infection.<sup>8,9</sup> Using the US Bureau of Labor Statistics CPI Inflation Calculator, the equivalent 2009 amounts are US\$48,110 to US\$80,468.<sup>10</sup> Compared to patients with other invasive fungal infections such as candidiasis, histoplasmosis, and cryptococcosis, those with aspergillosis had the highest per-patient treatment costs (US\$37,921/patient for inpatient care and US\$34,871/patient for outpatient follow-up care).<sup>9</sup> When adjusted to 2009 dollars the total cost to treat a patient with aspergillosis is US\$94,991 which is consistent with 2003 estimates provided by Tong and colleagues.<sup>11</sup>

Although voriconazole is considered first-line therapy for the primary treatment of invasive aspergillosis, it does not have the lowest acquisition cost of the FDA-approved treatments of invasive aspergillosis. Therefore the purpose of this article is to review the pharmacoeconomic studies that included voriconazole for the treatment of invasive

aspergillosis. An overview of voriconazole is provided as background information.

## Overview of voriconazole

Voriconazole is a synthetic, broad spectrum triazole antifungal agent that inhibits fungal cytochrome p450-dependent enzyme lanosterol 14- $\alpha$ -demethylase, ultimately decreasing the biosynthesis of ergosterol, an essential component of the fungal cell membrane. Voriconazole is FDA-approved for the treatment of invasive aspergillosis, esophageal candidiasis, candidemia in nonneutropenic patients, invasive candidiasis and infections due to *Scedosporium apiospermum* and *Fusarium* species in patients refractory to or intolerant of other therapy.<sup>12</sup>

Voriconazole is available as both oral and parenteral formulations. The oral tablet has a bioavailability exceeding 90%, which permits switching between formulations when clinically appropriate. The kinetics of voriconazole are nonlinear, dose-dependent, and exhibit a high degree of inter-patient variability. It is metabolized by the P450 (CYP) enzymes CYP2C19, CYP2C9, and CYP3A4 to inactive metabolites. Its metabolism is saturable; increasing doses of voriconazole result in disproportional increases in drug exposure.<sup>13</sup>

Voriconazole is generally well tolerated. The most commonly reported adverse reactions, occurring in at least 5% of patients, include visual disturbances, elevated hepatic enzymes, fever, rash, nausea and vomiting.<sup>12,14,15</sup> Visual and auditory hallucinations have also been occasionally reported in patients receiving voriconazole.<sup>12,15</sup> Plasma voriconazole levels exceeding 5.5  $\mu$ g/mL have been linked to higher incidences of neurologic events, visual disturbance and hepatotoxicity.<sup>6,7</sup>

Voriconazole has numerous drug-drug interactions, which may limit its usefulness in certain populations. Voriconazole is both a substrate and inhibitor of P450 (CYP) enzymes CYP2C19, CYP2C9, and CYP3A4.<sup>12,14,15</sup>

Voriconazole is available for IV use as a 200 mg powder for reconstitution and for oral use as 200 mg and 50 mg tablets and a 200 mg/5 mL powder for suspension.<sup>12</sup> Average wholesale prices are US\$121.63 per 200 mg iv vial, US\$10.33 per 50 mg tablet, and US\$41.33 per 200 mg tablet.<sup>16</sup>

## Clinical outcomes

Historically, invasive aspergillosis-associated mortality rates have ranged from 60% to 90%, with central nervous system or disseminated infection or disease in HSCT patients

conferring graver prognoses.<sup>17–20</sup> Changes in transplantation practices, diagnostic procedures, and the extensive use of voriconazole have been credited with significant reductions in mortality rates.<sup>17,21</sup>

In 2002, Herbrecht and colleagues published the pivotal Global Comparative Aspergillosis (GCA) study sponsored by Pfizer.<sup>22</sup> The investigators compared the efficacy and safety of voriconazole and conventional amphotericin B desoxycholate (CAB) for the primary treatment of invasive aspergillosis in immunocompromised patients. This prospective, randomized trial involved 277 patients ( $n = 144$ , voriconazole;  $n = 133$ , CAB) aged 12 years or greater with definite or probable aspergillosis. Most had an underlying diagnosis of allogeneic HSCT or hematologic cancer and nearly half were neutropenic. The most common site of infection was the lungs.<sup>22</sup>

Voriconazole was dosed at 6 mg/kg iv every 12 hours  $\times$  2 doses, then 4 mg/kg iv twice daily for at least 7 days, at which time it could be switched to oral administration of 200 mg twice daily. CAB was dosed at 1.0 to 1.5 mg/kg iv daily. Other licensed therapy was permitted in the case of therapeutic failure or drug intolerance, which occurred in 52 patients in the voriconazole and 107 patients in the CAB groups. The planned duration of therapy was 12 weeks.<sup>22</sup>

At week 12, voriconazole was associated with significantly improved response rates and survival and fewer adverse reactions than CAB. Successful response, defined as clinical improvement or resolution and at least 50% improvement of radiologic findings, was achieved by 52.8% of patients receiving voriconazole and 31.6% of patients receiving CAB (absolute difference 21.2%; 95% CI 10.4% to 32.9%). The survival rate was 70.8% in the voriconazole group versus 57.9% in the CAB group (HR 0.59; 95% CI 0.40 to 0.88). Renal impairment and infusion-related fevers and chills were more common in patients receiving CAB while voriconazole-treated patients were more likely to experience visual disturbances and dermatologic reactions.<sup>22</sup>

Based on the results of this trial, voriconazole replaced amphotericin B as first-line therapy for the treatment of invasive aspergillosis. A recent observational study using data compiled by the multicenter Prospective Antifungal Therapy (PATH) Alliance registry demonstrated mortality rates consistent with those reported by the Herbrecht trial.<sup>21</sup> In this study, the epidemiology and outcomes of 144 HSCT patients with invasive aspergillosis were examined. Eighty-five percent of these patients received treatment with voriconazole, 47% in combination with at least one other

antifungal agent. Six- and 12-week mortality rates were 21.5% and 35.5%, respectively.<sup>21</sup>

## Economic outcomes

A Medline search using the terms “cost analysis” or “pharmacoeconomic analysis” plus “aspergillosis” plus “voriconazole” was serially repeated, substituting voriconazole with caspofungin, amphotericin B, and itraconazole. Studies were limited to those published in the English language that compared both the costs and outcomes of invasive aspergillosis therapy and included a voriconazole arm. Ten publications met the inclusion criteria. These articles are summarized in Tables 1 to 5. These ten studies are compared globally by the type of analysis, methods used to estimate the cost and outcomes, results, transparency, and other methodological issues.

The 10 pharmacoeconomic analyses were conducted in six different countries as indicated in Table 1. Voriconazole was compared to CAB,<sup>23–30</sup> liposomal amphotericin B (L-AMB),<sup>31</sup> itraconazole,<sup>24</sup> and caspofungin.<sup>32</sup> Generally speaking all of the studies used the appropriate procedures for conducting pharmacoeconomic analyses with regard to their research question, modeling procedures, data sources, resource valuation, transparency, discounting, use of sensitivity analyses, and use of incremental analyses.<sup>33</sup> Any exceptions to these standards are noted in this section. Overall, the 10 studies had well-defined research questions, and they were transparent indicating that the data sources and methods for calculating expected costs and outcomes were obvious.

Eight of the studies were cost-effectiveness analyses (CEA),<sup>23–29,31</sup> one was a cost-minimization analysis (CMA),<sup>32</sup> and one was a cost analysis (CA).<sup>30</sup> No cost-utility analyses of voriconazole were identified, which is not surprising given the limited treatment period and the overall poor health condition of people with invasive aspergillosis.

Eight of the voriconazole pharmacoeconomic studies used a decision analytic model such as a decision tree or Markov Model to estimate the expected costs and outcomes of therapy.<sup>23–29,31</sup> One of the studies calculated the costs and outcomes from actual clinical observations and used a decision tree to calculate the weighted average cost and outcomes.<sup>23</sup>

The three outcomes reported in the studies were successful response at 12 weeks, survival at 12 weeks, and mean survival time. Tables 2, 3, and 4 present the results according to each of these outcomes, respectively. Since the studies were conducted in different countries with different

**Table 1** Summary of pharmacoeconomic studies

Author	Year	Country	Perspective	Analysis type	Time frame	Source of medication cost data	Source of medical service cost data	Primary source of outcomes data	Secondary source of outcomes data
Rostreit <sup>23</sup>	2004	Canada	Payer	CEA	12 weeks	Government/payer cost reference	Government/payer cost reference	GCA – North American data	Expert panel and literature (itraconazole)
Jansen <sup>24</sup>	2005	The Netherlands	Payer	CEA	12 weeks and lifetime	Commercial drug databank	Government/payer cost reference	GCA	
Lewis <sup>25</sup>	2005	US	Health system	CEA	12 weeks	Local acquisition costs		GCA – modified ITT	
Wenzel <sup>26</sup>	2005	US	Health System	CEA	12 weeks	Commercial reference	Government/payer cost reference	GCA	
Garbino <sup>27</sup>	2006	Switzerland	Payer and health system	CEA	12 weeks	Local acquisition costs	Local acquisition costs	GCA	Literature
Jansen <sup>28</sup>	2006	Germany	Payer and health system	CEA	12 weeks and lifetime	Commercial reference and expert panel	Government/payer cost reference	GCA	
Ament <sup>31</sup>	2007	The Netherlands	Health system	CEA	12 weeks and lifetime	Commercial reference	[local] acquisition costs	Literature – multiple trials (including GCA)	
Dominguez-Gil <sup>32</sup>	2007	Spain	National healthcare system	CMA	Acute treatment period	Government/payer cost reference	Government/payer cost reference	Literature – multiple trials (including GCA)	
Greene <sup>29</sup>	2007	US	Payer	CEA	12 Weeks	Commercial reference	Literature	GCA – subset with thoracic CT scan	
Wingard <sup>30</sup>	2007	US	Payer and health system	CA	12 weeks	Commercial reference	Literature	GCA – modified ITT	

**Abbreviations:** CEA, cost-effectiveness analysis; CMA, cost minimization analysis; CA, cost analysis; GCA, the Global Comparative Aspergillosis study;<sup>22</sup> modified ITT, modified intention to treat.

**Table 2** Summary of cost-effectiveness studies using successful response as the outcome measure

Author	Year	Country	Currency (perspective)	Comparators	Analysis type	Expected cost per patient	Expected outcome (probability of successful response)	Cost/outcome	Incremental cost/outcome
Rotstein <sup>23</sup>	2004	Canada	2002 CAD (Payer)	voriconazole CAB	CEA	38,319 42,495	0.521 0.309	72,604 134,569	72,604 <sup>a</sup> Dominated
Jansen <sup>24</sup>	2005	The Netherlands	2003 € (Payer)	voriconazole itraconazole CAB	CEA	26,794 22,007 24,509	0.53 0.43 0.32	50,759 51,179.07 77,666	47,870.00 <sup>a</sup> 51,179.07 Dominated
Lewis <sup>25</sup>	2005	US	2003 US\$ (Health system)	voriconazole CAB	CEA	5,447 6,408	0.528 0.316	10,317 20,278	10,316.78 <sup>a</sup> Dominated
Wenzel <sup>26</sup>	2005	US	2002 US\$ (Health system)	voriconazole CAB	CEA	30,664 34,144	0.528 0.316	58,075 <sup>b</sup> 108,124	58,075.19 <sup>a,b</sup> Dominated
Jansen <sup>28</sup>	2006	Germany	2005 € (Payer)	voriconazole CAB	CEA	25,353 20,092	0.529 0.326	47,926 61,632	25,916.26 <sup>a,b</sup> 61,631.90 <sup>b</sup>
Jansen <sup>28</sup>	2006	Germany	2005 € (Health system)	voriconazole CAB	CEA	22,090 19,637	0.529 0.326	41,758 60,236	12,083.74 <sup>a,b</sup> 60,236.20 <sup>b</sup>

<sup>a</sup>Cost-effective agent; <sup>b</sup>Calculated by the authors, not presented in the original article.

**Abbreviations:** CAB, conventional amphotericin B desoxycholate; CEA, cost-effectiveness analysis; CAD, Canadian dollar.

healthcare systems and different currencies, no attempt was made to combine the results. All cost-effectiveness analyses or cost-minimization analyses identified voriconazole treatment arms as the most cost-effective. This is not unexpected given the number of studies that used the results from GCA study as the primary source for outcomes data. However, the analyses that used multiple studies as the primary source for outcomes data reported similar results.<sup>31,32</sup>

None of the studies discounted costs or outcomes. This is appropriate for all of the studies that used the first two outcome measures since the study periods were less than 12 months. Three studies reported mean survival times. Given that some of the costs and outcomes in these studies occurred outside the 12-month window, they should have been discounted. Most likely this is not a major issue given that the average life expectancy of the people included in these analyses ranged from less than 12 months to 3 years.<sup>24,28,31</sup> These three studies are described in greater detail below.

Jansen and colleagues used the results of the GCA study<sup>22</sup> as the basis of their decision tree which estimated 12 week cost and outcomes in a Dutch population.<sup>24</sup> In the model, patients were treated initially with voriconazole, CAB, or itraconazole and were switched to other licensed antifungal agents in the case of severe toxicity or treatment failure. Since itraconazole was not included in the GCA study, they used other literature and expert opinion to identify resource use and probabilities of response and toxicities in the itraconazole arm. A Markov Model was then used to simulate the lifetime costs and outcomes of voriconazole, itraconazole, and amphotericin B as first-line treatments for invasive aspergillosis. Patients treated successfully at the end of 12 weeks remained in the “success” state until they died (an assumption of no relapses). Patients not successfully treated at the end of 12 weeks entered the Markov process in the “failure” state and remained there until they transitioned to the “success” or “death” states. Patients were transitioned from state to state on a weekly cycle based on probabilities derived from the GCA study. The mean survival times in this model were 174 weeks, 150.4 weeks, and 116.1 weeks for the voriconazole, itraconazole, and CAB groups respectively (see Table 4).<sup>24</sup>

Jansen and colleagues conducted a similar study for a German population. They used a decision tree and Markov model to simulate the 12 week and lifetime costs and outcomes of voriconazole and amphotericin B as first-line treatments for invasive aspergillosis.<sup>28</sup> The mean survival times in this model were 174 weeks and 116.1 weeks for the voriconazole and CAB groups respectively (see Table 4).<sup>28</sup>

**Table 3** Summary of cost-effectiveness studies using probability of survival as the outcome measure

Author	Year	Country	Currency (perspective)	Comparators	Analysis type	Expected cost per patient	Expected outcome (probability of survival)	Cost/outcome	Incremental cost/outcome
Rotstein <sup>23</sup>	2004	Canada	2002 CAD (Payer)	voriconazole CAB	CEA	US\$38,319 US\$42,495	0.708 0.579	54,123 73,395	54,122.88 <sup>a</sup> Dominated
Wenzel <sup>26</sup>	2005	US	2002 US\$ (Health system)	voriconazole CAB	CEA	30,664 34,144	0.708 0.579	43,310 58,971	43,310.31 <sup>a</sup> Dominated
Garbino <sup>27</sup>	2006	Switzerland	2004 CHF (Payer and health system)	voriconazole CAB	CEA	37,878 49,861	0.708 0.579	53,500 86,116	53,500.00 <sup>a,b</sup> Dominated <sup>b</sup>
Green <sup>29</sup>	2007	US	2002 US\$ (Payer)	Voriconazole (patients with halo sign) CAB (patients with halo sign) Voriconazole (patients without halo sign) CAB (patients without halo sign)	CEA	40,380 48,985 48,133 45,938	0.75 0.65 0.66 0.4	53,608 75,186 73,039 116,299	53,840.00 <sup>a</sup> Dominated 8,442.3 <sup>1a</sup> 114,845.00

<sup>a</sup>Cost-effective agent; <sup>b</sup>Calculated by the authors, not presented in the original article.

**Abbreviations:** CAB, conventional amphotericin B desoxycholate; CAD, Canadian dollar; CEA, cost-effectiveness analysis; CHF, Swiss francs.

Ament and colleagues created a model to compare voriconazole and L-AMB as first-line therapy. After severe toxicity or treatment failure, a patient in the model could be switched to any combination of other antifungal agents.<sup>31</sup> Seven different treatment combinations were compared in the final analysis: 1) voriconazole as first-line and L-AMB plus caspofungin as second-line therapy, 2) voriconazole as first-line and caspofungin as second-line therapy, 3) voriconazole as first-line and CAB as second-line therapy, 4) voriconazole as first-line and L-AMB as second-line therapy, 5) L-AMB as first-line and voriconazole plus caspofungin as second-line therapy, 6) L-AMB as first-line and voriconazole as second-line therapy, 7) L-AMB as first-line and caspofungin as second-line therapy. Probabilities used in the model were derived from multiple published studies. The mean survival times ranged from 1.109 to 1.307 years as summarized in Table 4.<sup>31</sup>

Four additional studies are described in greater detail to highlight their unique designs or contributions to the literature. Dominguez-Gil and colleagues conducted a cost minimization analysis comparing voriconazole and caspofungin from a hospital perspective. Based on probabilities obtained from multiple published studies, the authors determined or assumed that both agents would have equal efficacy. The average cost of the voriconazole-treated group was €1,132 lower than the caspofungin-treated group (see Table 5).<sup>32</sup>

Green and colleagues used a subset of patients from the GCA study that had thoracic computed tomographic (CT) scans at baseline to look at the cost-effectiveness of voriconazole compared to CAB.<sup>29</sup> They divided the patients into two groups, those with and without a halo sign on the CT scan at baseline. The probabilities of toxicity and success in these patients were used to model the expected cost and outcomes in each group. The probability of survival at 12 weeks was the outcome measure. Both groups had similar costs, but the group with the halo sign had better survival rates than the group without the sign. This resulted in lower costs per outcome in the group with the halo sign. Voriconazole was the most cost-effective agent in both groups (see Table 3).<sup>29</sup>

Wingard and colleagues conducted a cost analysis using data from the GCA study as the primary source of outcomes data.<sup>30</sup> Consideration was not given to any outcome measure, but the patients were subdivided into survivors and nonsurvivors. The group treated with voriconazole had lower treatment costs compared to the group treated with CAB resulting in US\$16,758 savings in the survivor group. Conversely, the non-survivor group treated with CAB had savings of US\$10,176 compared to the voriconazole group.

**Table 4** Summary of cost-effectiveness studies using survival time as the outcome measure

Author	Year	Country	Currency (perspective)	Comparators	Analysis type	Expected cost per patient	Expected outcome survival time in weeks)	Cost/outcome	Incremental cost/outcome
Jansen <sup>24</sup>	2005	The Netherlands	2003 € (Payer)	voriconazole	CEA	32,651	174	188	149.83 <sup>a</sup>
Jansen <sup>28</sup>	2006	Germany	2005 € (Payer)	itraconazole	CEA	29,115	150.4	194	193.58 <sup>b</sup>
				CAB		33,616	116.1	290	Dominated
				voriconazole		30,026	174	172	62.36 <sup>a</sup>
Jansen <sup>28</sup>	2006	Germany	2005 € (Health system)	CAB	CEA	26,596	119.4	223	222.74 <sup>b</sup>
				voriconazole		26,440	174	151	6.95 <sup>c</sup>
Ament <sup>31</sup>	2007	The Netherlands	2005 € (Health system)	CAB	CEA	26,058	119.4	218	224.44 <sup>b</sup>
				voriconazole/L-AMB + caspofungin		10,141	67.964 <sup>b</sup>	149	2,177.42 <sup>b</sup>
Jansen <sup>28</sup>	2006	Germany	2005 € (Health system)	voriconazole/caspofungin	CEA	6,631	66.352 <sup>b</sup>	100	99.94 <sup>a,b</sup>
				voriconazole/CAB		6,957	64.844 <sup>b</sup>	107	Dominated
				voriconazole/L-AMB		8,239	64.844 <sup>b</sup>	127	Dominated
				L-AMB/voriconazole + caspofungin		17,542	60.424 <sup>b</sup>	290	Dominated
				L-AMB/voriconazole		16,005	57.98	276	Dominated
				L-AMB/caspofungin		16,460	57.668	285	Dominated

<sup>a</sup>Cost-effective agent; <sup>b</sup>Calculated by the authors, not presented in the original article.**Abbreviations:** CAB, conventional amphotericin B desoxycholate; CEA, cost-effectiveness analysis; L-AMB, liposomal amphotericin B.

When all patients were considered together, patients treated with voriconazole had a US\$4,997 savings compared to patients treated with CAB (see Table 5).<sup>30</sup>

Overall the results of all of the analyses were robust to the assumptions made during the modeling process. This means that the results of the analysis did not change when the key assumptions of the models were tested in sensitivity analyses (ie, varied from high to low values). However the results of four studies were sensitive to drastic changes in either costs, the weight of the patient used to estimate the medication dose, or the renal toxicity of CAB.<sup>23,27,31,32</sup> In the model used by Roststein and colleagues, patients were switched to L-AMB due to toxicity or treatment failure of voriconazole or CAB. If the cost of L-AMB was cut in half, then the CAB arm became more cost-effective.<sup>23</sup> In the model used by Garbino and colleagues, when the renal toxicity of amphotericin B was assumed to be less than 7%, then the CAB arm became more cost-effective.<sup>27</sup> The results published by Dominguez-Gil and colleagues were robust as long as the patients weight was less than 102 kg.<sup>32</sup>

Testing the conclusions of the pharmacoeconomic analyses with sensitivity analyses described above is one way to validate study results. In an attempt to further validate the results of a similar pharmacoeconomic analysis that has not been published, Van Campenhout and colleagues compared the results of the model to actual data collected from 116 patients in 13 different hematology–oncology intensive care settings in Belgium.<sup>34</sup> The clinical response rate at 12 weeks was similar (53% from the model, 50% from the observational study). However the model underestimated the mortality rates at 84 days (29% vs 42%) and slightly overestimated the per-patient cost of hospitalizations (€21,298 vs €19,674).<sup>34</sup>

Two of the studies included in this review accounted for the cost of the galactomannan assays,<sup>24,28</sup> but none included the costs of voriconazole levels. The galactomannan assay is a diagnostic test, therefore the cost of this test would be incurred regardless of the therapy selected. In other words, including the cost of this diagnostic test in any of the pharmacoeconomic analyses would not change the results. The current treatment guidelines do not address the routine use of voriconazole levels. An observational study by Pascual and colleagues evaluated the impact of measuring voriconazole blood levels.<sup>6</sup> Patient with troughs less than 1 mg/L had worse outcomes compared to those with troughs between 1 and 5.5 mg/L, while patients with troughs higher than 5.5 mg/L had more toxicity.<sup>6</sup>

**Table 5** Summary of cost minimization and cost analysis studies

Author	Year	Country	Currency	Comparators	Analysis Type	Expected cost per patient	Cost difference	Comments
Dominguez-Gil <sup>32</sup>	2007	Spain	2006 €	voriconazole caspofungin	CMA	6,042 7,174	-1,132.18	Cost-effective agent Dominated
Wingard <sup>30</sup>	2007	US	2005 US\$	Voriconazole (all patients)	CA	78,860	-4,997.00	Cost savings
				CAB (all patients)		83,857		
				Voriconazole (survivors)		79,913	-16,758.00	Cost savings
				CAB (survivors)		96,671		
				Voriconazole (non-survivors)		76,326	10,176.00	No cost savings
CAB (non-survivors)		66,150						

**Abbreviations:** CAB, conventional amphotericin B desoxycholate; CA, cost analysis; CMA, cost-minimization analysis.

The median number of troughs drawn per patient was 4.5 with the first drawn a median of 5 days after therapy and every 7 days thereafter. The cost of this test is difficult to identify; however, the Centers for Medicare and Medicaid Services (CMS) 2009 Clinical Diagnostic Laboratory Fee Schedule limits for other drug assays ranges from US\$17.40 to US\$27.00.<sup>35</sup> Thus if one assumes the cost to a payer would be the upper end of this limit (US\$27 per trough) with five troughs per patient, then an additional US\$135 would be added to the cost of therapy. When the cost of the assay is added to the expected costs calculated in each of the US-based pharmacoeconomic studies in this review, the results do not change. Voriconazole remains the most cost-effective therapy.

## Conclusions

Amphotericin B and its lipid formulations, itraconazole, voriconazole and caspofungin, are all indicated for the primary treatment of invasive aspergillosis; however, voriconazole is preferred.<sup>1</sup> The GCA study by Herbrecht and colleagues provided the clinical evidence to support voriconazole's clinical role.<sup>22</sup> This publication also served as the basis for multiple pharmacoeconomic analyses which demonstrated that voriconazole is cost-effective in the primary treatment of invasive aspergillosis.

Of the agents indicated for the primary treatment of invasive aspergillosis, the US average wholesale price of L-AMB is the highest followed by caspofungin, voriconazole, itraconazole, and CAB.<sup>16</sup> While the acquisition costs of voriconazole are higher than those of conventional amphotericin B, the toxicity profile and treatment success rate associated with voriconazole result in lower total treatment costs per successfully treated patient.<sup>23–30</sup>

## Disclosure

The authors declare no conflicts of interest.

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