J Antimicrob Chemother 2014; **69**: 1993–1999
doi:10.1093/jac/dku053 Advance Access publication 21 March 2014

Journal of Antimicrobial Chemotherapy

Evaluation of antifungal use in a tertiary care institution: antifungal stewardship urgently needed

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Received 8 December 2013; returned 16 January 2014; revised 4 February 2014; accepted 8 February 2014

Objectives: To assess the quality of antifungal use, to propose a point score for this evaluation and to estimate the potential economic savings of an antifungal stewardship programme.

Methods: From December 2010 to January 2011, we identified 100 adult inpatients receiving systemic antifungals. Antifungal use was evaluated by means of a predefined score that considered indication, drug selection, dosage, adjustments after microbiology results, switching to an oral agent and length of treatment. Total antifungal prescriptions [in defined daily doses (DDDs) and days of therapy (DOTs)] and potential cost savings were calculated.

Results: Overall, 43% of prescriptions came from medical departments, 25% from haematology/oncology and 17% from intensive care units. The main reasons for starting antifungals were empirical (42%), pre-emptive (20%) and targeted treatment (20%). Antifungals were unnecessary in 16% of cases. Inadequacies in other aspects of antifungal prescription were: drug selection, 31%; dosing, 16%; no switch from intravenous to oral administration, 20%; no adjustment after microbiological results, 35%; and length of therapy, 27%. The number of antifungal DDDs per 1000 patient-days was 65.1. The total number of DOTs was 1556, which added a direct cost of €219 364. Only 51.3% of DOTs were considered optimal. The potential estimated savings would be €50 536.

Conclusions: Major efforts should be made to improve the selection and duration of antifungal therapy. Our study demonstrated the potential cost savings that could be achieved by optimizing antifungal therapy. A stewardship programme should include an instrument to objectively evaluate the adequacy of antifungal use.

Keywords: economic savings, invasive aspergillosis, candidaemia

Introduction

Invasive fungal diseases (IFDs) are a major problem in hospitals owing to their increasing incidence, high morbidity and mortality rates, and associated healthcare costs.[1,2] The availability of new broad-spectrum antifungal agents with improved tolerability has increased the use of these agents by non-expert practitioners in both the prevention and the treatment of IFDs.[3]

The need for an antifungal stewardship programme is recognized by many institutions.[3–8] However, the logistics of implementing and evaluating such a programme is far from clear. Indicators to assess the problem and to monitor the impact of interventions and training are urgently required.

Our objectives were to assess the quality of use of antifungal agents, to propose a point score for this evaluation and to estimate potential cost savings as first steps toward an antifungal stewardship programme.

Methods

Study setting and patient population

This study was conducted at a 1550 bed tertiary teaching hospital in Madrid, Spain. Our institution is a referral centre for solid organ transplantation, heart surgery, stem cell transplantation and HIV/AIDS care. An estimated 1500 patients per year receive systemic antifungal therapy at a

total cost for drug acquisition of ~€3 million. Routine antifungal susceptibility testing is performed according to the criteria of the CLSI.[9,10] Both adult and paediatric infectious diseases consultation services are readily available.

The prescribing physicians were unaware that the study was being performed at the time of the chart review, and no feedback was maintained with them until the end of the study. The hospital's Institutional Review Board approved the study.

Study design and data collection

Starting in December 2010 and using a pre-established protocol, we prospectively evaluated 100 consecutive inpatients (aged ≥18 years) who received systemic antifungal therapy. Patients were monitored by the study team until discharge. Patients receiving antifungal therapy were visited at least three times: when the drug was first administered; when microbiological laboratory results became available; and at discharge, when the final diagnosis was confirmed.

A chart review was performed in order to collect the following data: (i) patient characteristics [age, gender, comorbidities, severity of the underlying medical conditions (Charlson comorbidity index) and presence of IFD risk factors (underlying immunosuppression, central venous catheter, surgery in the last 3 months, corticosteroids, total parenteral nutrition and continuous renal replacement therapy)]; (ii) fungal disease [indication for antifungal prescription, clinical and radiological signs, microbiological and histopathological findings, culture and susceptibility test results and serological test results (i.e. *Aspergillus* galactomannan)]; (iii) antifungal therapy [drug prescribed (dosage, administration route and dates of initiation and end of therapy) and request for infectious diseases consultation]; and (iv) appropriateness of antifungal use and reasons for inappropriate use.

The number of defined daily doses (DDDs) per 1000 patient-days (according to WHO methodology)[11] the number of days of therapy (DOTs), and drug costs (€) were calculated on the basis of the actual dose administered and the purchase price to the institution after mark-up by the pharmacy, excluding administration costs. All data were collected by two investigators and recorded using a data collection tool.

Definitions

Antifungal therapy was classified as follows: prophylaxis for a fungal infection; empirical treatment for a suspected infection; and pre-emptive treatment or tailored treatment for a documented fungal infection. In neutropenic patients, empirical therapy was defined as antifungal drugs administered to treat patients with persistent fever who had received broad-spectrum antibacterial therapy, with no signs or symptoms of IFD and no positive microbiological results. In non-neutropenic patients, empirical therapy was defined as treatment initiated in febrile critically ill patients with risk factors for invasive candidiasis in the absence of any other known cause of fever. Pre-emptive therapy was defined as early treatment based on the proposals of Almyroudis and Segal,[12] Ostrosky-Zeichner[13] and Playford *et al*.[14] The objective of pre-emptive therapy was to treat suspected early IFD using clinical or radiological data and/or laboratory markers to define the likelihood of the IFD.

The criteria used to define the appropriateness of antifungal prescription were adopted from the treatment guidelines of the Infectious Diseases Society of America and the European Conference on Infections in Leukaemia,[15–17] and according to local susceptibility patterns. Adequate dosage recommendations, dose adjustments for hepatic and/or renal dysfunction and drug interactions were also taken into consideration. Significant candiduria was defined as yeast counts $>10^5$ cfu/mL, pyuria and recovery of identical *Candida* species from two or more urine samples and/or from samples of blood and urine.[18,19]

The adequacy of antifungal use was evaluated using a point score previously defined by three senior infectious disease specialists and one senior pharmacist during three consensus meetings. This adequacy indicator provides a maximum score of 10 points (Table 1) and assigns a relative weight to each of the items evaluated based on adequacy, efficiency and safety. We decided to assign more impact (0 or 2 points) to mistakes that could imply a major risk for the patient (prescription of a not-needed antifungal agent) or to aspects that were clear intervention targets (lack of

Table 1. Score for evaluating antifungal adequacy

Feature	Question	Answer	Points
Indication	Did the patient need an antifungal?	Yes	2
		No	0
Selection	Did the antifungal cover the suspected fungi and was it the first option recommended by guidelines?	It covered the suspected fungi and was the first option	2
		It covered the suspected fungi but was the alternative option	1
		It did not cover the suspected fungi	0
Dosage[a]	Was the dosage correct according to the body weight, the liver and renal function and potential interaction with other drugs?	Yes	1
		No	0
Microbiological adjustment	Was the antifungal adjusted after microbiological results (microorganism identification, antifungal susceptibility tests and indirect tests) were available?	Yes	2
		No	0
Administration route	Was intravenous switched to oral when possible?	Yes	1
		No	0
Duration	Was the duration of therapy correct according to the guidelines?[b]	Yes	2
		No	0
Total score			0–10

[a]Both low and high doses were considered incorrect. Adjustment for renal and hepatic failure and drug-to-drug interactions was also addressed. At the time of the study, serum voriconazole and posaconazole drug monitoring was not available.
[b]Durations that were too short or too long were considered incorrect.

adjustment following receipt of microbiological information or excessive duration of treatment). Less detrimental mistakes, such as incorrect dosage or lack of switching to an oral form, were given a smaller impact (0 or 1 point) in the global score. In the case of drug selection, we decided to offer three possible values: prescription of a drug that did not cover the suspected fungal pathogen (major mistake: 0 points); prescription of a drug that covered the pathogen, although was not optimal according to our local guidelines (minor mistake: 1 point); perfect selection of the antifungal drug (2 points).

Any prescription with a global score other than 10 was judged inappropriate. This score was applied at discharge or at the end of therapy if the patient was discharged with antifungal treatment.

In addition to assessing the global score for antifungal prescription, each single DOT was also judged as optimal, non-optimal or incorrect on a daily basis according to the following protocol: (i) *optimal* if the DOT was in accordance with the guidelines for all previous items evaluated and adapted to microbiological data; (ii) *non-optimal* if the DOT was indicated and the dosage and administration route were also appropriate according to guidelines, even though a more appropriate alternative was available (i.e. excessive coverage); and (iii) *incorrect* in cases of no indication for antifungal therapy, insufficient coverage, a non-recommended combination or inappropriate dosage or administration route.

The potential saving in antifungal acquisition cost was also calculated assuming 100% optimal DOTs. Measurements were performed by a senior infectious diseases specialist and a senior pharmacist specialized in mycology, neither of whom were involved in the daily clinical routine of the infectious diseases department. Any discordance in the assessment of appropriateness was resolved by a second senior infectious diseases specialist.

Statistical analysis

Data were entered into a database created using Microsoft Access®. Qualitative variables are presented with their frequency distribution. Quantitative variables are expressed as the mean and standard deviation (SD) when they have a normal distribution or median and IQR when they have a non-normal distribution. In order to compare how scores differed according to departments, the *t*-test or analysis of variance was used. The proportion of inappropriate prescriptions according to infectious diseases consultation was compared using the χ^2 test. All statistical tests were two-tailed. The level of statistical significance was set at $P=0.05$. All statistical procedures were performed using SPSS Version 16.0 software (SPSS Inc., Chicago, IL, USA).

Results

Demographic and clinical characteristics

Antifungal use was evaluated in 100 consecutive adult patients. Most were men (65%) and the median age was 66 years. Overall, 62% were immunosuppressed. The patient's admission ward, associated risk factors for fungal infections, indications for antifungal therapy and final diagnosis are summarized in Table 2.

Prophylaxis was most frequently prescribed in oncology and haematology units (40.0%). Empirical treatment was most frequently prescribed in medical departments (42.9%). Pre-emptive treatment was very common in intensive care units and surgery departments (35.0% each) and was mainly based on the *Candida* score.[20] Tailored therapy was most frequently prescribed in medical wards (80.0%).

Fungal cultures were obtained in 78.8% of patients with a non-prophylactic indication and were positive in 56.7%. The epidemiology of fungal infections is shown in Table 2.

Table 2. Demographic and clinical characteristics of 100 patients receiving antifungal treatment

Characteristic	
Age (years), median (IQR)	66 (50–74)
Male sex, %	65
Charlson comorbidity index, median (IQR)	4 (2–6)
Hospital department, %	
medical	42
intensive care units	21
oncology	19
surgical	12
haematology	6
IFD risk factors, %	
immunosuppression	62
solid organ cancer with chemotherapy/radiotherapy	31
liver transplant	9
leukaemia/lymphoma	9
HIV infection	8
haematopoietic stem cell transplantation	3
cardiac transplant	2
other	
central venous catheter	65
surgery in the last 3 months	50
corticosteroids	45
total parenteral nutrition	30
continuous renal replacement therapy	9
Indication for antifungal therapy, %	
antifungal prophylaxis	15
empirical therapy	42
pre-emptive therapy	20
tailored therapy	20
unclassifiable	3
Final diagnosis, %	
oral thrush	13
skin and soft tissue infection	7
urinary fungal infection	6
fungaemia/disseminated IFD	6
intra-abdominal infection	5
peritonitis	2
CNS infection	2
pulmonary infection	2
vaginitis	2
others	4
no IFD	36
Cultures obtained (patients with non-prophylaxis indication), *n* (%)	67 (78.8)
Positive culture, *n* (%)	38 (56.7)
Candida albicans	22 (25.9)
Candida glabrata	7 (8.2)
Candida parapsilosis	3 (3.5)
Candida tropicalis	2 (2.4)
Candida krusei	1 (1.2)
Aspergillus fumigatus	2 (2.4)
Cryptococcus neoformans	1 (1.2)
Kodamaea ohmeri	1 (1.2)
Leishmania	4 (4.7)

IFD, invasive fungal disease.

Antifungal therapy

Overall, the most frequently used antifungal agent was fluconazole (58.3%), followed by caspofungin (14.2%), micafungin (9.5%), liposomal amphotericin B (4.7%), voriconazole (3.9%) and posaconazole (3.9%). In 21% of patients, more than one drug was received sequentially (19%) or simultaneously (2%). The two cases receiving two antifungals at the same time were patients with probable invasive aspergillosis in whom combined therapy was started as first-line empirical therapy in one case (voriconazole + caspofungin) and second-line therapy in the other (liposomal amphotericin B + caspofungin).

The initial drugs used for each indication are illustrated in Table 3. Fluconazole predominated for all indications except prophylaxis, owing to the large number of haematology/oncology patients (lymphoma, leukaemia and haematopoietic stem cell transplant recipients) and solid organ transplant recipients, for whom echinocandins were the preferred agents. Echinocandins were also widely used as pre-emptive therapy in critically ill patients. Liposomal amphotericin B was given most frequently for the tailored treatment of *Leishmania* infections (two of four total prescriptions). It is important to mention that there was an ongoing outbreak of leishmaniasis in the region of Madrid at the time of the study.

Prescriptions were made by the attending physicians in 75% of cases, by infectious diseases specialists in 23%, and by other specialists (neither infectious diseases specialists nor microbiologists) in 2%.

Adequacy of antifungal therapy

The overall prevalence of inappropriate antifungal use was 57%, and the mean point score for antifungal use in the study patients was 7.7 ± 2.6. A score of <5 points was recorded for 14% of prescriptions. Table 4 summarizes the frequency of and reasons for inappropriate antifungal prescriptions globally and according to therapy indication.

The main reason for the unnecessary prescription of an antifungal drug was colonization by *Candida* species. As for suboptimal antifungal selection, the most common errors were prescribing echinocandins to patients with azole-susceptible *Candida* infections (a microbiological adjustment was only made in 35.7% of empirical and pre-emptive treatments), and prescribing fluconazole for mild oral or vaginal infections that could have been treated with topical antifungal agents. The reasons for incorrect dosage were insufficient fluconazole dose and excessive echinocandin dose [no adjustment of caspofungin in a patient with Child C liver failure and a double dose of micafungin in another case].

The results of the point score varied between medical departments (7.8 ± 2.8), surgical departments (8.4 ± 2.2), intensive care units (8.0 ± 2.7), oncology (6.5 ± 2.1) and haematology departments (8.5 ± 2.0). No statistical differences were found between departments.

An infectious diseases consultation was requested for 42% of patients (54.8% from medical wards, 28.6% from intensive care units, 14.3% from surgical wards and 2.4% from the oncology and haematology wards). The proportion of inappropriate prescriptions was higher in patients for whom an infectious diseases consultation was not requested (74.1% versus 33.3%, $P < 0.001$).

Economic impact and potential cost savings

During the study period, the number of antifungal DDDs per 1000 patient-days was 65.1. The total number of DOTs used in the 100 patients was 1506, which led to a direct acquisition cost of €219 364 (€2194 per patient). Overall, 51.3% (772) of DOTs were considered optimal, 24.3% (366) non-optimal and 24.4% (368) incorrect.

The cost of acquisition calculated on the basis of 100% optimal DOTs ranged from €1 to €17 420 per patient, which represented a global saving of €50 536 (€505 per patient), i.e. 23.04% of the total cost. Table 5 illustrates the potential economic savings according to antifungal indication and department.

Discussion

A bedside audit of antifungal use in patients admitted to a general hospital showed that 57% of the prescriptions were non-optimal.

Table 3. Initial antifungal drug used for different indications

	Prophylaxis ($n=15$)	Empirical ($n=42$)	Pre-emptive ($n=20$)	Tailored ($n=20$)
Antifungal drug, *n* (%)				
fluconazole	3 (20.0)	33 (78.6)	14 (70.0)	13 (65.0)
echinocandins	6 (40.1)	8 (19.1)	6 (30.0)	2 (10.0)
caspofungin	1 (6.7)	7 (16.7)	5 (25.0)	—
micafungin	4 (26.7)	1 (2.4)	1 (5.0)	2 (10.0)
anidulafungin	1 (6.7)	—	—	—
posaconazole	4 (26.7)	—	—	—
liposomal amphotericin B	—	—	—	3 (15.0)
voriconazole	1 (6.7)	1[a] (2.4)	—	1 (5.0)
ketoconazole	—	—	—	1 (5.0)
itraconazole	1 (6.7)	—	—	—
Global therapy duration (days), median (IQR)	15.0 (9.0–28.0)	11.0 (7.0–18.0)	10.0 (8.0–15.3)	11.0 (3.3–21.5)

Three patients in whom the antifungal indication could not be determined were excluded from the analysis.
[a]In combination with caspofungin.

Table 4. Adequacy of antifungal therapy for different indications

	Prophylaxis ($n=15$)	Empirical ($n=42$)	Pre-emptive ($n=20$)	Tailored ($n=20$)	Overall ($n=100$)
Score, mean ± SD	9.1 ± 1.3	6.6 ± 2.7	8.3 ± 2.2	9.5 ± 1.9	7.7 ± 2.6
Inappropriate prescription, *n* (%)	6 (40)	33 (78.6)	10 (50)	5 (25)	57 (57)
Reason for inappropriate prescription, *n* (%)					
no microbiological adjustment	1 (6.7)	21 (50.0)	7 (35.0)	3 (15.0)	35 (35.0)
inappropriate antifungal selection	1 (6.7)	20 (47.6)	3 (15.0)	4 (20.0)	31 (31.0)
inappropriate duration	2 (13.3)	18 (42.9)	4 (20.0)	2 (10.0)	27 (27.0)
inappropriate administration route	1 (6.7)	12 (28.6)	4 (20.0)	3 (15.0)	20 (20.0)
unnecessary prescription (incorrect indication)	1 (6.7)	9 (21.4)	2 (10.0)	1 (5.0)	16 (16.0)
inappropriate dosage	2 (13.3)	9 (21.4)	2 (10.0)	1 (5.0)	16 (16.0)

In three patients, the antifungal indication could not be determined after the chart review.

Table 5. Antifungal use, antifungal cost and potential cost savings

	DOTs		Inadequate DOTs[a]		Total cost		Inadequate cost[a]	
	n	%	*n*	%	€	%	€	%
By indication								
prophylaxis	300	19.9	103	34.3	58114	26.5	4669	8.0
empirical therapy	576	38.2	398	69.1	77922	35.5	39743	51.0
pre-emptive therapy	249	16.5	100	40.2	41993	19.1	11771	28.0
tailored therapy	314	20.8	66	21.0	41273	18.8	−5526	13.4
unclassifiable	67	4.4	67	100.0	63	0.0	−121	192.1
By department								
medicine	563	37.4	216	38.4	66292	30.2	−5423	8.2
intensive care unit	356	23.6	172	48.3	112934	51.5	51698	45.8
oncology	315	20.9	282	89.5	487	0.2	−393	80.7
surgery	151	10.0	52	34.4	15401	7.0	4941	32.1
haematology	121	8.0	12	9.9	24250	11.1	−287	1.2
Total	1506	100.0	734	48.7	219364	100.0	50536	23.0

[a]Non-optimal and incorrect categories are included.

A simple score revealed opportunities for improvement and provided baseline data before starting an antifungal stewardship programme and is also a practical tool for assessing the results of interventions.

Adequacy of antifungal use in clinical practice and compliance with guidelines are emergent topics in the literature.[3,7,21] Some studies have focused on the treatment of candidaemia,[8,22–25] whereas others have evaluated the management of antifungal drugs in other IFDs, albeit with disparate results.[3–5,7,21,26,27] Studies evaluating the misuse of antifungal agents showed rates ranging from 26.9% to 74%. In our experience, 74.1% of the mistakes were made by the attending physician, who in some cases never requested the help of the ID specialists. Lopez-Medrano *et al.*[3] also found that most decisions on the prescription of antifungal drugs are made by physicians who are specialists in their own field, but who do not necessarily have the expertise required to make informed choices when choosing antifungal regimens.[3] Surprisingly, we found that the remaining 33.3% of inappropriate prescriptions were written with the advice of an infectious diseases specialist. This result underlines the importance of including physicians and pharmacists with specific expertise in mycology or antifungal therapy in antifungal stewardship programmes.

When implementing an antifungal stewardship programme, training and advisory efforts should be aimed at the departments with the largest numbers of prescriptions in order to monitor common prescribing errors and to understand prevailing practice.[28,29]

We found that empirical therapy was the major factor responsible for the inappropriate use of antifungal agents (up to 69% of empirical DOTs were defined as inadequate) and, therefore, for inappropriate expenditure (up to €39743 could be saved, i.e. 78.6% of total potential cost savings). In our study, most antifungal drugs were consumed in the intensive care unit, owing to the need for more expensive agents, such as echinocandins, over longer periods. This fact corroborates the need to work toward antifungal stewardship programmes that optimize the use of empirical treatment in the intensive care unit setting and toward providing advice on the selection and duration of therapy.[15–17]

These interventions should prevent common errors such as incorrect interpretation of IFD risk factors (i.e. misuse of *Candida* score), not performing fungal cultures (no sample for culture was obtained in up to 21% of cases), not performing microbiological adjustment according to local susceptibility patterns (in our institution the incidence of azole resistance in *Candida* is <5%, and a microbiological adjustment was only made in 35.7% of patients receiving echinocandins) and not stopping treatment when IFD risk factors disappear or sepsis is shown to be caused by another type of infection. We found that only 57.6% of patients receiving empirical or pre-emptive treatment had confirmed IFD.

The incidence of prescribing errors was lower in other types of antifungal treatment, such as tailored treatment and prophylaxis. With respect to dosage, a common mistake was to prescribe an insufficient dose of fluconazole, even though failure to achieve pharmacodynamic targets for fluconazole has been associated with worse outcomes.[30–33]

In order to evaluate the impact of antifungal stewardship, it is very important to define baseline indicators that measure the adequacy of prescriptions and expenditure. We propose a point score-based bedside approach including qualitative and quantitative indicators that can be used to assess the adequacy of prescription in a non-biased way. Our scoring system proved to be practical and centred on the most important clinical features of antifungal prescription: (i) adequacy of the indication; (ii) choice of the optimal drug according to local guidelines and resistance patterns; (iii) dosage adjustment considering individual characteristics such as weight, hepatic or renal failure and concomitant medication; (iv) adjustment that should be made on receipt of culture results; (v) switching from a parenteral to an oral agent whenever possible; and (vi) adequate duration of therapy.

In our opinion, a bedside intervention using this scoring system, by which an infectious diseases expert and senior pharmacist provide advice on antifungal prescription, is mandatory given that is easier to change prescribing habits by working side by side with the attending physicians. A recent study showed that successful strategies require open dialogue with colleagues from different specialties on antimicrobial prescribing behaviour and prevailing practice, and collaboration with existing clinical groups.[29]

In order to achieve accurate estimates of drug consumption and potential cost savings, we considered that the optimal approach was to use both DDDs and DOTs. DDDs are the standard units applied to compare antifungal prescription between hospitals.[11] However, the actual dose often differs from the DDD, which can lead to overestimation of the use of fluconazole, itraconazole and liposomal amphotericin B. Furthermore, in populations with renal or hepatic insufficiency, and for drugs requiring renal or hepatic dose adjustment, the DDD may be less accurate than DOTs.[34]

The cost of antifungal drugs has increased dramatically in recent years.[28] In our hospital, annual expenditure on antifungal agents at the time of the study stood at around €3 million per year. This amount is higher than that of other European tertiary teaching hospitals, which spend from €1.0 million to €2.4 million per year.[3,7,26] Overall, assuming a conservative figure of 1000 patients treated per year and potential corrections to at least 50% of treatments owing to inadequacy, as much as €250 000 per year could be saved in our institution and other institutions like ours. Taking into account the relatively low cost of additional staff required, our study clearly demonstrates a potential good return on investment.

Our study is subject to a series of limitations. First, as this study was performed at a single tertiary care centre, the results may not be applicable to other less specialized institutions. Second, we prospectively evaluated antifungal treatment in 100 consecutive hospitalized inpatients without taking into consideration possible biases (e.g. seasonality). Third, some information was not recorded, such as the use of antimicrobial agents or the effect of suboptimal antifungal therapy on patients' outcomes. Fourth, when we performed the study, therapeutic monitoring of voriconazole and posaconazole was not available in our centre. Fifth, although the purchase price and drug mark-ups were included in our cost estimates, we acknowledge an underestimation of costs owing to the exclusion of administration costs. Sixth, price may differ from the officially established price, owing to discounts negotiated with drug suppliers.

In conclusion, we showed that there are opportunities to optimize the use of antifungal therapy in tertiary care hospitals. An antifungal stewardship programme should include a bedside instrument—as proposed in this study—that makes it possible to objectively evaluate the adequacy of antifungal use and determine the impact of specific training interventions. In our opinion, such a programme must include infectious diseases specialists and clinical pharmacists working together on behalf of the local pharmacy and therapeutics committee, and with the support of the general administration of the hospital. This study was our first step toward an antifungal stewardship programme that is currently in place at our institution.

Acknowledgements

This study was partially presented at the Fifty-first Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, IL, USA, 2011 (Poster M-283).

We would like to thank Thomas O'Boyle, who works for the Instituto de Investigación Sanitaria Gregorio Marañón, for the language editing and proof-reading of this manuscript prior to submission.

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Funding

This study was partially supported by the PROMULGA Project, Instituto de Salud Carlos III (grant number PI1002868).

Instituto de Investigación Sanitaria Gregorio Marañón provided the funding for the language editing and proof-reading of this manuscript by Thomas O'Boyle.

Transparency declarations

None to declare.

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