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The Cost of Treating Systemic Fungal Infections

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Abstract

The increasing incidence of systemic fungal infections and rising medical costs have highlighted the need for an economic appraisal of antifungal agents to determine the most cost-effective therapeutic option. Cost savings derived from the prophylactic or empirical use of antifungal agents have been difficult to estimate because of the lack of information on the costs of systemic fungal infections. Fluconazole is effective in prophylaxis and represents a direct cost saving compared with polyenes. However, itraconazole oral solution, an effective and widely used antifungal prophylactic agent, has not been analysed for cost effectiveness. In empirical therapy, the development of new formulations of existing agents has prompted a number of cost comparisons. In particular, the cost of treatment with conventional amphotericin-B has been compared with the costs of the new lipid-associated formulations of amphotericin-B or the new intravenous (IV) formulation of itraconazole. The acquisition costs of lipid-associated amphotericin-B and IV itraconazole are higher than the cost of conventional amphotericin-B; however, these costs appear to be offset by reductions with both these agents in the cost for increased length of hospital stay and treating adverse events seen with conventional amphotericin-B. In neutropenic patients and bone marrow transplant recipients, IV itraconazole may be the most cost-effective option for empirical therapy.

In recent years, the incidence of HIV infection, the intensity of chemotherapy regimens for cancer and the use of bone marrow transplantation have all increased. The resultant increase in the incidence of systemic fungal infections in this immunosuppressed population is well documented.[1,2] Most infections are caused by *Candida* spp. or *Aspergillus* spp., both of which are associated with high death rates (up to 80%).[3,4]

Fluconazole, itraconazole, and amphotericin-B are the most frequently used antifungal agents (see Meis and Verweij[5]**)**. However, the newly developed formulations of itraconazole and lipid-associated formulations of amphotericin-B have provided new treatment options for systemic fungal infection.

Increasing medical costs highlight the need to quantify the burden of systemic fungal infections and to make accurate economic assessments of the available treatments. The cost analysis of fungal infections can be separated into two phases: a descriptive phase, in which the burden of illness is estimated, and an analytical phase, in which interventions and their costs, and the consequences of removing the burden of illness, are evaluated. Because lipid-associated amphotericin-B and IV itraconazole are as effective as conventional amphotericin-B for empirical therapy in persistently

neutropenic patients, the relative direct and associated costs of these agents are important factors to consider when selecting the most appropriate therapy. The available data on the relative costs of the prophylactic or empirical use of antifungals are summarised here.

1. Cost of Illness

The cost of any illness is the sum of direct, indirect and intangible costs. The direct costs include the use of medical and non-medical resources, the indirect costs include the costs of work absenteeism, and intangible costs include the effects of illness on the quality of life of the patient. It is difficult to generalise about the costs of systemic fungal infections because the incidence of such infections and the most frequent causative organisms vary from country to country and centre to centre. In addition, most studies have been concentrated on the direct costs of antifungal agents; intangible costs, indirect costs and even some direct costs, such as length of stay in hospital, are often ignored.

Two recent reports assessed the direct costs of *Candida* infections.[6,7] In surgical intensive care units (ICUs), the cost of hospital care for a patient with a presumed *Candida* infection (fever that is unresponsive to broad spectrum antibiotics) was $US41 000 more than the cost for a patient whose fever resolved after treatment with broad spectrum antibiotics.[7] Approximately 10% of these additional costs were pharmacy costs and most of the remainder were costs for surgical ICU room and board and other hospital charges (such as tests and procedures).[7] The additional cost of care for a patient with candidaemia in any hospital department was estimated to range from $US34 000 per patient to $US44 500 per patient.[6] As for the surgical ICU patients, the pharmacy costs accounted for approximately 10% of these additional costs.

According to Rentz et al.,[6] the annual incidence of confirmed candidaemia in the USA is approximately 6326 cases, incurring an overall direct cost of candidaemia of more than $US200 million per year. However, the total direct cost of systemic fungal infection is likely to be greater than this because many systemic fungal infections are undiagnosed and many other fungal species, in particular *Aspergillus* spp., can be responsible for infection. The costs incurred during *Aspergillus* infection may vary considerably from those incurred during *Candida* infection.

In addition, both the reports described here underestimate the true cost of systemic fungal infections per patient because they did not measure the indirect and intangible costs associated with morbidity and mortality. Indirect costs can be estimated by multiplying the number of missed days of work by the national average daily salary. According to the 1994 Healthcare Cost and Utilization Project (HCUP-3)[8] of the US Agency for Healthcare Policy and Research, the increased length of hospital stay (and therefore the number of missed days of work) for any patient with a severe systemic fungal infection was approximately 13 days; other studies estimated a greater increase in the length of hospital stay – of more than 20 days.[6,7] The true cost of systemic fungal infections must therefore be considerable.

2. Comparing the Cost of Antifungal Agents

Because the cost of systemic fungal infections is not known, the cost savings attained with treatment cannot be analysed; therefore, comparisons of the cost of different antifungal regimens must suffice. Cost analyses of antifungal agents must compare the direct costs of the agent over the course of treatment, the costs of second-line therapies needed for nonresponders, the costs of any tests or of treating adverse events associated with the agent, and the costs associated with length of hospital stay. Costs are usually expressed as an incremental cost-effectiveness ratio (ICER), which is a ratio of the additional cost per additional unit of outcome (e.g. the number of life-years saved or the number of patients treated successfully). Most cost-effectiveness analyses also involve a theoretical model that combines collected information on treatment patterns, clinical probabilities, outcomes and costs. These models can be used to define an

Table I. The cost of antifungal prophylaxis

Patients	Treatment regimen	Cost ($US)	Reference
HIV	No prophylaxis	36 100/patient	11
	Fluconazole 100 mg/day when CD4+ cell count < 200/mm^3	40 500/patient	
	Fluconazole 100 mg/day when CD4+ cell count < 100/mm^3	37 900/patient	
	Fluconazole 100 mg/day when CD4+ cell count < 50/mm^3	36 900/patient	
BMT[a]	Fluconazole (100 mg/day; 12 weeks)	46 330/patient free from infection	12
	Oral polyenes (400 000IU nystatin or amphotericin-B 40 mg/day; 12 weeks)	52 430/patient free from infection	
	Amphotericin-B-liposomal (2 mg/kg 3 times weekly; 12 weeks)	85 160/patient free from infection	

a Prophylaxis for oropharyngeal infections.

BMT = bone marrow transplantation.

average or baseline ICER; the assumptions in the model can then be varied and the sensitivity of the ICER to these variables can be tested.[9] Although there is no consensus on a cost-effectiveness threshold for antifungal prophylaxis or treatment, a maximum cost of $US50 000 per year of life saved (YLS) is often used for other medical interventions.[10]

2.1 Prophylaxis

Successful prophylaxis can prevent the costs of illness and is therefore potentially very cost effective. In general, however, the cost effectiveness of antifungal prophylaxis is difficult to estimate because poor diagnosis results in an underestimation of the incidence of systemic fungal infection and therefore an inaccurate estimation of the effectiveness of prophylaxis. Most studies analysing the cost of antifungal prophylaxis compare fluconazole with oral polyenes (table I).

The direct medical costs of treating a patient with AIDS were estimated to be $US36 100, and the use of fluconazole prophylaxis added an additional $US4400 per patient to this cost (based on a dose of 100 mg/day, costing $US206 per month) if started when the patient's CD4+ cell count decreases to less than 200/mm^3.[11] This produces an ICER of $US240 000 per YLS. Delaying prophylaxis until the CD4+ cell count decreases to less than 100/mm^3 or 50/mm^3 reduces the cost but increases the ICER; hence the timing of antifungal prophylaxis is important.[11] Fluconazole prophylaxis in AIDS patients is therefore unlikely to be cost effective even in areas endemic for fungal infections (ICER = $US96 000 per YLS).[11] Perhaps this is not surprising in patients with AIDS because the treatment of secondary infections cannot substantially extend the life of the patient: this can only be achieved by suppressing HIV and reconstituting the immune system.

In other patients at high risk, such as bone marrow transplant recipients, the period of risk of fungal infection is more clearly defined; it might be expected, therefore, that successful antifungal prophylaxis would produce lower ICERs. In one study of this patient group, fluconazole was the most cost-effective option for prophylaxis (table I).[12] The increased costs of using amphotericin-B-liposomal are a result of increased acquisition costs, whereas the increased costs of using oral polyenes result from reduced efficacy and the need to treat subsequent fungal infections.[12]

A review of the literature confirmed that fluconazole (100 mg/day) was more cost effective (direct costs only) than oral polyenes or a combination of fluconazole and oral polyenes in the prevention of systemic fungal infection in patients receiving chemotherapy or bone marrow transplants.[13] However, clinical interviews in UK hospitals contradicted the literature review by suggesting that prophylaxis with oral polyenes or a combination of fluconazole and oral polyenes was

more cost effective in patients receiving chemotherapy or bone marrow transplants.[13]

A more relevant comparison of prophylactic agents would be one which included fluconazole and itraconazole capsules or oral solution: the itraconazole oral solution provides more effective prophylaxis than fluconazole in patients with haematological malignancies, particularly against infections caused by *Aspergillus*.[14] However, except for one analysis of itraconazole prophylaxis in lung transplant recipients and one in heart transplant recipients, no cost analyses have included itraconazole. The conclusion of the study in lung transplant recipients was that, in centres where *Aspergillus* frequently causes infections, the addition of itraconazole capsules (200 mg/day for 3 months) to immunosuppressive regimens containing tacrolimus reduced overall costs.[15] This was a reflection of the pharmacokinetic interactions of itraconazole and tacrolimus. Similarly, in heart transplant recipients, itraconazole may be useful for the prophylaxis of aspergillosis, and the additional cost of adding itraconazole capsules to the regimen is offset by the reductions in cost associated with the reduced cyclosporin dose.[16]

Meta-analyses show that antifungal prophylaxis reduced morbidity and death related to fungal infection in neutropenic cancer patients,[17] but doubt has been cast on the effectiveness of antifungal prophylaxis and empirical therapy by others.[18] However, the high mortality associated with fungal infections encourages clinicians to continue to use antifungal agents in these settings. In future, improvements in diagnosis of systemic fungal infections will help to direct therapy and thus reduce costs. However, the intensive use of currently available diagnostic procedures (in patients with possible aspergillosis) increases the overall costs of managing systemic fungal infections.[19]

2.2 Treatment of Confirmed Fungal Infections

When a systemic fungal infection is confirmed, the cost effectiveness of different antifungal regimens can be estimated more accurately. Because the most widely used antifungal treatment is the conventional formulation of amphotericin-B, studies of the cost of antifungal treatment have generally been focused on the different formulations of this agent. The results of some published cost analyses are given in table II.[20-22]

In a comparison of conventional amphotericin-B and amphotericin-B-liposomal in organ or bone marrow transplant recipients with confirmed fungal infections (table II),[20] the additional costs of amphotericin-B-liposomal were low enough to conclude that the liposomal formulation was cost effective in all the patient groups studied. However, this was a retrospective analysis that may have been biased by other factors – the antifungal doses are not reported.

Using data from published trials, Tollemar and Ringden[21] calculated the cost of treating confirmed fungal infections in a variety of immunocompromised patients with lipid formulations of amphotericin-B. With doses of amphotericin-B-liposomal (NeXstar Pharmaceuticals), amphotericin-B-colloidal dispersion (AstraZeneca) and amphotericin-B-lipid-complex (the Liposome Company) that produce equivalent efficacy, the cost of treatment is almost equal (table II). Although it is hard to draw conclusions from this study on the cost effectiveness of the different lipid formulations of amphotericin-B, this study and others[23] indicate that findings on the cost effectiveness of one lipid-associated formulation of amphotericin-B (in any study) may be applicable to the other lipid-associated formulations.

The cost of treating candidaemia in non-neutropenic patients with IV fluconazole was shown to be higher than with conventional amphotericin-B (table II).[22] Although the cost of treating adverse events was higher in patients receiving amphotericin-B, this was outweighed by both the acquisition costs of IV fluconazole and the longer period of therapy required. In the sensitivity analysis, if patients were switched to oral fluconazole after 7 days of treatment with IV fluconazole, the cost was reduced and was equivalent to the cost of therapy with conventional amphotericin-B.

Table II. Summary of published reports of the cost of treatment of confirmed fungal infection

Patients	Treatment	Regimen[a]	Cost ($US)	Reference
Organ or bone marrow transplant recipients	Treatment of confirmed systemic fungal infection	Conventional amphotericin-B versus amphotericin-B-liposomal for a mean of 21 days	25 000/YLS more with amphotericin-B-liposomal than with conventional amphotericin-B in BMT, and kidney and pancreas transplant recipients; 32 000/YLS more with amphotericin-B-liposomal than with conventional amphotericin-B in liver transplant recipients[b]	20
Patients with haematological malignancies, immunological disease or AIDS, and bone marrow or organ transplant recipients	Treatment of confirmed systemic fungal infection	Amphotericin-B-liposomal approx. 1.7 mg/kg/day for a median of 24 days	12 992/patient (range: 3248 to 20 416) from 9 studies	21
		Amphotericin-B-colloidal dispersion 2.8 mg/kg/day for a mean of 20 days	12 614/patient from 1 study	
		Amphotericin-B-lipid-complex approx. 5 mg/kg/day for approximately 28 days	11 437/patient (range: 10 040 to 12 754) from 3 studies	
Non-neutropenic patients	Treatment of confirmed candidaemia	Conventional amphotericin-B 0.6 mg/kg/day for 17 days	1580/patient[c]	22
		IV fluconazole 800 mg/day followed by 400 mg/day for 24 days	2385/patient[c]	

a Mean doses.

b Assuming $US1 = 6 Swedish krona.

c Assuming $US1 = 1.5 Canadian dollars.

BMT = bone marrow transplantation; **IV** = intravenous; **YLS** = year of life saved.

The limited data on the cost of treating confirmed systemic fungal infection do not provide evidence of a clear cost benefit of any single agent. More studies are needed, and these should include the new formulations of itraconazole.

2.3 Empirical Treatment

The problems with diagnosis of systemic fungal infections mean that in most settings patients receive empirical antifungal therapy, rather than treatment of confirmed infection. Knowing the cost of empirical therapy is therefore probably more useful to the healthcare profession. Not all patients who receive empirical therapy will have fungal infections and therefore the true costs of antifungal agents per patient with fungal infection are probably higher than the studies in the previous section suggest.

To date, most cost analyses of empirical therapy have appeared only in abstract form (table III).[24-28] However, from these limited data some conclusions can be drawn. Compared with first-line empirical therapy with conventional amphotericin-B, first-line therapy with amphotericin-B-liposomal is not cost effective (table III).[24,25,28-31] Sensitivity analysis showed that the incremental cost per YLS ($US183 000) is highly sensitive to the daily cost of amphotericin-B-liposomal.[25] Although using a lower initial dose of amphotericin-B-liposomal (1 mg/kg/day) reduces costs,[24] it also reduces efficacy and is lower than the recommended dose in many countries.[29,32] It is estimated that the acquisition costs of amphotericin-B-liposomal would have to be less than 50% of their current cost to be cost effective.[28,30,31]

In contrast, the cost of amphotericin-B-lipid-complex in empirical therapy was justified

compared with conventional amphotericin-B, despite the higher hospital and pharmacy charges.[26] However, amphotericin-B-lipid-complex was used selectively in this study, for example, when serum creatinine was elevated. In general, the first-line empirical use of any lipid-associated formulations of amphotericin-B is likely to be too costly.

One study has included the new IV itraconazole formulation in a cost analysis. Empirical treatment of systemic fungal infections in neutropenic patients and bone marrow transplant recipients with IV itraconazole, conventional amphotericin-B or amphotericin-B-liposomal was compared (table III).[27] In general, costs were higher with all three agents in bone marrow transplant recipients than in neutropenic patients, but in both groups IV itraconazole was the most cost effective. As expected, the acquisition cost of amphotericin-B-liposomal increased its cost-effectiveness ratio, and treatment with conventional amphotericin-B was more expensive than with IV itraconazole because of increased length of hospital stay and the

Table III. Summary of published reports of the cost of empirical antifungal treatment

Patients	Treatment	Regimen[a]	Cost ($US)	Reference
Neutropenic patients	Empirical therapy	Conventional amphotericin-B switched if necessary to amphotericin-B-liposomal 1 mg/kg/day	13 674/cure	24[b]
		Amphotericin-B-liposomal 1 mg/kg/day increased if necessary to 3 mg/kg/day	15 509/cure	
		Amphotericin-B-liposomal 3 mg/kg/day increased if necessary to 5 mg/kg/day	20 024/cure	
Neutropenic patients	Empirical therapy	Conventional amphotericin-B followed by amphotericin-B-liposomal versus amphotericin-B-liposomal alone	183 000/YLS more with amphotericin-B-liposomal alone than with conventional amphotericin-B followed by amphotericin-B-liposomal	25[c]
Not specified	Empirical therapy	Conventional amphotericin-B for 15 days	Hospital charges: 113 448/patient Pharmacy charges: 38 082/patient	26[d]
		Amphotericin-B-lipid-complex for 14 days	Hospital charges: 152 140/patient Pharmacy charges: 55 904/patient	
Neutropenic cancer patients and bone marrow transplant recipients	Empirical therapy	Conventional amphotericin-B 0.95 mg/kg/day	Neutropenia: 10 235/patient BMT: 12 890/patient	27[e]
		Amphotericin-B-liposomal 2 mg/kg/day	Neutropenia: 13 880/patient BMT: 16 320/patient	
		IV itraconazole 400 mg/day for 2 days, then 200 mg/day	Neutropenia: 8814/patient BMT: 11 173/patient	
Persistently febrile neutropenic patients	Empirical therapy	Conventional amphotericin-B 0.6 mg/kg/day	43 183/patient	28
		Amphotericin-B-liposomal 3 mg/kg/day	48 962/paitent	

a Mean doses.

b In all 3 strategies, the first-line treatment is given for 10 days, which if unsuccessful after 5 days is switched to second-line therapy for 10 days.

c Reference 25 does not state when patients were switched to amphotericin-B-liposomal.

d Hospital charge differences reflect differing lengths of stay, differences in patient groups, etc.

e Costs shown are combined drug, test and hospital costs.

BMT = bone marrow transplantation; **IV** = intravenous; **YLS** = year of life saved.

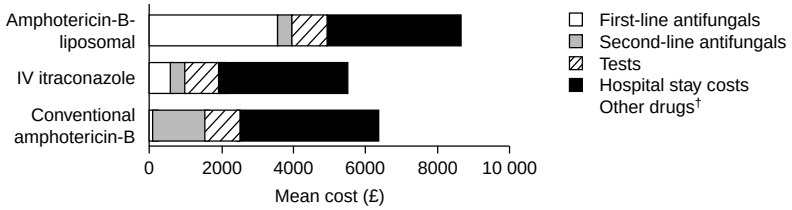

Fig. 1. Average costs per patient (neutropenic patients and bone marrow transplant recipients) of empirical treatment with conventional amphotericin-B, amphotericin-B-liposomal and intravenous (IV) itraconazole. Although not obvious from the figure, length of stay and test costs with conventional amphotericin-B are increased.
† Costs for 'Other drugs' associated with these treatments were as follows: £17 (conventional amphotericin-B); £13 (IV itraconazole); and £14 (amphotericin-B-liposomal).

need for second-line antifungal agents (i.e. when there was insufficient response patients were switched to amphotericin-B-liposomal) [fig. 1]. Increased length of hospital stay with conventional amphotericin-B was partly due to drug-associated nephrotoxicity, which can result in increased costs of up to $US39 000 per patient.[33] Defervescence with no severe toxicity was used as the successful unit of outcome in calculations of ICERs. For amphotericin-B-liposomal versus IV itraconazole, the ICER was high for amphotericin-B-liposomal ($US213 648 per patient with defervescence and no severe toxicity), but the ICER for amphotericin-B-liposomal versus conventional amphotericin-B was more favourable for amphotericin-B-liposomal ($US28 510 per patient with defervescence and no severe toxicity).[27]

3. Conclusion

The small amount of available data on the cost of systemic fungal infections means that the cost savings from the prophylactic or empirical use of antifungals are difficult to estimate. In prophylaxis, fluconazole is more cost effective than conventional or liposomal formulations of amphotericin-B in bone marrow transplant recipients, but other agents have not been included in comparative cost analyses. The development of lipid-associated formulations of amphotericin-B and the IV formulation of itraconazole for empirical therapy has prompted a number of comparisons of the costs of empirical therapy. Under certain circumstances, such as when patients are intolerant of conventional amphotericin-B, the lipid-associated formulations of amphotericin-B may be cost effective, but in general they appear to be too costly for first-line use. The IV formulation of itraconazole may be more cost effective than either conventional or liposomal formulations of amphotericin-B when used as empirical therapy for neutropenic patients with persistent fever despite broad spectrum antibiotic therapy, but further studies are required.

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