Peer reviewed article

Invasive aspergillosis: Is treatment with "inexpensive" amphotericin B cost-saving if "expensive" voriconazole is only used on demand?

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Summary

Background: Voriconazole for the treatment of invasive aspergillosis (IA) shows superior clinical outcome and tolerability compared to conventional amphotericin B. However, the latter is often used as initial treatment due to lower drug acquisition costs. Therefore we performed a cost-effectiveness analysis.

Methods: A decision analytic model was designed to compare the cost-effectiveness of a regimen of voriconazole followed by conventional amphotericin B to a regimen of conventional amphotericin B followed by voriconazole. Patients initiated on treatment either completed initial therapy or switched to second line therapy due to toxicity or non-response. Probability of a switch was based on clinical trial data and local rates of renal toxicity. Resource use in the hospital was taken from the Global Comparative Aspergillosis (GCA) study. Costs were based on local drug acquisition costs, local cost estimates for hospitalisation and adjusted additional costs of amphotericin B-induced acute renal failure from the literature. Effectiveness was defined as survival at 12 weeks from the GCA study. An incremental cost-effectiveness ratio was estimated as the incremental cost per life saved comparing voriconazole to conventional amphotericin B.

Results: Based on this model, initial therapy of IA with voriconazole reduced total costs when compared to initial therapy with conventional amphotericin B (CHF 37 878/patient vs CHF 49 861/patient) and resulted in better survival at 12 weeks, making it the dominant treatment in terms of incremental cost-effectiveness. Results were most sensitive to alternative assumptions of the incidence of acute renal failure, but cost savings were sustained for voriconazole over a wide range of values.

Conclusion: Considering that initial therapy with voriconazole is both cost-saving and results in better clinical outcomes, voriconazole is the dominant cost-effective option for initial therapy of IA, despite very low drug acquisition costs of conventional amphotericin B.

Key words: adverse event; amphotericin B; cost-effectiveness analysis; hospitalisation resources; invasive aspergillosis; nephrotoxicity; renal failure; voriconazole

Introduction

Invasive Aspergillosis is a severe infectious disease marked by high morbidity and mortality frequently affecting patients with prolonged neutropenia such as immunosuppression in transplant recipients. For decades, amphotericin B deoxycholate has been an established treatment despite suboptimal responses and tolerability [1]. Unfortunately, the incidence of amphotericin B nephrotoxicity is very high and acute renal failure is common, despite some risk reduction by supportive manipulations [2]. In response to high rates of toxicity, it has been proposed to administer amphotericin B deoxycholate by continuous infusion over 24 hours combined with strict salt repletion to reduce the known nephrotoxic effects [3, 4]. Nevertheless, no comparative trial using this regimen has proved its efficacy [5]. Although new lipid formulations of amphotericin B have been developed which show a better safety profile, drug related renal impairment is still of concern and the acquisition cost of these therapies is high [6].

Recently, new antifungal drugs like voricona-

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zole have been developed for the treatment of invasive aspergillosis. By modification of the azole structure, antifungal potency and fungicidal activity has been enhanced and the range of susceptibility in moulds increased. Since the bioavailability of oral voriconazole is greater than 90%, the compound is available as both parenteral and oral formulations (tablets and powder for oral solution), allowing a switch from intravenous to oral application without therapeutic drug monitoring. Furthermore, voriconazole has been shown to be safe and well tolerated. Adverse events reported are intermittent visual disturbances with altered or enhanced light perception, hepatic disturbances and infrequent skin reactions [7]. In the largest prospective study performed in patients with proven or probable invasive aspergillosis (GCA: Global Comparative Aspergillosis study), voriconazole has been shown to have a significantly better outcome in the primary endpoint of successful treatment (defined as complete or partial response). Moreover, mortality rate was significantly reduced by 13%, with a survival rate of 70.8% versus 57.9% in amphotericin B treated patients [8]. This high efficacy in moulds leads to new opportunities to extend bone marrow or stem cell transplantation to high-risk patients with severe and prolonged immunosuppression. Even patients with previous known or suspected invasive fungal infections are actually submitted to induction treatment with reasonable prognosis [9].

There is one common fact in all new antifungal agents such as lipid formulations of amphotericin B, caspofungin or voriconazole: compared to conventional amphotericin B deoxycholate, the drug acquisition price of these agents are substantially higher [10]. Due to general cost pressure in the health care sector, most hospitals are now affected by budget restrictions. Therefore, drug selection for treatment is increasingly influenced by economic considerations. In case of invasive aspergillosis, conventional amphotericin B is often used as initial treatment due to lower drug acquisition costs. A common rationale is that there is a possibility to switch the treatment at anytime to voriconazole in case of treatment non-response or toxicity. However, this rationale does not consider excess costs due to hospital resource use or toxicity that may be associated with this alternative therapeutic approach.

Acute renal failure with amphotericin B is not only associated with poorer clinical outcomes, it also has a marked impact on the cost of treatment. Bates et al. used a multivariate regression approach with hospital data to estimate the additional costs associated with acute renal failure in patients with invasive fungal infections being treated with conventional amphotericin B deoxycholate [11]. Renal failure was associated with a mean increase in hospital stay of 8.2 days, and a mean increase in costs of $ 29.823. In an analysis of clinical trial data, Cagnoni et al. performed a descriptive analysis of hospital costs comparing amphotericin B deoxycholate with liposomal amphotericin B [12]. Compared to those without renal toxicity, patients with renal toxicity showed a mean increase in hospital stay of 7 days and a mean increase of $ 25.206 in hospital costs when the study anti-fungal drug costs were excluded ($ 34.415 without renal toxicity compared to $ 59.621 with renal toxicity). These incremental costs were of similar magnitude in the two amphotericin arms, although they occurred with greater frequency in the conventional amphotericin B patients. Each of these analyses are considered in a decision model by Wingard et al., comparing caspofungin to amphotericin B for treatment of candidaemia [13]. This analysis concluded that the added costs of renal toxicity offset the added drug acquisition costs of caspofungin, accounting for several varying assumptions of renal toxicity frequency and costs.

Meanwhile, extensive data regarding switching incidence and alternative treatment patterns due to treatment non-response or toxicity, as well as further information on usage of hospital resources, are available from a large randomised trial comparing conventional amphotericin B to voriconazole [14, 15]. Based on this information, we designed a decision analytic model to compare the cost-effectiveness of conventional amphotericin B and voriconazole as initial treatment in invasive aspergillosis. The question to be answered was whether the added costs of renal toxicity and hospital resource use with conventional amphotericin B would offset the low acquisition costs in a regimen starting with amphotericin B and switching to voriconazole, compared to a regimen with voriconazole as initial treatment. The model takes the perspective of the hospital and is taking into account not only drug acquisition costs, but also estimates of local hospitalisation costs at the University Hospital of Geneva. In addition, the model adjusted costs related to adverse events according to a large retrospective evaluation on mortality and costs of acute renal failure associated with amphotericin B therapy [11, 16].

Material and methods

Model design

An Excel-based decision tree model was designed to compare the cost-effectiveness of a regimen of conventional amphotericin B followed by voriconazole to a regimen of voriconazole followed by conventional amphotericin B. After initiation of therapy, patients either completed therapy with initial treatment or switched to the second line therapy due to renal toxicity or lack of response (figure 1).

Model inputs

Model and cost inputs including data sources are summarised in tables 1 and 2. The probability of switching due to lack of response was based on the Global Comparative Aspergillosis (GCA) study [17]. Probability of switch due to renal toxicity was defined by locally observed frequencies for acute renal failure [16]. We assumed a serum creatinine level increase of more than 100% or absolute values over 177 µmol/L (2 mg/dL) as a reason to switch the antifungal regimen. Effectiveness was defined as survival at 12 weeks, also obtained from the GCA study [8].

Overall length of hospitalisation and length of stay at the ICU was taken from the GCA study [15]. Due to the perspective of the hospital, treatment duration was assumed to be 28 days, with 10 days of IV voriconazole prior to switching to oral voriconazole. In the case of a switch, the number of days before the switch was estimated as 16 for amphotericin and 26 for voriconazole, reported as the average time to switch following toxicity from voriconazole or amphotericin B [17]. Following a switch, a complete course of second line therapy (voriconazole or amphotericin B) was added to the initial course.

Costs were based on local drug acquisition costs, local cost estimates for hospitalisation and locally observed incidences of renal toxicity due to amphotericin B treatment [16]. Adjusted (without hospital and ICU components) additional costs of amphotericin B induced acute renal failure were estimated from data reported by Bates et al. [11]. These adjusted cost estimates from Bates were converted to Swiss Francs (CHF) using 2004 Purchasing Power Parities from the Organisation for Economic Co-operation and Development (OECD).

Model assumptions

Patients were expected to be 65 kg and treated according to the recommended treatment dosages of both agents. Only a single course of second line therapy was assumed, and all patients were switched from either voriconazole to amphotericin B or amphotericin B to voriconazole. Efficacy, survival, and resource utilisation was supposed to be similar to that observed in the clinical trial, since there is no basis for alternative estimates of these effects.

Primary analysis

Costs for each pathway were estimated as the sum of drug costs, hospitalisation costs, and incremental renal toxicity costs, where appropriate, for each pathway. The average predicted cost for each regimen was estimated as the product of the costs of each decision pathway and the probability of experiencing each respective pathway. An incremental cost effectiveness ratio was calculated for voriconazole compared to conventional amphotericin B as the difference in average costs divided by the difference in survival at 12 weeks, based on base case assumptions described above.

Sensitivity analyses

Due to uncertainty around the incidence and cost impact of renal toxicity, multiple one-way sensitivity analyses were conducted to test the impact of our assumptions

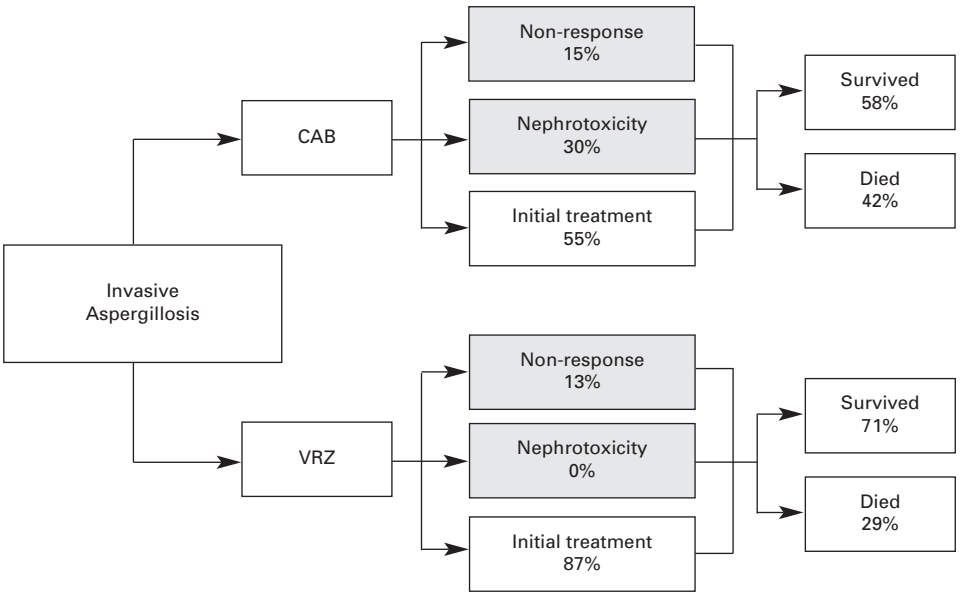


Figure 1

Decision tree for the treatment of proven or probable invasive aspergillosis. The probabilities were obtained from the GCA study [8, 17] and locally observed incidences of renal toxicity due to amphotericin B treatment [16]. Following switch (shaded), a complete course of second line therapy (voriconazole or amphotericin B) was added to the initial course. CAB = conventional amphotericin B; VRZ = voriconazole

Table 1

Model inputs are derived from the Global Comparative Aspergillosis Study database (GCA) as published by different authors. In a local retrospective analysis at the University Hospital of Geneva (HUG), an incidence of 30% acute renal failure due to treatment with amphotericin B deoxycholate was found [16].

	Amphotericin B	Voriconazole	Source [Reference]
Total days of hospital treatment	28	28	GCA study [15]
Days of intensive care	8.1	5.6	GCA study [15]
Days to IV-PO switch	0	10	GCA study [8]
Days to switch if switching	16	26	GCA study [17]
Percent non-response (%)	15	13	GCA study [17]
Acute renal failure (%)	30	0	HUG [16]

Table 2

Cost inputs: Local cost estimates for hospital resources as well as drug acquisition costs for treatment according to dosing recommendations by the manufacturer. Costs for renal toxicity according to Bates [11] was converted to Swiss francs (CHF) using purchasing power parity (2004).

Costs	CHF
Hospitalisation	
Medical ward	900.00
Intensive care unit (ICU)	1500.00
Drug costs (patient 65 kg)	
Amphotericin B 1 mg/kg	97.24
+ additional application costs	18.90
+ IV administration set	19.37
Voriconazole 6 mg/kg IV	443.24
Voriconazole 4 mg/kg IV	295.49
+ IV administration set	19.37
Voriconazole 200 mg PO	60.00
Toxicity induced costs	
Acute renal failure	42 203.55

on the model results. These calculations were performed to test the impact of variables, which may influence the cost-effectiveness outcome. Theses variables included: patient weight, duration of voriconazole IV treatment after switching from amphotericin B (second line), cost estimates for daily costs of hospital resources and per day in ICU, cost estimates per case of acute renal failure and different incidence rates regarding acute renal failure.

Results

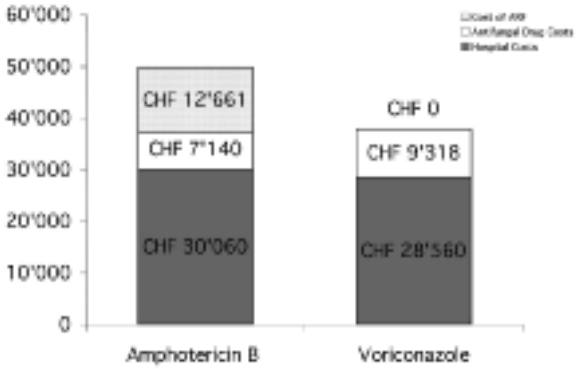
Costs

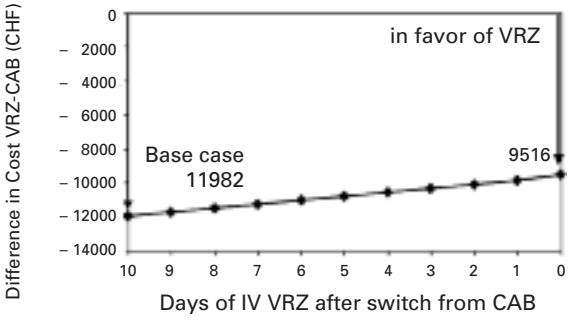
Total treatment costs of CHF 37 878/patient and CHF 49 861/patient were estimated for voriconazole and conventional amphotericin B, respectively (figure 2). This results in a cost savings potential of approximately CHF 12 000 if voriconazole is chosen as initial therapy.

Within these costs, the sum of drug acquisition costs (including application devices, hydration, and first and second line therapies) was CHF 7140 in the initial amphotericin B regimen compared to CHF 9318 in the initial voriconazole regimen. The cost of health care resources used was CHF 28 560 for patients initially treated with voriconazole and CHF 30 060 for those initially treated with conventional amphotericin B. Nephrotoxicity resulted in an additional cost burden of more than CHF 12 000 for patients treated

Figure 2

Average total cost estimates for conventional amphotericin B or voriconazole as initial treatment for invasive aspergillosis: Total treatment costs of CHF 37 878/patient and CHF 49 861/patient resulted for voriconazole and conventional amphotericin B, respectively. Despite a small gain in absolute drug costs if conventional amphotericin B was used as first line treatment and only changed to voriconazole in case of renal failure or non-response, overall costs including use of hospital resources and additional costs due to renal toxicity resulted in cost savings if treatment of invasive aspergillosis was initiated with voriconazole.
ARF = acute renal failure; CHF = Swiss francs





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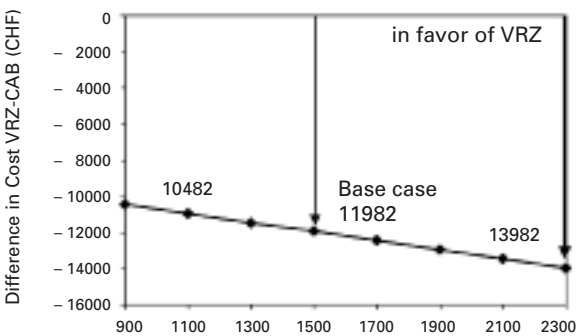

B

Figure 3

A. Sensitivity analysis depending on days of parenteral voriconazole application (IV) after switching from amphotericin B due to non-response or nephrotoxicity: Cost savings estimated for voriconazole over amphotericin B was reduced with early initiation of oral voriconazole treatment. VRZ = voriconazole, CAB = conventional amphotericin B; CHF = Swiss francs
B. Sensitivity of costs due to different intensive care unit (ICU) cost per day: Independent on the cost assumptions for the stay on the ICU, voriconazole treatment remained cost-effective even in case daily ICU cost estimates were equalised to the normal cost estimates on the medical ward (CHF 900/day).
VRZ = voriconazole, CAB = conventional amphotericin B; CHF = Swiss francs

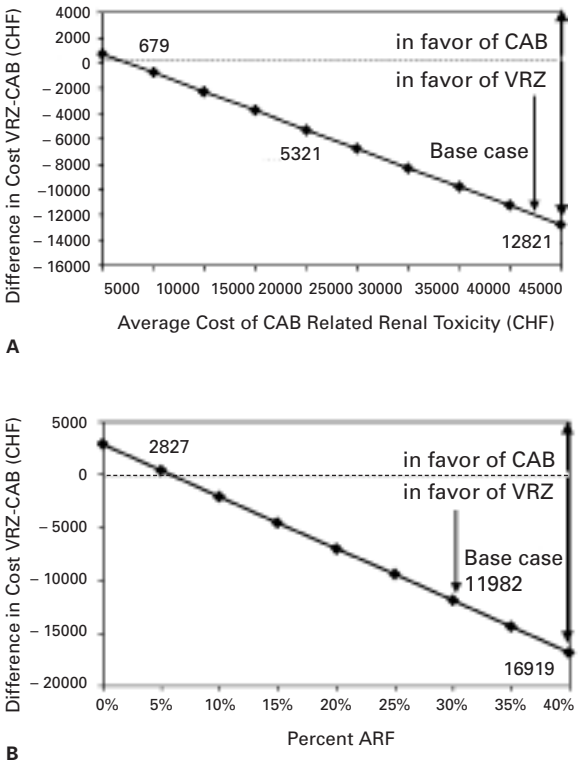

Figure 4

A. Sensitivity of cost difference due to costs related to acute renal failure: Cost assumptions regarding additional costs due to amphotericin B induced renal toxicity have been evaluated. Cost savings were calculated for voriconazole treatment over a wide range of cost estimates if larger than CHF 5000 per case of nephrotoxicity. VRZ = voriconazole, CAB = conventional amphotericin B; CHF = Swiss francs B. Sensitivity of incidence of acute renal failure on difference in total costs: Initial treatment with voriconazole became cost-saving for an incidence of acute renal failure >7%. VRZ = voriconazole, CAB = conventional amphotericin B; ARF = acute renal failure; CHF = Swiss francs.

with conventional amphotericin B assuming a renal toxicity rate of 30%.

Cost-effectiveness

By nesting these figures with the superior survival rate of 70.8% versus 57.9% for voriconazole and amphotericin B, respectively, voriconazole was considered the dominant initial treatment for invasive aspergillosis since it was both cost-saving and had a better effectiveness. Therefore, an incremental cost-effectiveness ratio was negative and could not be interpreted numerically. Considering each treatment separately, the average cost per life saved at 12 weeks was CHF 53 500 per surviving patient treated initially with voriconazole and CHF 86 115 per life saved for conventional amphotericin B.

Sensitivity analysis

Sensitivity analyses were used to estimate the impact of model assumptions on the difference in costs. Drug costs were sensitive to both the weight of the patient (data not shown) and the duration of IV application of voriconazole after switching (0–10 days), but did not alter the finding of cost savings observed with voriconazole (figure 3A). Furthermore, results remained in favour of voriconazole over a wide range of cost estimates of daily costs for hospital resources (CHF 500 – CHF 2000) (data not shown) and daily costs for stay in ICU (CHF 900 – CHF 2300) (figure 3B).

Assumptions regarding renal toxicity incidence and costs had the greatest effect on cost-effectiveness, however the results of the model were robust to substantial changes in these assumptions. When costs per case of nephrotoxicity were modified results remained in favour of voriconazole over a wide range of assumptions (range CHF 5000–45 000) (figure 4A). Cost savings were maintained for voriconazole over a wide range of assumed values for the incidence of renal toxicity, remaining the dominant alternative if the incidence of nephrotoxicity due to amphotericin B was any value larger than 7% (figure 4B).

Discussion

Since new antifungal agents are not only highly effective and safe, but also expensive regarding net drug acquisition costs, their cost-effectiveness has to be evaluated. Recently, a pharmacoeconomic evaluation of the landmark study comparing voriconazole to conventional amphotericin B showed the cost-effectiveness of this new antifungal agent from the United States' healthcare system perspective [17]. Compared with this evaluation, our model showed some substantial differences in switching assumptions: according to protocol of the original GCA study, in case of non-response or toxicity, it was only allowed to switch from the study treatment to another licensed antifungal treatment (OLAT). Therefore the change from conventional amphotericin B to voriconazole was not possible at this time [8]. Due to budget restrictions of hospitals and the high drug acquisition costs of voriconazole, physicians tend to initiate the therapy with the less expensive amphotericin B. "High-price" voriconazole is used as second line treatment in case of non-response or acute renal failure. The aim of this study was to compare this approach against initial therapy with voriconazole in invasive aspergillosis from the perspective of the hospital.

With this model, substantial overall cost savings of voriconazole were predicted compared to conventional amphotericin B. It has to be mentioned that after weighting the results for switching incidence due to renal toxicity and non-response, the difference of the costs for drugs and their application additives were small (around CHF 2000 in favour of amphotericin B). This financial benefit may be compensated by costs for hospital resource use by means of days on ICU; ICU stay differed by 2.5 days in favour of voriconazole [15]. Unfortunately only crude cost estimates based on local average patient costs per day have been available. Therefore the real costs attributed to ICU stay (including nursing, lab costs and all other treatments) would probably be much higher

Table 3

Creatinine concentration (percent increase of baseline) under conventional amphotericin B continuous infusion to reduce nephrotoxicity (adapted from Imhof et al. [18]).

Amphotericin B dose	Percent of subjects with % increase of creatinine concentration		
	50% increase	100% increase	200% increase
1 mg/kg/d (n = 40)	33%	15%	0%
1.5 mg/kg/d (n = 14)	29%	7%	0%
1.75 mg/kg/d (n = 9)	11%	22%	0%
2.0 mg/kg/d (n = 10)	10%	10%	10%

in these difficult-to-treat patients, and bias the result in favour of conventional amphotericin B.

Since switching for treatment non-response was not markedly different in the two groups (13% vs 15% for voriconazole and amphotericin B respectively) [17], the main difference in costs derived from renal toxicity of conventional amphotericin B. This occurred in a previous study in approximately 30% of the patients treated for invasive aspergillosis at the University Hospital of Geneva [16]. In a large pharmacoeconomic evaluation, Bates et al. calculated the average added costs due to amphotericin B-induced nephrotoxicity by comparing the costs of 212 patients with acute renal failure under treatment, defined as a >50% increase of baseline creatinine level, with a peak of >2 mg/dL (177 mmol/L), to the costs of 495 treated patients without signs of renal toxicity [11]. Based on these data, we estimated the costs for renal toxicity in the model by adjusting for purchasing power parity (as of 2004) and the above-mentioned costs of hospital resources, and subsequently weighting with the incidence of acute renal failure in the conventional amphotericin B arm. The cost savings predicted for voriconazole in this model were therefore sensitive to the acute renal failure percentage. This benefit was sustained for voriconazole over a wide range of assumed values. These values included published and comparable incidence data of renal failure over ranges observed in the case where amphotericin B deoxycholate was given in a continuous infusion over 24 h to reduce nephrotoxicity [18] (table 3).

As in all model based cost-effectiveness analysis, some limitations were intrinsic [19]. Nevertheless two very large databases including several hundred patients were the backbone of this evaluation [8, 11]. The validity of the model result has been tested by sensitivity analysis of factors with impact on the calculations: patient weight, hospital resources estimates, duration of parenteral voriconazole application after switching as well as lower cost estimates per case of nephrotoxicity. None of these factors applied over a range of reasonable values changed the conclusion of the analysis.

Finally it should be mentioned that initial treatment with voriconazole might be crucial regarding clinical outcome. Based on the recently published secondary analysis of the GCA study results regarding clinical success rates after changing to other licensed treatments (OLAT) Patterson et al demonstrated a significant difference in favourable outcome for those patients receiving voriconazole only (55%) compared to those initially given amphotericin B deoxycholate (32%) [20].

Therefore it can be concluded that initial therapy with voriconazole was cost-saving and resulted in better clinical outcomes. Based on this model, voriconazole is the dominant cost-effective option for initial therapy of invasive aspergillosis, despite very low drug acquisition costs of conventional amphotericin B. No cost advantage could be achieved when a treatment was started with amphotericin B and only changed to voriconazole in case of renal failure or non-response. This effect was sensitive to the acute renal failure percentage, but cost savings were sustained for voriconazole over a wide range of assumed values including reported nephrotoxicity incidence data of amphotericin B continuous infusion.

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