Antimycotic treatment for immunocompromised patients with neutropenia and persistent fever with suspicion of systemic aspergillosis: a cost-effective analysis in Mexico

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Abstract

Background: Systemic mycosis has a great impact on medical care costs. The objective of this study was to assess the most cost-effective empirical treatment for systemic aspergillosis, evaluating amphotericin B, caspofungin and voriconazole in patients with persistent fever and neutropenia.

Methods: A decision-tree model was used to estimate expected clinical results and costs associated with the treatment for systemic aspergillosis. The study used a healthcare payer’s perspective (Mexican Institute of Social Security, IMSS). Time frame was 12 weeks. Effectiveness measure was complete remission of mycotic infection. One-way and probabilistic sensitivity analyses were performed.

Results: Average total expected costs per patient for the voriconazole treatment were US$57,378.58, for amphotericin B US$72,833.96, and for caspofungin were US$49,962.37. The total expected remission rate without any adverse events was 37.0% for caspofungin, 43.6% for voriconazole and 51.1% for amphotericin B. Probabilistic sensitivity analysis showed that voriconazole would be a cost-effective treatment with 65% confidence, regardless of the willingness to pay the IMSS.

Conclusions: The results of the study agree with the recommendation that voriconazole must be the empirical treatment for systemic aspergillosis, proposed as a standard first-line antifungal drug.

Keywords: invasive aspergillosis, systemic fungal infection, antifungal agents, cost-effectiveness

Introduction

Systemic mycoses impact on the morbidity and mortality of immunocompromised children, greatly increasing the costs associated with their medical care. In some hospitals, the prevalence of invasive aspergillosis in children has been higher than that of systemic candidiasis.1,2 Systemic aspergillosis is a severe fungal infection that affects immunocompromised patients, especially those who have undergone bone marrow transplant or who suffer from a hematological disease.3-6 Neutropenia and its duration are the most important risk factors for the development of fungal infections in these patients.3,7 Systemic mycosis may be suspected in patients with neutropenia and fever when this persists after the use of broad-spectrum antibiotics or when

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pulmonary edema or lung cysts have been identified through computed tomography. Patient’s characteristics and local epidemiological data are also important factors to be considered.8,9 It has been recommended that patients with risk factors are subjected to empirical treatment when a fungal infection is suspected. This has been associated with an improved survival rate10,11 because there is a low diagnostic sensitivity (~50%) for systemic mycoses.

The incidence of systemic mycoses in the U.S. from Aspergillus species has increased 4.5 times yearly.12 Despite advancements in the treatment of these infections, the mortality rate is 57%-100%.13-17

Amphotericin B was considered the primary treatment against systemic aspergillosis until 2000;18 however, its effectiveness is variable (14%-83%) and depends on the infection site and the underlying primary disease.4,13 In spite of the high incidence of adverse effects (nephrotoxicity), its low cost encouraged the medical community to continue prescribing it.19 Voriconazole is considered nowadays as the primary treatment against systemic aspergillosis because it presents a lower incidence of adverse effects and has a higher effectiveness rate than amphotericin B.18,20 Despite the increasing rate of pediatric aspergillosis, the number of studies on the subject is limited; therefore, we consider it appropriate to estimate its prevalence using available data for the adult population.21 It has been reported that caspofungin is indicated for patients who do not respond well to amphotericin B or voriconazole or patients who have low tolerance to these drugs.22

The cost per patient of the empiric treatment with complete remission of systemic mycoses in patients with neutropenia has been estimated to be between $13,674USD and $20,024USD, in patients with cancer and neutropenia between $8,814USD and $13,880USD, in patients with cancer and bone marrow transplant between $11,173USD and $16,230USD, and in patients with neutropenia and persistent fever between $43,183USD and $48,962USD.23 In the U.S., the costs associated with children hospitalized from systemic aspergillosis were >25 million USD.24

We found that none of the cost-effectiveness studies on the treatment of systemic mycoses compared the three aforementioned antifungal drugs simultaneously.19,25-29 This comparison is important because the three antifungal drugs are in the Mexican “Basic Formulary Medications” and it is essential to identify which offers the best cost-effectiveness ratio. According to results of other studies on initial treatments of systemic aspergillosis, the use of voriconazole in Spain reported an incremental cost-effectiveness ratio of 25,266€ when compared to amphotericin B25 and 1132.18€ when compared to caspofungin.29 In Germany, an incremental cost-effectiveness ratio of 62€ was reported per additional survival week when comparing voriconazole against amphotericin B.27 These studies showed there are more clinical benefits when using voriconazole instead of amphotericin B or caspofungin because of its higher effectiveness in aspergillosis remission and lower incidence of adverse effects.27

The main difficulty for administrators is to be certain of what is the best antifungal drug that should be prescribed, based on the available evidence of efficiency and safety, as well as in regard to associated costs, budgetary constraints and opportune costs.19 Therefore, in the present study we evaluated three possible treatments for systemic aspergillosis: amphotericin B (deoxycholate), voriconazole and caspofungin. We carried out a cost-effectiveness analysis for treatment in neutropenic patients with persistent fever using a healthcare payer’s perspective and a time frame of 12 weeks.

The Mexican Institute of Social Security (IMSS) is the largest healthcare institution in Mexico and covers the health needs of ~30% of the population.30 The IMSS covers only affiliated workers and their families and the covered population is equivalent to the working population in other Latin American and developing countries with similar healthcare systems.30 Although most of the described studies refer to patients diagnosed with systemic aspergillosis, it is very important to evaluate the best cost-effective treatment in suspected systemic aspergillosis. The purpose of our study was to identify the most cost-effective antifungal drug for the empiric treatment of systemic aspergillosis in neutropenic patients with persistent fever.

Methods
The cost-effectiveness analysis used a decision-tree model that represents the possible clinical events that would occur as a consequence of the empirical treatment prescribed for patients with aspergillosis, severe neutropenia and persistent fever. The model considers the adult population because the available
The alternatives evaluated were voriconazole (loading dose of 400 mg/12 h on the first day of treatment), amphotericin B (loading dose of 70 mg/day, 1 mg/kg/day) and caspofungin (loading dose of 70 mg on the first day). Maintenance doses were voriconazole (200 mg/12 h), amphotericin B (70 mg) and caspofungin (50 mg).

The decision-tree model has three nodes for each therapeutic alternative (Figure 1). There are three possible results for each antifungal drug: a) complete remission without complications, b) partial remission with severe collateral effects (nephrotoxicity and possible death), c) therapeutic failure where the patient does not respond to treatment and systemic mycosis continues (possible systemic failure, multiple organ failure or death). The possibility for total remission and survival is also shown in Figure 1.

Costs
The study uses a healthcare payer’s perspective (IMSS) and therefore only considers direct costs. All costs were obtained from the financial and accounting information of the institution\textsuperscript{31} updated March 2004 and estimating inflation for 2008. The costs of antifungal drugs as well as of those used to treat primary neutropenia were obtained from the IMSS website.\textsuperscript{32} The time frame used to evaluate costs was 12 weeks, assuming that during this period other clinical events could occur (clinical suspicion of aspergillosis, patient discharge, adverse effects associated with antifungal drugs, ADR treatments and even death of the patient). For this period, we considered the use of resources according to clinical events and evaluated unit costs. We applied no discounted rate because of the time frame.

In order to identify the use of IMSS resources, we assumed patients >25 years old with leukemia, lymphoma or bone marrow transplant who present severe neutropenia and, very likely, aspergillosis. We considered only the adult population in order to compare our results with other similar studies. We gathered a group of seven institutional medical experts who had experience with all evaluated drugs and we requested them to provide an estimation of resources required to handle patients and the possible clinical events described in the model including laboratory and clinical tests, hospital stay, visits from other specialists (pneumology, infectology), medicines (antifungals and others), peritoneal dialysis sessions, minor surgeries (catheter for dialysis), assisted mechanical ventilation,
blood transfusions, surgical equipment and warehouse expenses. Laboratory test costs were obtained from the monthly report produced by the IMSS National Medical Center “XXI Century”.32

**Effectiveness**
The effectiveness parameter was defined as the complete remission ratio of aspergillosis without adverse events. The effectiveness measure used in our study was the percentage of patients with complete remission per 1000 patients with suspected aspergillosis. In order to identify the effectiveness of studied antifungal drugs and the presentation probability of clinical events described in Figure 1, we carried out a systematic literature review between 1994 and 2004 using the Ovid-Medline, Elsevier-ScienceDirect, Proquest, Ebsco-E-Journal services and Interscience databases. We included all clinical trials in English or Spanish that tested the studied antifungal drugs on adult patients with hematological cancer/bone marrow transplant who presented persistent fever and severe neutropenia. Selected trials should include the percentages for total remission, partial remission and therapeutic failure as well as the description of adverse events such as nephrotoxicity. Only two trials met our criteria; however, it was necessary to verify other cohort studies/trials about the treatment of other systemic mycoses to identify the prevalence of complications under therapeutic failure.33-43

We included in our model the following data from clinical trials as follows:

**Voriconazole**
Herbecht et al.41 carried out a clinical trial to compare the effectiveness of voriconazole vs. amphotericin B to treat aspergillosis in patients with severe neutropenia. They included 114 patients in the voriconazole group, reporting 20% with complete remission and 38% with therapeutic failure. Severe adverse effects were documented in 13% of cases and, of these, 7% presented nephrotoxicity.

**Amphotericin B**
Herbecht et al.41 also reported that amphotericin B had an effectiveness of 16% for complete remission and 58% as therapeutic failure. Adverse events occurred in 24% of cases and, of these, 42% were classified as nephrotoxicity.

**Caspofungin**
Walsh et al.35 studied 1095 patients, of which 556 received caspofungin. They reported 34% as total remission, 5% as therapeutic failure, and 5% as adverse events; of these, 2% were related to nephrotoxicity.

To complete our model we identified, using cohort studies for ICU patients with aspergillosis, that 84% of patients who presented therapeutic failure from any antifungal drug developed multiple organ failure and, of these, 50% fully recovered after a second treatment but 32% died.36,37

**Analysis**
We carried out the analysis of empirical antifungal treatment for patients with neutropenia and persistent fever through a thorough cost-effectiveness evaluation. The cost-effectiveness analyses compared direct and indirect costs as well as savings that present two or more medical treatments to obtain a similar result in the patient’s health (for instance, number of saved lives or number of patients who avoided a given disease). The net total costs of a given intervention, also known as incremental costs, are estimated and divided by the difference between clinical result effectiveness. In summary, the incremental cost-effectiveness ratios are obtained through the following expression:

\[
iCER = \frac{(\text{Total Costs}_A - \text{Total Costs}_B)}{(\text{Effectiveness}_A - \text{Effectiveness}_B)}
\]

where the incremental cost-effectiveness ratio (iCER) is obtained by dividing the net total costs (incremental costs) by the net effectiveness (incremental effectiveness) for two alternative medical treatments (A and B) (Table 1).

**Sensitivity Analysis**
We carried out three sensitivity analyses. Analysis of the scenario allowed us to evaluate results if voriconazole price had changed. The threshold analysis evaluated if initial model results were changed when the total remission rate was modified for any treatment. Finally, we carried out a sensitivity probabilistic analysis through a Monte Carlo simulation generating 10,000 iCER iterations obtained from distribution of parameters. We obtained acceptability curves for all studied treatments using the software Tree Age Pro 2004.

**Results**
We determined that the expected average cost for treating patients with hematological cancer or bone
marrow transplant who also develop systemic aspergillosis is about $60,058.30USD at an exchange rate of 1 USD = 11.16 MXN. However, this estimation varies considerably (between $25,441.22USD and $119,438.18USD) according to the patient’s evolution considering the following scenarios: complete remission without complications, normal aspergillosis evolution with severe consequences and even patient’s death.

The results of our cost-effectiveness analysis are shown in Table 1. The average treatment cost for a patient with severe neutropenia and aspergillosis using amphotericin B is $72,833.96USD, using voriconazole $57,378.58USD and using caspofungin $49,962.37USD. In a secondary probabilistic analysis we found no statistically significant differences between voriconazole and caspofungin costs (Mann-Whitney U test; \( p > 0.05 \)), although both showed statistically significant differences with amphotericin B. As for effectiveness, the aspergillosis remission rate without adverse events was higher using amphotericin B (51.1%), followed by voriconazole (43.6%) and caspofungin (37%). This shows that caspofungin is the least expensive antifungal drug as well as being the least effective; amphotericin B is the most effective drug and also the most expensive (because of an increased nephrotoxicity probability); voriconazole is more effective than caspofungin and slightly more expensive; however, it is less expensive than amphotericin B. These data are shown in Table 1. We observed no absolute or extended dominance for any of the studied options; therefore, it was necessary to carry out a probabilistic analysis to determine the most cost-effective treatment.

With the scenario analysis we observed that if voriconazole increased its price by 25% this would be dominated by amphotericin B and caspofungin (data not shown). The threshold analysis showed that voriconazole can dominate amphotericin B when the complete remission rate is 40% because the total number of patients in a cohort of 1000 is 517 vs. 511 for amphotericin B. Voriconazole would need to have a complete remission rate (without complications) >35% to be more cost-effective than caspofungin. This is from a deterministic point of view; however, monetary evaluation derives its conclusions from probabilistic sensibility analyses because the former results do not include uncertainty from parameters used in our model.

Voriconazole and amphotericin B used as empiric antifungal treatments could be potentially cost-effective; therefore, it is necessary to use other tools such as probabilistic sensibility analysis to determine which is more cost-effective by including uncertainty (statistical distribution of model parameters). Therefore, we developed acceptability curves (including all possible statistical probabilities for each outcome) for all three antifungal treatments in order to determine which would be the most cost-effective option according to the willingness of the IMSS to pay for each treatment. Figure 2 shows acceptability curves for antifungal treatments.

The probabilistic sensitivity analysis with acceptability curves shows that voriconazole has 65% probability of being the most cost-effective treatment, independent

### Table 1. Results from cost-effectiveness analysis (Mexican pesos, 2008)

<table>
<thead>
<tr>
<th></th>
<th>Total expected cost</th>
<th>Incremental Cost</th>
<th>Effectiveness</th>
<th>Incremental Effectiveness</th>
<th>Average C/E</th>
<th>Incremental C/E ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amphotericin B</strong></td>
<td>72,833.96</td>
<td></td>
<td>51.1%</td>
<td></td>
<td>142,532.21</td>
<td></td>
</tr>
<tr>
<td><strong>Voriconazole</strong></td>
<td>57,378.58</td>
<td>- 15,455.38</td>
<td>43.6%</td>
<td>-0.075</td>
<td>131,602.25</td>
<td>206,071.73</td>
</tr>
<tr>
<td><strong>Caspofungin</strong></td>
<td>49,962.37</td>
<td>- 22,871.59</td>
<td>37.0%</td>
<td>-0.141</td>
<td>135,033.43</td>
<td>162,209.86</td>
</tr>
</tbody>
</table>

C = cost; E = effectiveness. Incremental cost-effectiveness ratio (iCER) is calculated as:

\[
\text{iCER} = \frac{\text{Cost of Treatment A} - \text{Cost of Treatment B}}{\text{Effectiveness of Treatment A} - \text{Effectiveness of Treatment B}}
\]

The average cost-effectiveness ratio analyzes each treatment independently and in this analysis voriconazole has the lowest ratio (more cost-effective per remission%).
of the willingness of the IMSS to pay, followed by caspofungin with 25% and amphotericin B with 10% (Figure 2). Thus, if the three drugs were used to treat immunocompromised patients, voriconazole would be the most effective and least expensive treatment (65% certainty), followed by caspofungin (25% certainty).

**Discussion**

Systemic mycoses can be associated with *Aspergillus* spp. in up to 58% of patients with hematological diseases in certain hospitals. Their prevalence has increased recently and they have been associated with mortality in 57%-100% of cases. A meta-analysis including 50 studies found that the mortality rate from systemic aspergillosis in patients with acute leukemia or lymphoma was 60% and in patients with bone marrow transplants reached 90%.

Timely treatment of systemic aspergillosis is one of the essential factors to reduce mortality rates. In children, delayed treatment may be related to 80% mortality, whereas timely treatment reduces mortality to 29%. It is important to begin empirical treatment in high-risk patients given the difficulty to diagnose systemic mycoses where there is a reasonable suspicion of the disease. Empirical treatment depends on several factors such as agent frequency in the population, expected result considering the primary disease, difficulty in diagnosis, drug effectiveness, drug interactions, safety and cost.

Average costs for the treatment of systemic mycosis range between $13,674USD and $152,140USD per patient. This significant variation depends on the patient’s evolution that can have several outcomes. We considered 10 possible clinical scenarios in our study (Table 1).

We found that voriconazole was the most cost-effective option when suspecting systemic aspergillosis although there was no absolute dominance over caspofungin or amphotericin B. We found in the probabilistic sensitivity analysis that treatment with voriconazole was the most cost-effective option of the three evaluated medications with 65% of cases and independent of the willingness of the IMSS to pay.

Most studies on the subject have compared only two antifungal drugs; therefore, we decided to compare three of them. It is important to highlight that there are very few studies where children or adolescents are involved; therefore, it has been recommended that the information obtained in studies with an adult population is applied to the pediatric population.

For patients with neutropenia and persistent fever who have not responded to broad-spectrum antibiotics and who also have a high suspicion of aspergillosis, the recommended treatment is voriconazole because it provides superior clinical results with lower costs. The few studies where children were included reached similar conclusions. Our study shows that voriconazole is the most cost-effective option. We observed in the stochastic analysis that voriconazole could be chosen as the most cost-effective option with 65% certainty. It is important to remember that the model in the present study considers an empirical treatment when systemic aspergillosis is suspected. When the disease has been diagnosed, voriconazole is associated with lower costs. On the other hand, willingness to pay thresholds are not available in Mexico or in the IMSS; however, if we adjust the parameters to those used by the British National Institute of Health ($50,000USD) or to those recommended by WHO (<3 GDP per capita), we found that results are within acceptable levels.

Another advantage of voriconazole over amphotericin B is that 100% *Aspergillus* spp. are sensitive *in vitro*, whereas only 37.5% of species are sensitive to amphotericin B. No resistance has been reported for voriconazole by *Aspergillus*; however, there is an increasing number of fungi that are resistant to amphotericin B. On the other hand, it has been reported that antifungal drug intolerance presents faster when using amphotericin B than when using voriconazole (10 days vs. 77 days). Also, severe adverse drug events have been associated with voriconazole in 13.4% of cases, whereas amphotericin B has been related to 24.3%. Exanthema and visual impairment are the most frequent adverse events reported in children associated with the use of voriconazole.

Sensitivity analysis in our study demonstrated that if voriconazole showed 40% complete remission, it would have an absolute dominance over amphotericin B and caspofungin; Denning et al. and Herbrecht et al. reported a success rate of 48% and 52.8%, respectively, when combining complete remission and partial remission. This supports the usage of voriconazole as the first antifungal empirical treatment against suspected...
systemic aspergillosis.

Studies from both Germany\(^ {27}\) and the U.S.\(^ {26}\) showed that voriconazole is the most cost-effective treatment. Results were robust and demonstrated that voriconazole was the dominant strategy in all evaluated sensitivity scenarios.\(^ {26}\)

Another advantage for maintenance treatment is that voriconazole can be administered orally, whereas amphotericin B and caspofungin are only injectable.\(^ {23}\) This increases costs for the treatment of systemic aspergillosis because it is recommended that the patient remains in the hospital; in children, hospital stay may last for 16 days.\(^ {24}\)

We used the international literature to calculate model probabilities and did not refer to the Mexican population. However, we found no reliable information in Mexico to develop our model. On the other hand, all the models (including ours) share a hospital environment approach, which gives comparable results.\(^ {19,25-29}\) We consider as a possible restriction that the literature used in the model was not updated to reflect inflation for 2008. Another restriction is that antifungal drugs were not combined or alternated as a possible treatment; however, we consider this is more useful when the agent has been fully identified.\(^ {18,20,56}\)

Our study evaluates the results with a time frame of 12 weeks, which is common with current cost-analysis studies.\(^ {19,23,25-27}\)

One of the advantages of the present study is that probabilities included in our model were based on the average of probabilities reported in the literature, which allows the reduction of the possibility of bias because a given study may overemphasize the probability of certain events such as death, complete remission, or toxic effects in favor of or against a given antifungal drug. By using the average of probabilities, we weighed biases and could have reduced them.\(^ {57}\) We also included in the probabilistic sensitivity analysis the effectiveness variability reported in the literature.

With regard to recommended dosages in our study, we found that they coincide with those suggested in 2008 studies and, therefore, regard our model as current.\(^ {20}\)

At the present time, the British Society for Medical Mycology recommends voriconazole as the first-choice therapy to treat systemic mycoses.\(^ {58}\) When it is not available, amphotericin B is also recommended and has shown good results in children.\(^ {44}\) Caspofungin is recommended as a second-choice therapy and is well tolerated in children.\(^ {58,59}\) Although caspofungin has reported good results against *Aspergillus* spp., this antifungal drug has shown little effectiveness against other fungi;\(^ {58,60,61}\) therefore, voriconazole is a better empirical treatment for systemic aspergillosis because it has a broader spectrum against unsuspected or undetected fungi.\(^ {16,62}\) Amphotericin B has been recommended over voriconazole when i) concomitant drugs with higher doses of voriconazole are being used, such as use of drugs with more interaction such as sirolimus, rifampin or warfarin; ii) there is significant hepatic damage; iii) there is high suspicion of zygomycosis; iv) when there is the presence of heart factors such as prolonged QT-interval or other cardiac risk factors.\(^ {20}\)

Finally, we can highlight that in a developing country whose social security system is focused towards workers and their families, the most cost-effective option to treat a suspected aspergillosis is voriconazole. It is important to consider that the willingness to pay is affected by the probability of adverse drug events, which can be regarded as more severe, leading to choose one of the treatment alternatives.\(^ {63,64}\) Nowadays, modern healthcare systems cannot adopt one therapeutic alternative considering only its effectiveness and if it is well tolerated, but they should keep in mind pharmacoeconomic parameters, and voriconazole is the best empiric treatment against systemic
aspergillosis. Nevertheless, further studies are necessary to evaluate the effectiveness of voriconazole, amphotericin B and caspofungin in the pediatric population who presents cancer with neutropenia and fever because currently available randomized trials are scarce. In conclusion, voriconazole is the most cost-effective antifungal drug to treat suspected systemic aspergillosis in patients with lymphoma, leukemia or bone marrow transplant in a social security institution in a developing country. These results may be extended to the pediatric population.

References