Cost-Effectiveness Analysis of the Empirical Antifungal Strategy in Oncohaematological Patients

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Abstract

Objective: Observational study performing a cost-effectiveness analysis of the empirical antifungal strategy in high-risk oncohaematological patients, from the hospital perspective and with an average time horizon of 10.8 days of treatment.

Method: Data gathered: effectiveness, purchase costs, and other costs (diagnostic tests, hospitalisation, and second-line antifungal therapy). A total of 107 patients were analysed, 115 invasive fungal infection sub-episodes, and 138 empirical treatments.

Results: The effectiveness and average cost/treatment were: voriconazole 88% and €20 108.8, caspofungin 68% and €49 067.7, amphotericin B lipid complex (ABLC) 58% and €30 375.2, and amphotericin B liposome (AB-L) 50% and €38 234.5. The first tree designed shows voriconazole as the dominant option, although there are few case studies. The second tree selects ABLC in comparison to AB-L and caspofungin, with an average CE of €52 371, the nearest figure to the established availability to pay (€50 000). The sensitivity analysis evaluates the most influential parameters. The variation in the cost of purchasing do not modify the sense of the analysis, and the modification of 25% in other costs for caspofungin reverses the ratio, making this the most cost-effective option. The ICE indicates that using voriconazole instead of caspofungin saves €144 794. With regard to caspofungin, ABLC increases the cost by €186 925, a deceptive figure influenced by a level of effectiveness that is not very different; and AB-L increases the cost by €60 184.

Conclusions: The analysis provides relevant information from the perspective of clinical practice in spite of the limitations of the unconsidered costs (nephrotoxicity). This type of analysis contributes to rationalising the use of antifungal agents in the hospital setting and in high-risk patients such as oncohaematological ones.

Key words: Cost-effectiveness. Antifungal agents. Empiric therapy. Immunocompromised host.

Estudio coste-efectividad de la estrategia empírica antifúngica en pacientes oncohematológicos

Objetivo: Estudio observacional que realiza un análisis coste-efectividad de la estrategia antifúngica empírica en pacientes oncohematológicos de alto riesgo, desde la perspectiva hospitalaria y con un horizonte temporal de 10,8 días de media de tratamiento.

Método: Se ha recogido: efectividad, costes de adquisición y otros costes (pruebas de diagnóstico, hospitalización, terapia antifúngica de segunda línea). Se analizan 107 pacientes, 115 subepisodios de infección fúngica invasiva y 139 tratamientos empíricos.

Resultados: La efectividad y el coste medio/tratamiento fue: voriconazol, 88% y 20.108,8 €; caspofungina, 68% y 49.067,7 €; anfotericina B complejo lipídico (ABCL), 58% y 30.375,2 €, y anfotericina B liposómica (AB-L), 50% y 38.234,5 €. El primer árbol diseñado señala voriconazol como opción dominante, aunque su casuística resulta escasa. El segundo árbol selecciona ABCL frente a AB-L y caspofungina, con un CE medio de 52.371 €, el más próximo a la disponibilidad a pagar establecida (50.000 €). El análisis de sensibilidad evalúa los parámetros más influyentes: la variación del coste de adquisición no modifica el sentido del análisis; y la modificación de un 25% de otros costes para caspofungina invierte la relación, convirtiéndose ésta en la opción más coste/efectiva. El CEI indica que voriconazol en lugar de caspofungina ahorra 144.794 €. Respecto a caspofungina, ABCL incrementa el gasto en 186.925 €, cifra engañosa influenciada por una efectividad no muy distinta, y AB-L lo incrementa en 60.184 €.

Conclusiones: El estudio aporta información relevante desde la perspectiva de la práctica clínica pese a las limitaciones de costes no considerados (nefrotoxicidad). Este tipo de estudios contribuye a racionalizar el uso de antifúngicos en el entorno hospitalario y en los pacientes de alto riesgo como los oncohematológicos.

Palabras clave: Coste-efectividad. Antifúngicos. Terapia empírica. Pacientes oncohematológicos..

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INTRODUCTION

Invasive fungal infections (IFI) have increased in the hospital setting in a significant manner over recent years, both in terms of frequency and complexity. Many patients have become particularly predisposed hosts, such as immunocompromised patients.[1-3] The risk affecting oncohaematological patients is related to variables such as: duration and intensity of the neutropaenia, underlying disease, use of new immunochemotherapy regimens, and/or a history haematopoietic stem cells transplantation (HSCT).[4] IFI are observed in 10%-50% of patients presenting neutropaenia or HSCT recipients, and they head the list of infectious causes of death. Mortality rates have remained very high over the last few decades: no lower than 30% in candidemia and above 50% in invasive aspergillosis, reaching figures of almost 70%-80%.[1,5] All this added to the difficulty of an early, sure diagnosis, having been described up to 75% of IFI not diagnosed in living patients.[1,5,6]

Furthermore, the appearance of new antifungal agents during the past 5 years which belong to classic families (azoles) or aimed at new targets (echinocandins), have represented an important innovation in the management of IFI. In clinical trials, these alternatives have been shown to be effective and safe, at least similarly and even better than conventional antifungal agents and in some cases allow sequential treatment or combination therapy. Some pharmacoeconomic studies which have been published associate higher levels of effectiveness with these new molecules, fundamentally in prophylaxis or treatment of IFI,[8-13] but also cost-effectiveness benefits in the empiric therapy for persistent febrile neutropaenia.[14-16] Most of the studies make comparisons with the "gold standard" used until that time: amphotericin B deoxycholate (ABd).

This new situation, also taking its economic impact into account, requires limiting criteria to be used to support daily therapeutic decisions. This ensures the selection of the most efficient therapeutic option in each case, given the high percentage of the hospital drug budget taken up by systemic antifungal agents and taking into account that an IFI prevented means a significant cost saving. The objective of this study is to perform a cost-effectiveness analysis of the empirical antifungal strategy used in the hospital in oncohaematological patients at high risk of IFI.

METHOD

The economic assessment has been made based on the effectiveness results and the consumption of resources obtained from a retrospective and prospective observational study covering 12 months (2003–2004) and using hospital cost unit values.

Description of the Study

Patients

Oncohaematological neutropaenic patients at high risk of IFI, to whom an empiric antifungal therapy was administered at the hospitalisation unit during the data-gathering period. The stay in the intensive care unit (ICU) is included. The only patients excluded from the final analysis were those with an incomplete follow up, whose information could change the results, and these were minimal (2 cases).

Diagnostic Tests

The main tests for the clinical and mycological diagnosis, as well as for identifying the fungus causing the IFI were:

- Culture: smear (nasal, oropharyngeal), bronchoalveolar lavage (BAL, obtained via fibrobronchoscopy), blood culture, sputum, faeces, urine, skin, and other organs biopsies...
- Serology: *Aspergillus* galactomannan antigen detection
- Anatomopathological study of guided biopsies of certain organs
- Imaging techniques: computed axial tomography (CAT) of the chest or abdomen, paranasal sinuses, central nervous system, and nuclear magnetic resonance (NMR)

IFI Criteria

The criterion for IFI was defined as the clinical situation in which a patient with febrile neutropaenia is detected in spite of continuous anti-infectious treatment, with signs or symptoms leading to a suspicion of an IFI. Information relating to episodes of IFI detected during the follow up period has been gathered, in a manner that the same patient may present several episodes during this period of time.

Antifungal Treatment

In our study, the antifungal treatment referred to is an empiric therapy[17]: early administration of the antifungal agent, at the beginning or during the episode of febrile neutropaenia, in neutropaenic patients with persistent or recurring fever, at high risk of IFI, but without yet having the diagnosis of the mycosis.

Type of Economic and Financial Analysis

Cost-effectiveness-type pharmacoeconomic model analysis based on designing a decision-making tree for the empiric therapeutic strategy. For its preparation, the programme TreeAge Pro Suite 2006 (TreeAge Software, Inc, Williamstown, MA) was used.

Perspective of the Analysis and Time Horizon

The perspective of the economic assessment has been that of the healthcare services provider, in this case, the university hospital Hospital Universitario La Fe (HULF). The time horizon for the empiric therapy has been the mean days of treatment until resolution of the episode of IFI (10.8 [8.1]; 95% CI, 9.5–12.1). The analysis has centred on the profile of the new antifungal

agents incorporated in the hospital, voriconazole and caspofungin, compared to the preferred therapy used as standard to date, the different formulations of amphotericin B: lipid complex (ABLC) and liposome (AB-L). The study period coincided with a stage of ABd shortage, which accounts for its low level of use in the analysis.

Estimate of Effectiveness

Effectiveness has been defined as the obtaining of a partial or complete response with or without adverse drug reaction (effective with or without ADR, not effective with or without ADR) and ADR means the detection of initial treatment intolerance or any adverse effects motivating, in any of the cases, a switch to another, second-line antifungal therapy. Effectiveness has been established in terms of the response of each individual episode of IFI to the antifungal treatment. Associations were not taken into consideration, because of the difficulties involved attributing effectiveness to one of the antifungal agents. The response classification has been based on criteria previously assigned and shown in different studies,[18,19] counting on the clinician's consensus for their evaluation. The types of response were:

– *Complete response*: resolution of all the clinical signs and symptoms attributable to the IFI, and complete or practically complete disappearance of radiographic signs
– *Partial or stable response:* an important improvement or resolution of the clinical signs and symptoms, and an improvement of at least 50% in the radiological manifestations, or a slight improvement (radiological <50%), or short treatments with very little assessment of the response
– *Unfavourable or incomplete response:* stable, non-progressive disease
– *Treatment failure:* progression of the disease or death of the patient, whether or not due to IFI. In these patients with complex pathologies it is difficult to directly associate the death with the IFI developed, and it is not the purpose of this study to make this association

The episodes of IFI have been divided into sub-episodes according to the antifungal agent used (start and end dates), in a manner that complete treatment of a single episode can be broken down into different stages (or sub-episodes) according to the antifungal agent administered. Consequently, a patient can have several episodes and several treatments for the same episode. In each sub-episode, the overall response to the treatment administered is assessed as is the appearance of adverse effects, although these were not followed up.

Cost Estimate

The economic consequences of the options compared have been calculated using the direct medical costs related to each episode, estimated for each of these. The costs calculated are:

– Cost of pharmacotherapeutic treatment:

  • Cost of the complete antifungal therapy
  • Cost of the second-line antifungal therapy in the event of initial failure, intolerance, or adverse effects

– Other associated costs:

  • Cost of diagnostic tests
  • Cost of laboratory testing (biochemistry, CBC, haemostasis)
  • Cost of the hospital stay

They are estimated by determining the weighted cost obtained multiplying the frequency of appearance per unit cost.

The cost of managing and monitoring the adverse effects (longer hospital stay, larger number of tests) and the direct, and indirect medical costs relating to the treatment of the underlying diseases have not been included. Neither have the costs of intravenous administration been taken into account (needed materials and time used for preparing, and administering) because these are very similar for all the options evaluated. Drug cost is calculated at PVL (ex-factory price, as they are acquired by our hospital) and the other costs have been obtained from the Economic Information System (EIS) at the hospital.

The basic statistical analysis was initially carried out by Euroclin Institute. Subsequently, we have used both the Statgraphics® 5.0 statistical software and Microsoft® Excel®.

Cost-Effectiveness Analysis

The results of the analysis are presented as the average cost per sub-episode, incremental cost, average cost/effectiveness, and incremental cost/effectiveness. The amount available to pay for an episode treated has been estimated at € 50 000 in all cases, taking into account the complexity of this type of patients.

Sensitivity Analysis

A simple univariate 2-way sensitivity analysis has been carried out with the purpose of determining the validity of the decisions obtained, modifying those variables presenting the greatest degree of uncertainty.

RESULTS

A total of 77 patients coinciding in different branches have been included, meaning the analysis took a total of 107 patients into consideration. The absolute number of suspected IFI has been 94, broken down into 116 sub-episodes when assessing each branch (the same episode repeated with different treatment) and associated to 139 empiric therapies, corresponding to the antifungal agents included in the cost/effectiveness analysis: AB-L (46.0%), ABLC (25.9%), caspofungin (22.3%), and

voriconazole (5.8%). The mean days of antifungal treatment per episode were 10.8 (95% CI, 9.5-12.1). A total of 89.6% of the patients were neutropaenic, while 96.1% were febrile, and 97.4% had received previous antibiotic treatment, which confirmed the clear presence of risk factors predisposing to IFI. A multivariate analysis (ANOVA) has allowed the lack of significant differences to be determined between the branches with regard to gender and age, although they are observed in the duration of the treatment, being the treatment with caspofungin the one with longest duration. Table 1 sets out the data regarding the branches. With regard to the underlying disease, the inclusion of the small sample of voriconazole influences the results, showing a difference between the groups, (χ^2=54.03 *P*=.002) which disappears when only mainstream treatments are compared (χ^2=24.10; *P*=.15).

Analysis of Effectiveness

Favourable response (partial or complete) was reached in 58.3% of the 139 treatments considered overall. This implies that in almost half of the cases it was necessary to intervene in some of the treatments in order to resolve the episode of IFI, modifying the dosing schedule, changing the antifungal agent, or combining it with another antifungal agent (70.7%).

Cost Analysis

In Table 2, the unit costs are detailed, as are the purchase costs (€ year 2004) and the dose of each alternative. The first decision tree considers all the therapeutic options used in the empiric therapy (Figure 1). The branches have been distributed considering

Table 1. Characteristics of the Patients, Episodes of IFI, and Antifungal Treatments of the Branches Included in the Cost/Effectiveness Analysis[a]

	AB-L	ABLC	Caspofungin	Voriconazole	
Total No. patients (n=107)	53	25	25	6	
No. IFI episodes (n=115)	55	26	28	6	
No. antifungal treatments (n=139)	64	36	31	8	
Mean dose (SD), (range)	205 (59) (70–390)	189 (102) (50–400)	49 (3.8) (35–50)	iv: 440 (80) (400–560) Oral: 500 (200) (400–800)	
Mean age (SD), (range)	46.2 (14.4) (16–75)	48.8 (12.2) (29–75)	43.9 (19.1) (16–75)	55.1 (17.3) (20–75)	P=.25
Gender					χ^2=0.45 *P*=.93
Males (%)	34 (53.1)	18 (50)	18 (58.1)	4 (50)	
Females (%)	30 (46.9)	18 (50)	13 (41.9)	4 (50)	
Underlying disease					
AML	(n=42)	19	9	13	1
ALL	(n=16)	7	5	4	–
CML	(n=7)	7	–	–	–
Multiple myeloma	(n=7)	4	–	1	2
Lymphoma	(n=7)	4	2	–	1
APL	(n=5)	3	1	1	–
MDS	(n=4)	3	1	–	–
CLL	(n=4)	2	1	1	–
Other diagnoses	(n=17)	4	6	5	2
			χ^2=24.10[b] *P*=.15	χ^2=54.03[c] *P*=.002	
Duration of treatment					*P*=.001
Mean (SD), days	9.7 (7.4)	8.2 (6.6)	16.4 (8.5)[d]	9.8 (8.4)	
Median	9	6.5	17	8.0	
Minimum–maximum value	1–36	1–24	2–34	2–25	

[a]AML indicates acute myeloid leukaemia; ALL, acute lymphoblastic leukaemia; CML, chronic myeloid leukaemia; APL, acute promyelocytic leukaemia; MDS, myelodysplastic syndrome; CLL, chronic lymphoblastic leukaemia.
[b]No significant differences when the 3 most representative groups are compared (AB-L, ABLC, and caspofungin).
[c]Significant difference when voriconazole is included as a consequence of the small sample.
[d]Statistically significant difference in comparison to the other branches (95% confidence level)

the ADR, which correspond mostly to intolerance and in some cases to adverse effects. The analysis includes the cost of the second-line therapy that is needed when these ADR appear. Voriconazole is the most CE branch; however, the small number of cases gathered makes it difficult to draw clear conclusions. Consequently, another tree has been prepared eliminating voriconazole, but showing the choice of ABLC as the most CE option (Figure 2).

Table 3 shows the costs broken down by each branch. The cost components which most influence the total cost are not pharmacological ones. The antifungal treatment accounts for 8.4% of the total cost for voriconazole, 9.5% for ABLC, 16.9% for caspofungin, and 18.5% for AB-L. According to the results obtained, the average probability of favourable or effective response was 88% for voriconazole (95% CI, 47.3-99.7), 68% for caspofungin (95% CI, 51.3-84.2), 58% for ABLC (95% CI, 42.2-74.4), and 50% for AB liposome (95% CI, 37.2-62.2).

Table 4 shows the average CE ratio calculation for the different branches, with the incremental analysis (ICE). None of the options exceeds the €50 000 limit per patient treated with regard to average cost, although CE is somewhat higher except for voriconazole and ABLC.

Sensitivity Analysis

The sensitivity analyses carried out assessed the impact of the most influential parameters or those with the greatest degree of uncertainty on the results: purchase cost of the antifungal agent (where a reduction also makes reference to a shorter duration of the therapy) and other costs of the episode. In all cases, the mean

Table 2. Description of the Healthcare Resources and Their Unit Costs Considered in the Cost-Effectiveness Analysis, as Well as the Average Doses Used[a]

Healthcare Resource	Cost, €			
Stay/day				
Haematology	658.59			
ICU/ARD	1077.52			
Rx	17.94			
CT	110.00			
Testing				
Biochemistry	6.69			
Haemostasis	8.26			
Haematology	1.13			
Fungus (*Aspergillus* spp) identification methods				
Sputum culture	10.37			
BAL culture	10.37			
Smear culture	10.37			
Blood culture	13.58			
→ Antifungigram	→ 14.12			
Galactomannan antigen detection (ELISA)	17.51			
Cost of Antifungal Agents (PVL) and Dose				
	Per Unit, €	**Dose/Day, €**	**Mean Dose (SD) (Range)**	**Dose mg/kg/day (70 kg)**
Amphotericin B limposome (Ambisome®) 50 mg vial	138.53	554.12	205 (59) (70–390)	2.9
ABLC (Abelcet®) 100 mg vial	97.52	195.04	189 (102) (50–400)	2.7
Caspofungin (Cancidas®)				
70 mg vial	608.00	Day 1: 608.00	49 (3.8) (35–50)	–
50 mg vial	478.00	Remainder: 478.00		
Voriconazole (Vfend®)				
200 mg vial	142.00	284.00	iv: 440 (80) (400–560)	iv: 6.3
Tablets 200 mg	38.00	95.00	Oral: 500 (200) (400–800)	

[a]BAL indicates bronchoalveolar lavage; CT, computed tomography; ICU, intensive care unit.
Costs obtained from the Economic Information System (Economic Management) and the Farmasyst Management database (Pharmacy Department) of the Hospital Universitario La Fe.

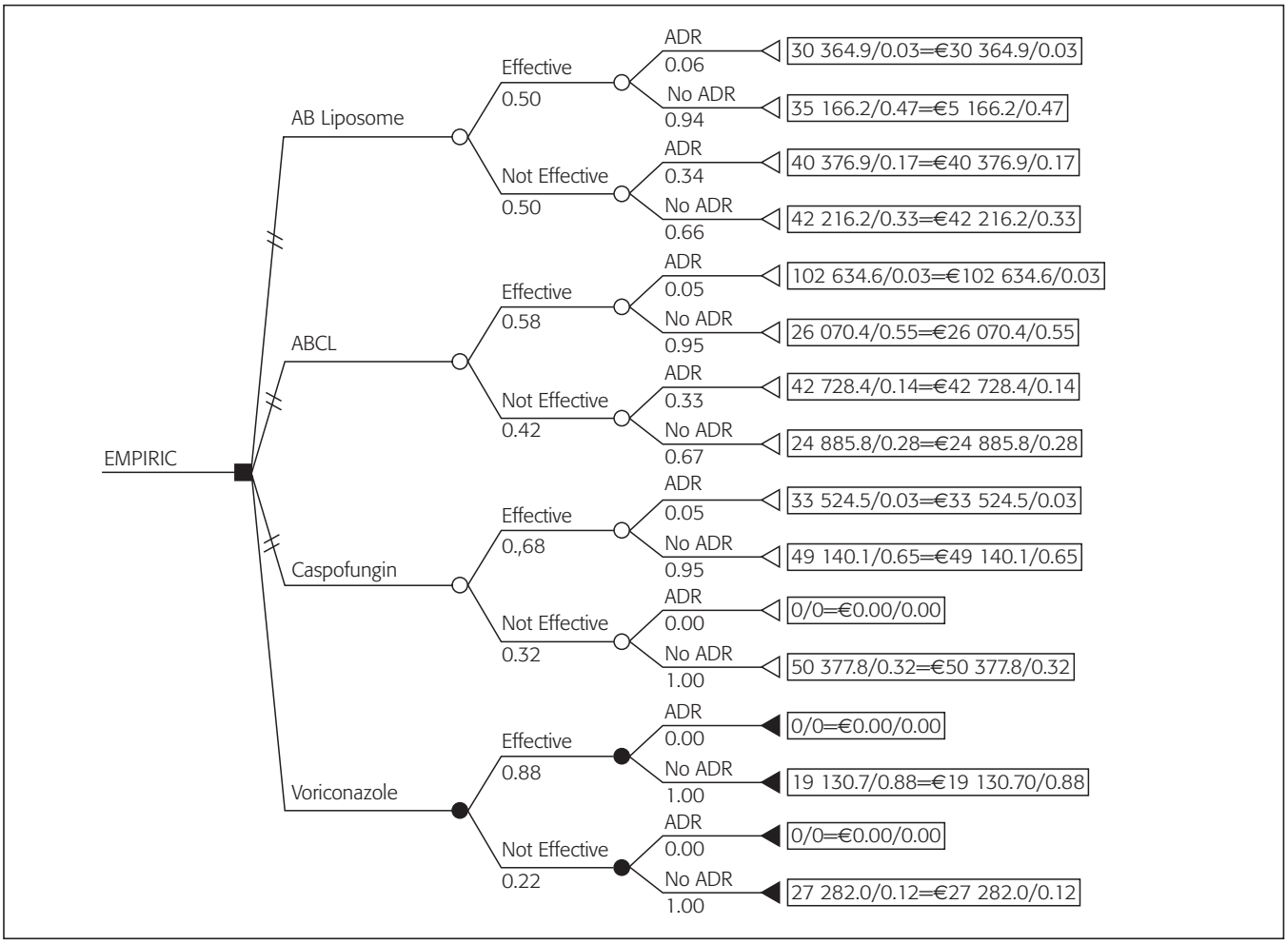

Figure 1. *Decision tree for the empiric therapy strategy.*

value of the most CE alternative has remained constant and the remainder has been modified up to the extreme values of the confidence interval.

The variation in the purchase costs does not modify the result (Figure 3A), although in the case of caspofungin and AB-L, it has a greater impact on the overall cost than for voriconazole and ABLC. The variation of the other costs in the analysis excluding voriconazole modifies the sense of the analysis, not changing the dominance relationship when voriconazole is included. The reduction of 27% of the other costs associated with the caspofungin branch provides an average cost of €38 057, which is a plausible value since it is located within the confidence interval (95% CI, 36 802.7-61 332.6) (Figure 3B). The cost of the hospital stay (with regard to the duration) and the cost of the tests are, therefore, sensitive parameters for caspofungin. In the case of AB-L, the threshold value (or point where both alternatives are equal) corresponds to a CE (€28 713.8) which is outside the confidence interval (95% CI, 28 869.7-47 599.2).

DISCUSSION

The great availability of antifungal agents and the expectations produced by the new ones, alone or in combination, make it difficult to choose a therapy. Furthermore, the growing use of antifungal agents in the hospital setting together with the change and diversity of criteria for their use and the important consumption of resources they involve, make it necessary to carry out studies that allow the patterns of use of systemic antifungal agents to be understood.

The empirical strategy is the most interesting, because it requires maximum effectiveness with the aim of preventing the IFI from progressing and endangering patients' lives. However, it can also be the most expensive. In oncohaematological patients, frequent IFI and a high mortality rate require the initiation of early antifungal treatment.[8] However, few studies have analysed the relative effectiveness of each strategy used for empiric therapy; only 2 of them use effectiveness and consumption of resources data obtained

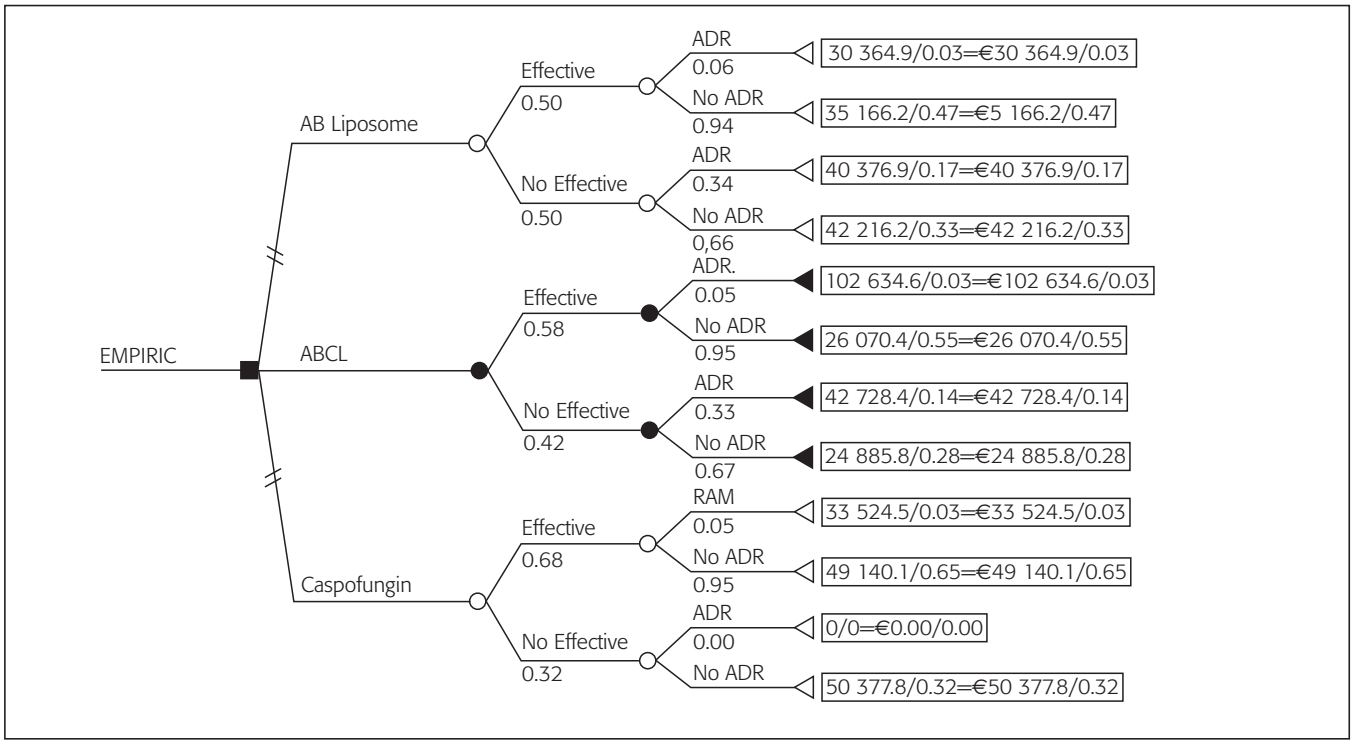

Figure 2. Decision tree for the empiric therapy strategy with the options used in the largest proportions.

in real clinical practice, and there have been none so far in Spain. This is why it is important to analyse the pharmacoeconomic profile of the available options with the purpose of determining which is the most efficient and thus maximising the social benefit of the resources invested.

Limitations

One of the limitations of our study lies without a doubt in the absence of ABd in the analysis, given the fact that its ostensibly lower cost could have been a factor favouring its choice, or it may have shown a better profile than other formulations. However, on the one hand, the study coincided with a period of general shortage of this preparation, which led to the promotion of ABLC as an alternative. On the other hand, in oncohaematological patients, especially transplant patients in extremely high-risk situations, the use of ABd would have been lower than that of other formulations, as their underlying condition makes it inadvisable to administer highly potent nephrotoxic antifungal therapies. Consequently, we consider the selection of antifungal agents analysed to be adequate and that the use of ABd in the patients included would not have been significant to be comparatively analysed from the pharmacoeconomic point of view.

Another limitation is the use of retrospective data, as obtaining the information from clinical histories may not show everything necessary for correct evaluation. However, specifying the uncertain parts with the help of the clinicians has enabled us to partially sidestep this fact, although the important aspect is the absence of demographic or clinical differences among the groups, with regard to the aspects evaluated (Table 1).

The possible relative limitation regarding the cost caused by the adverse effects (treatment, consumption of resources) is partly compensated by the fact that most of them are intolerances (rashes, itching, fever, shivering…). Managing these would involve a low cost and in most cases, the main consequence would be a change of antifungal agent, having included its cost. Cases attributable to nephrotoxicity were few and refer to those clinically considered as such, not to duplication of basal creatinine as defined in many other studies.[20-22] It is not unusual for these patients to have renal deterioration from other therapies or due to their actual clinical condition. Creatinine changes were observed only rarely (3 with AB-L and 0 with ABLC) and have been included in the intolerances within the so-called ADR, which have necessitated a change of therapy or its withdrawal. As a result, the only aspect that we have not included are the costs regarding nephrotoxicity as assigned in the literature (for example, longer hospital stay).[20] The 100% of the ADR with ABLC consisted of intolerances to the treatment (6 of 6 in both branches, effective, and not effective), which led to a short duration of this, perhaps not long enough to enable nephrotoxicity to develop as the appearance of this is related to the duration of the treatment.[20] It would seem logical to assume that the periods corresponding to ABLC and AB-L were relatively short to enable the development of this effect (mean, 2.3 and 3.5 days, respectively, only for the branches with ADR). Indeed, the average duration of the therapy indicated in some studies is between 7 and 14 days.[15,20,23,24] Consequently, in most patients,

Table 3. Results of the Costs From the Different Branches for the Empiric Therapy[a]

Branch No.		Total Cost of Antifungal Treatment, €	Other Costs,[b] €	Cost 2nd Line Treatment, €	Total Cost of the Branch, €	No. Treatments in Each Branch[c]	Probability	Average Cost/ Treatment in Each Branch (SD), €	Average Expected Cost,[d] €
	AB liposome					64		38 234.5	
1	Effective with ADR	8 865.9	50 419.8	1444.0e	60 729.[8]	2	0.03	30 364.9 (4681.9)	910.9
2	Effective without ADR	327 296.0	727 690.7	0.0	1 054 986.7	30	0.47	35 166.2 (23 088.1)	16 528.1
3	Not effective with ADR	13 300.0	350 458.4	80 388.0	444 146.4	11	0.17	40 376.9 (13 444.3)	6864.1
4	Not effective without ADR	103 760.0	564 669.1	218 111.0	886 540.1	21	0.33	42 216.2 (25 744.2)	13 931.4
	ABLC					36		30 375.2	
5	Effective with ADR	1463.0	89 221.6	11 950.0[e]	102 634.6	1	0.03	102 635	3079.0
6	Effective without ADR	83 102.0	438 305.9	0.0	521 407.9	20	0.55	26 070.4 (19 839.9)	14 338.7
7	Not effective with ADR	2927.0	171 420.9	39 564.0	213 911.9	5	0.14	42 782.4 (26 018.6)	5989.5
8	Not effective without ADR	15 409.0	203 922.3	29 526.2	248 857.5	10	0.28	24 885.8 (31 096.1)	6968.0
	Caspofungin					31		49 067.7	
9	Effective with ADR	4432.0	29 092.5	0.0	33 524.5	1	0.03	33 525	1005.7
10	Effective without ADR	192 785.0	790 016.8	0.0	982 801.8	20	0.65	49 140.1 (19 961.2)	31 941.1
11	Not effective with ADR	0.0	0.0	0.0	0.0	0	0.00	NA	0.0
12	Not effective without ADR	59 096.0	444 681.9	0.0	503 777.9	10	0.32	50 377.8 (30 759.4)	16 120.9
	Voriconazole					8		20 108.8	
13	Effective with ADR	0.0	0.0	0.0	0.0	0	0.00	NA	0.0
14	Effective without ADR	13 380.0	120 534.6	0.0	133 914.6	7	0.88	19 130.7 (16 048.6)	16 835.0
15	Not effective with ADR	0.0	0.0	0.0	0.0	0	0.00	NA	0.0
16	Not effective without ADR	228.0	21 513	5541.0	27 282	1	0.12	27 282[f]	3273.8

[a]AB indicates amphotericin B; ABLC, amphotericin B lipid complex; NA, not applicable.
[b]This includes the total cost of laboratory tests, radiological tests, hospital stay, and mould or yeast identification methods.
[c]Number of empiric therapies administered with the antifungal agent corresponding to each branch.
[d]The average cost expected is calculated by multiplying the average cost/treatment in each branch by the probability of each of these occurring and, by the summation of the branches of each of the antifungal agents considered, which will give the average cost/empiric antifungal therapy for an episode of IFI.
[e]Although the response was favourable, the antifungal agent was changed because of intolerance or the appearance of adverse effects.
fThe SD was not obtained because only 1 case exists.

Table 4. CE and Incremental Cost/Effectiveness in Empiric Therapy[a]

Therapeutic Option	Average Cost/ Empiric Therapy, €	Δ Cost, €	Effectiveness[b]	Δ Effectiveness	CE,[c] €	ICE, #euro
Empiric therapy strategy with all the antifungal treatments[d]						
Voriconazole	20 108.8		0.88		22 850.9	
Caspofungin	49 067.7	−28 958.8	0.68	−0.20	72 158.4	−144 794.5
ABLC	30 375.2	−10 266.3	0.58	−0.30	52 371.0	−34 221.3
AB liposome	38 234.5	−18 125.7	0.50	−0.38	76 469.0	−47 699.2
The AB liposome, ABLC, and caspofungin strategies are dominated by voriconazole						
Empiric therapy strategy without voriconazole[e]						
Caspofungin	49 067.7		0.68		72 158.4	
ABLC	30 375.2	18 692.5	0.58	0.10	52 371.0	186 925.0
AB liposome	38 234.5	10 833.2	0.50	0.08	75 531.4	60 184.4
The AB liposome strategy is dominated by ABLC						

[a]AB indicates amphotericin B; ABLC, amphotericin B lipid complex; CE, cost-effectiveness; ICE, incremental cost-effectiveness.
[b]An effective empiric therapy is that achieving a partial or complete response with or without the appearance of ADR.
[c]CE or average cost/effectiveness that represents the average cost/a successful empiric antifungal therapy administered in an episode of IFI.
[d]This coincides with the most CE option of the most effective branch.
[e]The most CE option does not correspond to the most effective branch, so that the ICE is calculated by the difference with the most effective branch, which is caspofungin.

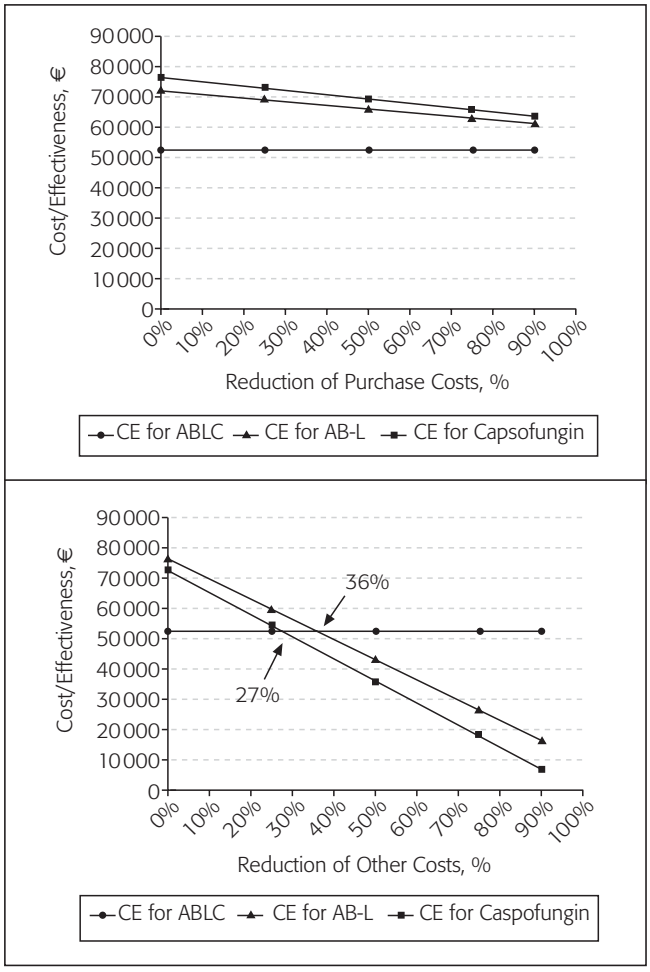

Figure 3. Sensitivity analysis outcomes regarding ABLC in the case without voriconazole. A: reduction of purchase costs of AB-L and caspofungin. B: reduction of value of other costs for AB-L and caspofungin branches.

the basal serum creatinine value doubles at 8-12 days of therapy.[25,26] Furthermore, at that time, our hospital's priority was to control a serious outbreak of aspergillosis causing worry among clinicians, in a manner that any initial indication of ineffective empiric therapy with AB led to an immediate change of antifungal agent (fundamentally to caspofungin and voriconazole), which could have contributed to reducing AB treatments. This same fact could justify the significantly longer duration of the therapy with caspofungin, with an early initiation and prolonged over time (mean, 16.4 days). That is, what would usually correspond to treatments with AB-L or ABLC, has been replaced by caspofungin in our study. Another drawback when it comes to attributing renal deterioration included in the ADR is that prior prophylaxis with AB could condition this attribution as it increases the risk, ie, it would not only be due to the empiric AB-L or ABLC but rather to the added effects of both strategies.

The comorbidity of the patients not reflected in this study could, without a doubt, determine the evolution of the IFI, especially with regard to the failure to respond (mortality). In the future it would be interesting to delimit the influence of these factors, as well as the influence of the seriousness of the underlying pathology. Finally, the contribution of the cumulative effect of the different antifungal agents used for the same episode has not been considered on the final effectiveness.

Discussion

Voriconazole was the most CE option in the first case. AB, the standard until that time for empiric therapy, has given variable results, observing in this study that 42%-50% of empirical treatments using both formulations have been ineffective. Response to voriconazole was high, although the small number of cases constituted an important limitation. However, it provides a significant starting point for future analyses. Some studies have indicated that voriconazole is the preferred empiric therapy due to its good CE profile, and both consensus documents and guides developed in hospital areas, including ours, consider it a suitable alternative to ABd, being the one chosen for the patients selected according to their clinical syndrome, such as the oncohaematological patients at low risk of IFI.[27-29] A retrospective study of cohorts includes hospital costs in its analysis, comparing voriconazole and AB-L in the empiric therapy of febrile neutropaenia. In spite of the fact that, as they state, there are also very few cases included, they find differences in the economic implication of both antifungal agents. The hospital cost per episode is $56 621 (€41 2476.71) and $56 495 (€41 184.86) for voriconazole and AB-L, respectively, being similar to ours for AB-L (€38 234.50), and higher for voriconazole, perhaps because of our small sample (€20 108.80). In any case, this study supports the use of voriconazole as CE empiric therapy.[29] A recent pharmacoeconomic analysis assesses the outcomes of the clinical practice in a similar way as we have, subsequently combining them with the bibliographical data and expert opinions, comparing AB-L with voriconazole.[26] As in our case, the authors accept the limitation of the retrospective nature of the data, neither do they include the costs of treating the typical intolerances of AB. The effective responses for AB-L are similar in both cases (48% vs 47% in our case), although the difference in cases analysed of voriconazole (32 vs 8) gives different results: 56% versus 88% (in our study). With voriconazole, an overall reduction in costs of 27% was seen: $14 950 USA (€10 901.42) and $20 591 USA (€15 014.68) with AB-L, lower figures than ours (€20 108.80 and €38 234.50), taking into account that they include the cost of nephrotoxicity but not that deriving from tests or the stay which increases our figures. In both analyses there is a difference in favour of voriconazole and they coincide in another limitation as they do not assess the impact of the possible breakthrough IFI which have a significant economic impact, although these are very infrequent and therefore, their incidence is still limited when it comes to obtaining sufficient statistical power.

The outcomes of the second tree can be interpreted more consistently. Although this same limitation can be applied to nephrotoxicity, the truth is that, as we have mentioned before, those detected in the AB branches were scarce and would probably hardly have any influence on the costs.

The ABLC branch is more CE for giving favourable results and involving lower associated costs. This stage coincided with an attempt to promote ABLC as a more economical alternative to ABd, while the new antifungal agents, voriconazole and caspofungin, had just been introduced in the market and in the hospital.

That is why a larger proportion of ABLC is used for this type of patients in comparison with earlier stages in which AB-L would have been the preferred option.

A pharmacoeconomic comparison found no significant differences in the hospital costs associated to the empiric therapy of febrile neutropaenic patients, values being $55 603 (€40 545.71) for AB-L 3mg/kg/day and $r46 442 (€33 865.51) 5mg/kg/day, as opposed to $49 684 (€36 229.57) for ABLC 5mg/kg/day. A drawback is its publication as a summary, which makes it difficult to make an appropriate, comprehensive interpretation; and the costs did not include the purchase price of the medications, these being given free of charge since they were aimed at patients included in the study.[30] However, the costs in our study are not very different from these. The average cost per treatment is also greater for AB-L to a similar mean dose (2.9 mg/kg/day): €38 320, in relation to ABLC with lower doses (mean, 2.7 mg/kg/day) and therefore lower cost: €30 375. AB-L implies greater economic impact and taking into account the effectiveness obtained, it is CE to use ABLC as empiric therapy.

In another pharmacoeconomic study comparing both formulations from the hospital perspective, an analysis of cost minimisation is carried out when obtaining equivalent clinical response rates (53% ABLC vs 60% AB-L), also being a retrospective design. In the level that includes all the hospital costs, the values obtained are quite similar to those we obtained in the case of ABLC: 43 814 USD (€31 957.9) versus €30 375.2, although the figure is lower for ABL: 31 433 USD (€22 927.2) versus €38 234.5.[16] The respective medians of the total cost associated with preventing or treating the adverse effects showed no significant differences (*P*=.984), which could support the fact that the inclusion in our study would not have modified the results.

With regard to the ICE, the most significant value corresponds to the ABLC in relation to caspofungin, of greater effectiveness, situated in a value of €186 925. This figure could perhaps be deceptive in that the difference in effectiveness is small in comparison to some rather distant costs. The most relevant influence on the overall cost corresponds to the other costs (hospitalisation, testing), which are associated with high figures in the case of AB-L and caspofungin, probably because they are used in seriously ill patients with longer hospital stays. In the sensitivity analysis, the reduction of 27% of the other costs associated with caspofungin inverts the sense of the analysis, making it the antifungal agent with the best CE profile in comparison to AB-L and ABLC (second tree). As this reduction is feasible, since it is included in the calculated confidence interval, it would be enough for it to be possible to reduce hospitalisation or the number of tests to some extent in order to obtain a more CE profile with caspofungin in comparison to ABLC and AB-L. Perhaps, this is viable in other hospitals, in terms of the usual cost of the hospital stay. The 36% reduction in the case of AB-L, the other cut-off point in figure 5B, exceeds the CI, so it is not probable that this could be achieved.

The total hospitalisation costs did not differ between both formulations in the abovementioned minimisation analysis; however, high sensitivity was observed in the economic result regarding purchase costs and dosing of the antifungal agent.[16] In our case, the influence of the purchase cost on the overall cost is 9.5% and 19.1% for ABLC and AB-L, respectively, meaning that even by increasing the cost of ABLC by 50% or reducing the cost of AB-L by 50%, the results remain unchanged, and that ABLC is still the most CE option.

Finally, a pharmacoeconomic analysis considering the purchase costs and those deriving from the treatment of renal failure, make it clear that caspofungin is more CE than AB-L in empiric therapy for febrile neutropaenia, which can be seen from a direct comparison of these 2 drugs in our study.[13] Similarly, this fact has been corroborated in a recent study which also analyses the breakthrough infections, survival and quality-adjusted life years (QALY), with caspofungin being more CE than AB-L for the treatment of suspected IFI.[31]

In short, according to the results obtained from the respective branches of caspofungin and voriconazole, second-line therapy is not usually required, its level of inefficiency is low and its cost is lower than that of the different formulations of AB. The use of oral voriconazole is also clearly influential in reducing the associated costs. The ICE shows that using voriconazole instead of caspofungin in empiric therapy also represents a €144 794 saving. In turn, ABLC involves a cost of €186 925 in comparison to caspofungin, but this figure is influenced by a not very different effectiveness, and the use of AB-L instead of caspofungin increases the cost by €60 184. The study provides relevant information with regard to the use of antifungal agents in the empirical strategy for oncohaematological patients from the perspective of clinical practice, in spite of the possible limitations referring to the costs that were not considered (treating adverse effects, nephrotoxicity). The CE analysis of the empirical strategy focused on high-risk oncohaematological patients (HSCT) has made it clear that voriconazole could be a preferred option from a hospital point of view, although it would be necessary to have a greater representativeness of cases to be able to conclusively show this. ABLC is a more CE alternative than AB-L and caspofungin, probably because it costs less than AB-L, being less effective, and caspofungin, is more effective but requires a treatment with longer duration. However, the results can only be applied to similar populations to those featured in this study, in a manner that the type of patients and therapies used in these settings may change the outcomes.

This type of pragmatic study can contribute to rationalising the use of antifungal agents in the hospital setting, and it is advisable to make more economic assessments that deal with some of the limitations of our study and contribute to situating each of the antifungal agents in the place where they provide the greatest effectiveness.

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