

# Cost-Effectiveness Analysis of Antifungal Prophylaxis in Patients Undergoing Hematopoietic Stem Cell Transplantation

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## ABSTRACT

**Background:** Micafungin sodium is indicated for the prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation (HSCT). One Phase III, multi-institutional, randomized, double-blind comparative trial involving 882 adult and pediatric patients found that micafungin was more effective, in terms of significantly lower rates of systemic fungal infections and empiric antifungal therapy (AFT), than fluconazole as antifungal prophylaxis during the neutropenic phase following HSCT. Thus, despite the higher cost of micafungin versus fluconazole, micafungin prophylaxis may be associated with reduced costs.

**Objective:** The aim of this analysis was to determine the cost-effectiveness of micafungin prophylaxis compared with fluconazole prophylaxis in patients undergoing HSCT.

**Methods:** Efficacy data were taken from the clinical study. The economic analysis was conducted from the hospital perspective, using costs incurred from admission through discharge. Each of the patients was assigned costs and effectiveness based on outcomes data from the clinical study. Published literature was used to estimate hospital costs associated with HSCT and prophylaxis, empiric AFT, and treatment of a probable or proven *Candida* or *Aspergillus* infection. Mean costs and effectiveness were calculated in each treatment group. To test the variability of the results using repeated sampling, a bootstrapping analysis was also conducted, with 1000 simulations of random samples of 100 patients from each treatment group. If appropriate to describe the results, incremental cost-effectiveness ratios were calculated, and sensitivity analyses were conducted by varying components of cost.

**Results:** This analysis included data from 882 patients (527 males, 355 females; micafungin, 425 patients, mean age, 43.2 years [range, 0.6–73.0 years]; fluconazole, 457 patients, mean age, 41.9 years [range, 0.6–71.0 years]). Total hospital costs per patient were \$121,098 and \$124,957 in micafungin and fluconazole recipients, respectively—a difference of \$3859.

The bootstrapping analysis found that micafungin prophylaxis was cost-saving in 72.4% of the samples compared with 9.2% with fluconazole prophylaxis. Sensitivity analyses on estimated hospital costs found that micafungin was a cost-effective therapy.

**Conclusion:** In this analysis of data from a clinical study in adults and children undergoing HSCT, micafungin prophylaxis was associated with reduced hospital costs, and resultant total patient costs, compared with fluconazole prophylaxis. (*Clin Ther.* 2008;30:964–973) © 2008 Excerpta Medica Inc.

**Key words:** cost-effectiveness analysis, antifungal prophylaxis, micafungin, fluconazole, hematopoietic stem cell transplant.

## INTRODUCTION

Fungal infection is a pervasive and costly problem in hospital care. In 1996, nearly 3 in 1000 hospitalized patients in the United States were affected, with candidiasis accounting for ~80% of systemic fungal infections.<sup>1</sup> Deep-seated *Candida* infections and candidemia occur in perhaps 2% to 3% of patients in intensive care units.<sup>2</sup> The economic impact of fungal infection is substantial, with candidiasis accounting for US ~\$48,732 in hospital costs beyond the cost of care in transplant recipients without fungal infection in 1998; and, although less frequent, aspergillosis was even more costly to treat with an estimated incremental cost per person of \$86,635 in transplant recipients in 1998.<sup>1</sup> Aspergillosis is associated with high morbidity and mortality, particularly in immunocompromised patients with risk factors such as bone marrow transplantation (BMT), solid-organ transplantation, neutropenia, hematologic malignancy, HIV, immune dys-

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function, chemotherapy, or corticosteroid therapy.<sup>3,4</sup> For example, pulmonary, sinus, and cerebral aspergillosis were associated with crude mortality rates of 86%, 66%, and 99%, respectively, in immunocompromised patients in the United Kingdom in 1996.<sup>5</sup> Approximately 1.1% of BMT hospitalizations were associated with a diagnosis of aspergillosis—2.5- to 7-fold the rate in other high-risk diagnosis-related group categories (eg, hematologic malignancy, HIV, chemotherapy, reticuloendothelial and immune disorders in 2003 in the United States).<sup>6</sup>

Various agents are indicated to prevent or treat fungal infection, and numerous clinical trials have documented these benefits.<sup>7-9</sup> Historically, agents used to combat fungal infection include amphotericin B, the azole agents, and lipid-based amphotericin formulations.<sup>10</sup> Despite the efficacy of these agents against many types of fungal infection, their use has been limited due to the toxicities and drug interactions associated with them.<sup>10</sup> The introduction of various antifungal therapies over the past decade has focused attention on prophylactic strategies as a means to decrease the burden of fungal infection.<sup>11</sup>

Fluconazole has been routinely used as prophylactic antifungal therapy (AFT) in many institutions and has been found to have antifungal effects in patients who have undergone autologous or allogeneic hematopoietic stem cell transplantation (HSCT).<sup>7,8</sup> However, its association with fungal infection breakthrough in some patients, high costs related to IV administration, and lack of efficacy in protecting patients from invasive aspergillosis created a need for more effective and less expensive alternative drugs.<sup>12</sup>

The recent development of echinocandins such as caspofungin, micafungin, and anidulafungin allows for more widespread prophylactic use of AFT because of the fewer drug interactions and adverse effects associated with the agents.<sup>10</sup> Micafungin is an antifungal agent in the echinocandin class approved by the US Food and Drug Administration in 2005 for prophylaxis and treatment of fungal infections in patients undergoing HSCT. It has been found to be more effective, in terms of lower rates of systemic fungal infections and empiric AFT, than fluconazole for prophylaxis of invasive candidal infections and has been associated with fewer drug interactions.<sup>10,12</sup>

In a multicenter, randomized, double-blind, head-to-head study, van Burik et al<sup>9</sup> compared the efficacy and tolerability of prophylaxis with micafungin and

fluconazole (the standard treatment for fungal infection) in 882 adults and children who underwent HSCT. Patients recruited into the study were  $\geq 6$  months of age and receiving an allogeneic HSCT for any indication, or autologous HSCT for hematologic malignancy. Patients were excluded if they had deeply invasive fungal disease or hepatic disease at the time of enrollment. The primary efficacy end point was *treatment success*, defined in the clinical trial as the absence of a proven, probable, or suspected systemic fungal infection through the end of the prophylaxis therapy, and the absence of a proven or probable systemic fungal infection through the end of the 4-week posttreatment period. The overall success rate with micafungin was significantly higher than the rate with fluconazole (80.0% vs 73.5%;  $P = 0.03$ ). However, costs were not considered in that study.

In routine clinical practice, the impact of fungal infection is of concern both clinically and economically. Because the costs of transplantation procedures are substantial and such costs can be significantly increased if these cases are complicated by fungal infection, cost-effective methods of preventing fungal infection have the potential to reduce overall transplantation costs.

The objective of this economic evaluation was to determine the cost-effectiveness of prophylaxis with micafungin versus fluconazole in patients undergoing HSCT.

## MATERIALS AND METHODS

### Analysis of Patient Clinical Data

Data from the study by van Burik et al<sup>9</sup> were used to classify each patient according to antifungal prophylaxis, treatment, and clinical outcomes. All patients were given a prophylactic regimen, with 425 receiving micafungin (50 mg QD, or 1 mg/kg in patients weighing  $< 50$  kg) and 457 receiving fluconazole (400 mg QD, or 8 mg/kg in patients weighing  $< 50$  kg). The total amount of prophylactic medication used by each patient was recorded. Patients with suspected development of fungal infection also received *empiric therapy*, defined as AFT initiated if a persistent fever  $\geq 38^\circ\text{C}$  developed and sustained  $\geq 96$  hours during the neutropenic phase despite broad-spectrum antibacterial therapy.<sup>9</sup> A total of 64/425 (15.1%) patients in the micafungin arm and 98/457 (21.4%) patients in the fluconazole arm received empiric therapy. If systemic fungal infection developed, patients received addi-

tional treatment with systemic antifungal agents. The overall incidences of proven or probable systemic fungal infection were 7/425 (1.6%) in the micafungin treatment arm and 11/457 (2.4%) in the fluconazole treatment arm. Thus, 7/425 (1.6%) and 11/457 (2.4%) of patients in the micafungin and fluconazole arms, respectively, received additional treatment beyond empiric therapy, leaving 13.5% (15.1% – 1.6%) and 19.0% (21.4% – 2.4%), respectively, receiving only empiric treatment.

Costs and effectiveness were assigned to each patient based on his or her clinical outcomes. Patients who did not receive empiric therapy or develop a fungal infection (ie, 84.9% in the micafungin arm and 78.6% in the fluconazole arm) were assigned a total patient cost associated with “successful prophylaxis.” Patients who required empiric therapy but in whom a fungal infection did not develop were assigned a total patient cost for “successful empiric therapy.” Patients who failed empiric therapy and had a documented fungal infection were assigned a “systemic fungal infection” total patient cost, with different costs, depending on the nature of the fungal infection. The percentages of patients assigned to each of the outcome groups defined in our analysis are shown in Table I.

## Costs

All costs used in this analysis were adjusted to 2006 US dollars based on the Consumer Price Index for hospital and related services.<sup>13</sup> The baseline costs presented in Table I were rounded to the nearest dollar, except for the per-milligram cost of prophylaxis.

### Cost of Drugs for Prophylaxis

Unit drug costs were obtained from a published source of average wholesale prices (AWPs).<sup>14</sup> The costs per milligram were \$2.24 with micafungin and \$0.12 with fluconazole. Prophylactic drug costs were then calculated individually for each patient by multiplying the cost per milligram by the total cumulative dose of drug administered to the patient. In an average adult patient, the daily prophylactic drug costs corresponded to \$112 with micafungin and \$48 with fluconazole.

### Hospital Costs per Patient, Successful Empiric Therapy

In a study by Cagnoni et al,<sup>15</sup> total hospital costs were \$115,734 and \$68,710, respectively, for allogeneic BMT and nonallogeneic BMT recipients requiring empiric therapy. To determine the mean cost for all BMT recipients, we weighted these values by the per-

Table I. Baseline analysis variables.

Measure	Micafungin	Fluconazole
Cost per milligram of prophylaxis, US \$ <sup>14*</sup>	2.24	0.12
Cost per day of prophylaxis, US \$*	112	48
Treatment outcomes, %		
Successful prophylaxis	84.9	78.6
Successful empiric therapy	13.5	19.0
Fungal infection, candidiasis	0.9	0.4
Fungal infection, aspergillosis	0.2	1.5
Fungal infection, other	0.4	0.4
Estimated hospital costs per HSCT patient, US \$*		
Successful empiric therapy	162,736	
Successful prophylaxis	109,555	
Proven fungal infection, candidiasis	200,087	
Proven fungal infection, aspergillosis	263,798	

HSCT = hematopoietic stem cell transplantation.

\*Data adjusted to 2006 US \$.

centage of patients with allogeneic BMT and autologous BMT from the study by van Burik et al<sup>9</sup> (ie, 54.0% and 45.8%, respectively, using the percentages with autologous BMT for the nonallogeneic value). These calculations yielded a weighted mean hospital cost of \$93,933 for successful empiric therapy in patients with a similar mix of characteristics as in the study by van Burik et al. When adjusted for inflation, the hospital cost per patient with successful empiric therapy was \$162,736 (in 2006 dollars). The total cost to the hospital for a patient receiving successful empiric therapy was the sum of this hospital cost and the patient's individual cost of drugs for antifungal prophylaxis.

#### **Hospital Costs per Patient, Successful Prophylaxis**

Wilson et al<sup>1</sup> calculated an average total hospital cost of \$72,706 for adult and pediatric transplant recipients undergoing prophylaxis for fungal infection in 1997 from the Maryland Hospital Discharge Data Set. This average cost represented a mix of patients, some receiving empiric therapy and some not. Because our cost-effectiveness analysis required a separate cost estimate in patients receiving prophylaxis but not empiric therapy, Wilson's figure had to be reduced to estimate costs for patients receiving only successful prophylaxis. By excluding possible empiric antifungal therapy costs using the method described in the next paragraph, we estimated the hospital costs (not including prophylaxis costs) of a patient with successful prophylaxis to be \$64,410 (adjusted for inflation, this value was \$109,555 [2006]). The total hospital cost for a patient with successful prophylaxis was obtained by adding individual prophylaxis drug costs to this figure. The figure of \$64,410 was determined as follows.

Based on the data from the study by van Burik et al,<sup>9</sup> 21.4% of patients receiving fluconazole prophylaxis required empiric therapy, and 78.6% did not. This same distribution was then assumed to describe the mix of patients in the Wilson study.<sup>1</sup> The estimated average total hospital cost for the (assumed) 21.4% of patients receiving empiric therapy in the Wilson study was \$93,933 (as determined above). By removing the costs for these patients from the total of the hospital costs for all transplant recipients undergoing prophylaxis for fungal infection in the Wilson study, the calculated average total hospital cost of the (assumed) 78.6% of patients who did not require empiric therapy was \$64,410. This figure did not include any costs for the prophylaxis itself.

#### **Hospital Costs per Patient, Proven Fungal Infection**

For the 18 patients in whom a systemic fungal infection developed in the van Burik study,<sup>9</sup> the additional hospital costs were higher than for those with successful empiric therapy. Of these patients, 6 developed *Candida* infection, 8 developed *Aspergillus* infection, and 4 developed another type of fungal infection. These additional costs were estimated separately for patients developing *Candida* infection and *Aspergillus* infection, and the 4 patients with some other type were assigned the same costs as patients with *Candida* infection. (Of these 4, 2 received micafungin and 2 received fluconazole.)

Wilson et al<sup>1</sup> determined that hospital costs were \$119,926 for transplant recipients with candidiasis and \$157,929 for those with aspergillosis. Adjusted for inflation, this yields a hospital cost of \$200,087 and \$263,798, respectively, in 2006 dollars. The total cost for a patient with systemic fungal infection was obtained by adding to this cost the patient's individual cost of drugs for prophylaxis.

#### **Base-Case Analysis**

Using the data from all patients, the average cost per patient receiving micafungin was calculated and compared with the average cost per patient receiving fluconazole. If the average cost for micafungin were more, the incremental cost-effectiveness ratio (ICER)—the ratio of the difference in mean costs to the difference in mean effectiveness—would then be computed for micafungin versus fluconazole, in which the effectiveness would be measured by treatment success (ie, proven, probable, or suspected systemic fungal infection avoided). However, if on the average the cost for micafungin were less, which might result from its greater efficacy in preventing infection, then micafungin would be the dominant method of prophylaxis (ie, micafungin is more effective and less expensive compared with fluconazole), and therefore it would be unnecessary to calculate an ICER.

#### **Sensitivity Analyses**

Multiple 1-way sensitivity analyses were conducted, each varying 1 component of cost while keeping other costs at their base-case values:

1. The cost of micafungin was increased by 50%.
2. The cost of treating a patient with breakthrough fungal infection was set equal to the cost for a

patient with successful empiric therapy, in essence setting the additional cost associated with a breakthrough infection to zero.

3. The cost of treating a patient with successful empiric therapy was set equal to the cost for a patient with successful prophylaxis, in essence setting the additional cost associated with empiric therapy to zero.

The intent of these sensitivity analyses was to provide information about which of the cost components have the greatest impact on the comparative costs of micafungin and fluconazole. In no way should these sensitivity analyses be interpreted to suggest that any prophylaxis actually reduces the additional cost of empiric therapy or treatment of breakthrough infection to near zero.

### Bootstrapping Analysis

Bootstrapping tests the reliability of the dataset. It allows one to assess the extent to which the distribution of characteristics, such as overall costs, is influenced by stochastic effects, such as the probability of the 3 key clinical outcomes: successful prophylaxis, successful empiric therapy, and development of fungal infection. Bootstrapping was used to examine the variability of the costs and effectiveness for each method of prophylaxis.<sup>16</sup> We generated 1000 random samples, with each sample containing 100 patients from each treatment group. For each sample, we calculated the average cost and effectiveness for patients receiving micafungin and for those receiving fluconazole. We compared the average difference in cost and effectiveness, as done in the base-case analysis. We then determined for each sample whether micafungin or fluconazole was dominant, or whether the calculation of an ICER was appropriate.

As opposed to the base-case analysis, for which it was known that micafungin was more effective over the entire group of patients, it would be possible for micafungin to be either more, less, or equally as effective as fluconazole in a particular sample of 100 patients receiving each type of prophylaxis depending on the probability distribution of clinical outcomes. Thus, bootstrapping results could show that one method of prophylaxis or the other possibly could be cost-saving, but not dominant, if both had equal efficacy in the sample of 100 patients receiving each type of prophylaxis. The frequency of samples falling into each cate-

gory (ie, dominant, cost-saving [but not dominant], or incrementally cost-effective) was determined, and this frequency was displayed in a 4-quadrant graph.<sup>16</sup>

After the bootstrapping analysis was completed for the base-case scenario, it was conducted separately for each of the 3 sensitivity analyses. In addition, the bootstrapping was repeated using both the base-case values and the 3 sensitivity analyses for additional sets of 1000 random samples, except with each sample containing 200 patients from each treatment group.

## RESULTS

This analysis included data from 882 patients (527 males, 355 females; micafungin, 425 patients, mean age, 43.2 years [range, 0.6–73.0 years]; fluconazole, 457 patients, mean age, 41.9 years [range, 0.6–71.0 years]).

### Base-Case Results

The base-case analysis found that mean hospital costs were \$3859 lower for patients who underwent HSCT and received micafungin prophylaxis compared with those who received fluconazole prophylaxis, with mean (SD) total hospital costs of \$121,098 (\$22,311) and \$124,957 (\$28,818), respectively (Table II). When combined with the results from the study by van Burik et al<sup>9</sup> showing greater efficacy among patients receiving micafungin, micafungin was found to be dominant.

### Sensitivity Results

The 3 sensitivity analyses, each varying 1 cost component, produced results showing how changes in each of these components affect the base-case findings (Table III).

When the cost of micafungin was increased by 50%, the average total hospital costs for patients receiving micafungin increased ~\$1000, to \$122,107. Because this value was still less than the cost for patients receiving fluconazole, micafungin remained dominant.

When the cost for a patient with breakthrough infection was set equal to the cost of a patient receiving empiric therapy, but with no breakthrough infection, with the cost of micafungin prophylaxis itself returned to the base-case value, the mean costs for both patients receiving micafungin and those receiving fluconazole were reduced. However, micafungin still remained less costly than fluconazole by \$2750, so it remained the dominant method of prophylaxis.

When the cost of empiric therapy was eliminated, so that the cost for a patient receiving empiric therapy

Table II. Results of baseline analysis for hematopoietic stem cell transplantation.

Measure	Micafungin (n = 425)	Fluconazole (n = 457)	Difference* in Mean Costs or Effectiveness†
Mean costs, US \$			
Prophylactic drugs	2018	843	1175
Hospital costs (other than prophylaxis)	119,079	124,114	-5035
Total hospital costs			
Mean	121,098	124,957	-3859
SD	22,311	28,818	-
Minimum	109,779	109,579	-
Maximum	264,134	265,505	-
Mean effectiveness‡	0.800	0.735	0.030

\* Positive (negative) dollar amounts indicate that micafungin costs are more (less) than fluconazole costs; positive effectiveness value indicates that micafungin is more effective than fluconazole.

† Based on the incremental cost-effectiveness ratio—obtained by dividing difference in total hospital costs by difference in mean effectiveness—lower costs, and greater effectiveness suggest that micafungin is dominant.

‡ That is, treatment success.

Table III. Results of sensitivity analyses (SA) for hematopoietic stem cell transplantation. Values are US \$ (2006).

Measure	Micafungin (n = 425)	Fluconazole (n = 457)	Difference* in Mean Costs
Baseline results			
Total hospital costs, mean	121,098	124,957	-3859
SD	22,311	28,818	-
SA 1†			
Total hospital costs, mean	122,107	124,957	-2850
SD	22,281	28,818	-
SA 2‡			
Total hospital costs, mean	120,332	123,082	-2750
SD	19,685	22,646	-
SA 3§			
Total hospital costs, mean	113,214	113,553	-339
SD	12,966	20,667	-

\* Negative dollar amounts indicate that micafungin costs were less than fluconazole costs.

† Price per milligram of micafungin increased by 50%.

‡ Hospital costs of fungal infection = successful empiric therapy.

§ Hospital costs of empiric therapy = successful prophylaxis.

was set equal to the cost for a patient with successful prophylaxis, the average costs for micafungin patients and fluconazole patients were reduced even further, to \$113,214 and \$113,553, respectively. In this case, the average costs were virtually equal, with micafungin patients costing ~\$339 less.

**Bootstrapping Results**

The bootstrapping analysis found that in 72.4% (724/1000) of the random samples micafungin was cost-saving compared with fluconazole (9.2% [92/1000] of samples). The scatter plot shown in the figure plots a point corresponding to the result of each sample, with the coordinates of the point corresponding to the difference in cost and difference in effectiveness between micafungin and fluconazole. Thus, points falling in quadrant IV of the graph represent results when micafungin prophylaxis was dominant, with both lower average costs and greater average effectiveness than for fluconazole. Micafungin prophylaxis was dominant in 55.5% of the samples—more

than three fourths of the 724 samples in which it was cost-saving. In contrast, only 6.4% of the sample results fell in quadrant II, where fluconazole prophylaxis was dominant.

**Bootstrapping Sensitivity Results**

In the first sensitivity analysis, when the cost of micafungin was increased by 50%, micafungin recipients had a lower average cost than fluconazole recipients in 69.1% of the random samples, compared with a higher cost in 15.3%. The bootstrapping results were similar for the second sensitivity analysis. The third sensitivity analysis, which essentially eliminated any additional cost associated with empiric therapy, resulted in a different distribution of bootstrapping samples, with micafungin showing cost-saving in 55.9% of samples and fluconazole in 40.3%.

The results of bootstrapping vary due to random sampling and depend on the sample size. For example, when the third sensitivity analysis was repeated, but with 200 patients per treatment group for each of

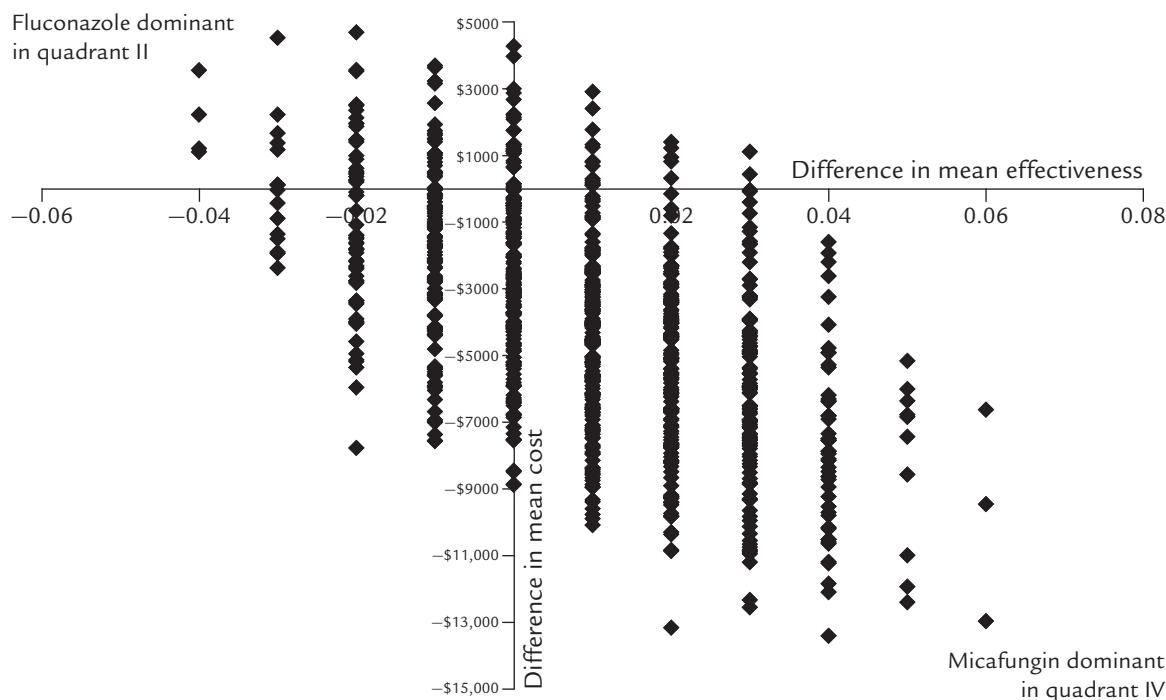


Figure. Scatterplot of bootstrapping analysis. The high concentration of results in quadrant IV, where mean costs are lower and mean effectiveness is greater for micafungin, suggests the dominance of micafungin prophylaxis.

the 1000 random samples generated, cost-saving was found in 56.5% of the samples for micafungin and 31.2% for fluconazole. With all variables reset to their original values, increasing the sample size to 200 patients per treatment group for the bootstrapping analysis led to results that were similar to the original bootstrapping, with 81.5% of the 1000 samples indicating micafungin as cost-saving compared with only 2.4% for fluconazole.

## DISCUSSION

Systemic fungal infection among transplant recipients is both life-threatening and costly.<sup>1,12</sup> Because successful prophylaxis can reduce the incidence of infection, it also has the potential to lower the overall costs of care. However, the costs of using various types of prophylaxis vary, as do their effectiveness, so that different regimens may not be equally cost-effective.

Despite the higher drug costs for micafungin compared with fluconazole, we found hospital cost-savings due to less need for empiric antifungal therapy and fewer breakthrough infections. Even if the price of micafungin were raised, sensitivity analyses found that it is still the dominant type of prophylaxis. Therefore, mean hospital costs and total costs were lower in this analysis when using micafungin as opposed to fluconazole. Our study adopted a conservative approach in using AWP to approximate the drug acquisition cost, when institutions could negotiate lower prices in clinical practice.

The sensitivity analyses provided some insight as to the main source of cost-savings that might be expected when using micafungin. When the analysis excluded the savings that would result from the lower use of empiric therapy (ie, the third sensitivity analysis) for patients receiving micafungin, the average total costs for all patients are almost identical for both types of prophylaxis. This analysis is equivalent to assuming that no patients receive empiric therapy and suggests that most of the cost-savings associated with micafungin prophylaxis (in the base-case scenario) stems from the resulting reduction in the need for empiric therapy. Of course, the greater effectiveness in preventing breakthrough infection also contributes to the cost-savings associated with micafungin use, as shown in the second sensitivity analysis, but this contribution is smaller. A prospective study<sup>12</sup> to evaluate the administration of micafungin 100 mg QD before allogeneic stem cell transplantation found a higher rate of

prophylactic success compared with fluconazole (87.8% vs 65.5%) in patients who were free of proven, probable, and possible invasive fungal infection until the end of prophylactic therapy. That study suggested that the administration of micafungin at a daily dose of 100 mg was clinically promising; however, the economic impact will need to be further determined.<sup>12</sup>

Our analysis had several limitations. First, we did not gather actual hospital cost information for HSCT patients enrolled in the clinical study published by van Burik et al.<sup>9</sup> Instead, our cost estimates were based on a compilation of previously published studies of HSCT patients undergoing prophylaxis, treated with empiric therapy, and experiencing breakthrough infection. As a result of using cost data from other studies, our hospital cost estimates are derived from actual costs found in other studies in similar patient populations. Although similar, those studies were conducted in somewhat different patient populations at various times. For example, when we calculated the hospital costs for successful prophylaxis, we used costs obtained from Cagnoni et al<sup>15</sup> and Wilson et al,<sup>1</sup> studies that were conducted in 1996 and 1998, respectively. Furthermore, the estimate for transplant recipients obtained from Wilson et al represented an unspecified mix of patients, not only those receiving HSCT. While the costs derived from these studies need to be interpreted with caution, we conducted 2 sensitivity analyses on the effects of empiric therapy costs and infection costs in the results by examining much more extreme changes in these costs. We believe that these sensitivity analyses have partially compensated for the limitations of synthesizing costs from various studies.

Second, although the bootstrapping method we used did vary effectiveness and cost simultaneously, the probability distribution used was necessarily basic because of the way that costs were assigned. Patients who received micafungin or fluconazole were assigned different probabilities of clinical outcomes that resulted in different costs and effectiveness. Within each treatment group, patients who developed fungal infection were randomly assigned 1 of 2 possible costs depending on whether the infection was candidiasis or aspergillosis. Likewise, patients in whom treatment was successful in preventing fungal infection were assigned 1 of 2 costs, depending on whether prophylaxis was successful or they needed an empiric therapy. Thus, the variability of the cost-effectiveness ratio

generated by bootstrapping was not the same as it would have been if a continuous cost distribution had been used. Even so, the results clearly indicate the dominance of micafungin in most cases.

Third, it is worth noting that the choice of empiric therapy was based on a retrospective billing data review, which focused on liposomal amphotericin B and conventional amphotericin B. Since the time of our study, AFTs such as voriconazole and caspofungin have been developed and used in hospitals; however, the cost implications of these newer therapies compared with the amphotericin B–based therapies in HSCT recipients have not been found. Because both liposomal amphotericin B and conventional amphotericin B are still widely used today, it is reasonable to believe that the empiric care of fungal infection in clinical practice would not deviate significantly from that estimated in our model.

Fourth, in our study, the effectiveness data were derived from the clinical trial, the result of which may not be fully generalizable to clinical practice because clinical trials are designed for scientific efficacy and tolerability with relatively small sample size and strictly defined patient population with respect to age, comorbidities, and prior and concomitant therapies. Therefore, the results of cost-effectiveness analysis must be interpreted with caution. Not every patient can be expected to experience lower hospital costs when using micafungin. Although the precise bootstrapping results (eg, the exact number of samples for which micafungin was dominant) are dependent on the choice of sample size, bootstrapping found that for any group of patients, micafungin was much more likely to be dominant or cost-saving than fluconazole.

Finally, our analysis did not take into account measures of quality or efficacy other than the use of empiric therapy or the rate of breakthrough infections. If other morbidities and/or mortality were included, a more comprehensive analysis would be possible. However, the evidence does not suggest a significant difference in survival rates. Although in the study by van Burik et al<sup>9</sup> numerically fewer micafungin recipients died compared with fluconazole recipients, those results were not statistically significant, and we were hesitant to use differential survival in our analyses. In addition, our study did not include the cost associated with treating adverse events induced by micafungin or fluconazole. However, the exclusion of costs for adverse events would not be expected to have a significant impact on our study re-

sults because the incidences of adverse events observed in the study by van Burik et al were similar.

## CONCLUSION

In this analysis of data from a clinical study in adults and children undergoing HSCT, micafungin prophylaxis was associated with reduced hospital costs, and resultant total patient costs, compared with fluconazole prophylaxis.

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