Do we need to adopt antifungal stewardship programmes?

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ABSTRACT

Background Although antimicrobial stewardship programmes are one of the highest priorities in healthcare systems and many articles have been published, few refer to the implementation of antifungal stewardship and highlight specific points on which efforts should be focused.

Objective To assess the percentage of patients with confirmed candidaemia in whom de-escalation was conducted, and the economic impact of step-down or step-up antifungal therapy. Additionally, we attempted to estimate the potential increase in drug minimum inhibitory concentrations or to detect resistant strains of *Candida* species.

Methods We selected, retrospectively, patients who had received systemic antifungal therapy between 2011 and 2016 for documented candidaemia. Statistical analysis and diagrams were used to assess the results.

Results Of 157 patients with confirmed candidaemia, 58 received azoles, 74 echinocandins and 18 liposomal amphotericin B for empirical therapy. 51 patients were eligible to step-down to fluconazole but only 23 patients did so. Furthermore, in nine patients unjustified step-up from fluconazole to echinocandins or liposomal amphotericin B was carried out. The additional cost incurred by the healthcare system due to high prices of echinocandins and liposomal amphotericin B in comparison with fluconazole was €211 837. Interestingly, it was found that one strain of *C. albicans* and two strains of *C. glabrata* were resistant to echinocandins.

Conclusion The presence of a multidisciplinary team, including an infection control specialist and a clinical pharmacist, would limit the prescription of advanced antifungal agents as empirical therapy. Moreover, this team would control the de-escalation process—where applicable—leading to a reduction in costs and, probably, a decrease in the emergence of resistant *Candida* species. These facts contribute to the broader discussion on the adoption of antifungal stewardship programmes.

failure.² It has often been found in immunocompromised patients and in critically ill patients in intensive care units (ICUs). *Candida albicans* is the most common cause of candidaemia, but increasingly other *Candida* species, such as *C. parapsilosis*, *C. glabrata*, *C. tropicalis* and *C. krusei*, have been isolated.³

Treatments for candidaemia include azoles (fluconazole, voriconazole), polyenes (liposomal amphotericin B) and echinocandins (anidulafungin, micafungin, caspofungin). The latest guidelines suggest that the initial antifungal agent should be an echinocandin.² However, breakthrough infections from resistant *Candida* species have led to speculation about their unnecessary use, their duration of use and their use as prophylactic agents.⁴ Moreover, both echinocandins and liposomal amphotericin B are expensive.⁵ Thus, treatment should be de-escalated to fluconazole both in neutropenic and non-neutropenic patients, when possible.⁶ This is known as step-down therapy and can be used to reduce the cost of treatment as fluconazole is inexpensive. De-escalation is not recommended for haemodynamically unstable patients, for patients suspected to have endocarditis and for those with species resistant to fluconazole.⁷ Deviation from the guidelines occurs frequently,⁸ because physicians do not believe that de-escalation will work.⁹

The aim of this study is:

- ▶ To examine the distribution of *Candida* species.
- ▶ To observe a potential increase in the minimum inhibitory concentration (MICs) of echinocandins and liposomal amphotericin B.
- ▶ To assess the percentage of patients for whom antifungal treatment was de-escalated after identification of the susceptibility of the strain according to the guidelines of antifungal therapy.
- ▶ To calculate the financial cost, in those cases where the patient met the criteria for de-escalation from echinocandins to fluconazole or for continuing treatment with fluconazole but this was not carried out.

INTRODUCTION

The term candidaemia is used to describe the presence of *Candida* species in the blood. The presence of *Candida* in a blood culture should always prompt a search for the source of the infection.¹ Clinical manifestations of infection with *Candida* species range from local mucous membrane infections to widespread dissemination with multisystem organ

METHODS

A retrospective analysis (2011–2016) of the clinical data of patients with confirmed candidaemia was performed. Data were obtained from patients' records, the microbiology laboratory and the pharmacy department. Patients were screened according to the following criteria:

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Inclusion criteria

- Patients aged >18 years.
- Candidaemia confirmed with blood cultures positive for *Candida* species.
- Empirical treatment with echinocandin or liposomal amphotericin B until culture results were obtained.
- Strain of *Candida* spp susceptible to fluconazole.
- Repeated blood cultures not positive for *Candida* spp
- No administration of vasopressors (epinephrine, norepinephrine, phenylephrine).

Exclusion criteria

- Age ≤18 years old.
- Diagnosis of endocarditis.
- Strain resistant to fluconazole.
- Contraindications for fluconazole administration.
- Repeated blood cultures positive for *Candida* spp.
- Administration of vasopressors (epinephrine, norepinephrine, phenylephrine).

The study was conducted at Hygeia Hospital in Athens, Greece, which is a private 280-bed general hospital, where an antimicrobial stewardship programme is in place, but antifungal agents are not used. The study was approved by the scientific and ethical committees of the hospital. Demographic characteristics, such as age, gender, comorbidities and duration of therapy, were recorded. The original cause of hospitalisation was documented and a search made for endocarditis and neutropenia; use of chemotherapy or radiotherapy; and administration of vasopressors. Twenty-eight day mortality was recorded. The defined daily dose (DDD) per 100 patient-days of echinocandins and liposomal amphotericin B was also documented. The study was based on blood cultures positive for *Candida* spp and MICs for each case. The MICs of each drug were defined by the revised Clinical and Laboratory Standards Institute (CLSI) antifungal breakpoints for resistance.¹⁰

Statistical analysis

Results were presented using descriptive statistics and non-parametric methods of analysis. The level of significance was set at $P < 0.05$. For the statistical analysis of data, SPSS software for Windows (edition 23.0; SPSS, Inc, IBM Company, Chicago, Illinois, USA) was used. Statistical analysis was carried out with diagrams, the non-parametric Kolmogorov-Smirnov method and the non-parametric Mann-Whitney and Wilcoxon methods.

RESULTS

Study population

Initial screening included 157 inpatients, which corresponded to 168 *Candida* positive blood cultures. Seven patients with endocarditis were excluded. Demographic data are presented in table 1.

The most common antifungal agents used for treatment were echinocandins (49.3%, specifically: anidulafungin 18.7%, micafungin 18.1%, caspofungin 12.5%), followed by azoles (38.7%, specifically: fluconazole 38.0% and voriconazole 0.7%) and liposomal amphotericin B (12%). Of the *Candida* species isolated, 42% were *C. albicans*, 24.9% *C. parapsilosis*, 13.1% *C. tropicalis*, 8.3% *C. glabrata*, 4.9% *C. krusei*, 3.1% *C. lusitanae*, 1.4% *C. kefyr*, 1.1% *C. lipolytica*, 0.6% *C. intermedia* and 0.6% *C. guilliermondii* (figure 1).

In an attempt to find a correlation between the consumption of echinocandins and amphotericin B and the MICs of each *Candida* species, we used DDDs of each year and the MICs of

Table 1 Demographic data

Age (years), mean (range)	66.2 (18–93)
Gender	Male: 62.5%, female: 37.5%
Comorbidities	Cancer: 28% Cardiovascular diseases: 16.7% Neurological diseases: 13.7%
Candidaemia per 100 bed-days	0.037
Endocarditis	4.45%
Neutropenia	9.6%
Chemotherapy/radiotherapy	7.1%
Intensive/intermediate care unit	38.9%
28-Day mortality	42.3%
Duration of treatment (days), mean (range)	18 (9–25)

each species. Specifically for *C. parapsilosis*, DDDs of echinocandins followed a similar pattern to the corresponding average MICs as shown in table 2 ($P = 0.11$).

Analysis of costs

The daily costs of each antifungal drug in Greece are shown in table 3.

Of 92 patients treated with echinocandins or liposomal amphotericin B, 51 were eligible for de-escalation to fluconazole, but this was done in only 23 (figure 2). Of 28 patients who were eligible but treatment was not de-escalated, 19 were being treated with echinocandins and nine with liposomal amphotericin B. Additionally, nine patients initially treated with fluconazole were unnecessarily re-escalated to echinocandins. The drug cost for these 37 patients was €294 375. If de-escalation had been implemented and unjustified re-escalation had not been carried out, the drug cost would have been €82 538—that is, a saving of €211 837 over 6 years or €35 306 a year ($P < 0.05$) (figure 3).

DISCUSSION

Although antimicrobial stewardship programmes are one of the highest priorities in healthcare systems and many articles have been published, few of them refer to the implementation of antifungal stewardship and highlight specific points on which efforts should be focused. In our 6-year retrospective study we examined the use of antifungal agents for confirmed candidaemia in hospitalised patients. In this study, candidaemia occurred more

Figure 1 Isolated *Candida* species.

Table 2 Presentation of defined daily does (DDDs) per 100 patient-days and the average minimum inhibitory concentrations (MICs) of caspofungin and micafungin for *C. parapsilosis* during 2013–2016

Year	DDDs per 100 patient-days	MIC	
		Caspofungin	Micafungin
2013	2.12	0.88	0.66
2014	1.81	0.527	0.62
2015	1.79	0.71	0.62
2016	2.29	0.77	0.65

Table 3 Daily cost in euros of antifungal agents*

Drug*	Loading dose (€)	Maintenance dose (€)
Fluconazole	44	22
Voriconazole	486.6	291.96
Caspofungin	425.35	332.05
Anidulafungin	651.3	325.65
Micafungin	312.6	312.6
Liposomal amphotericin B	761.11	761.11

*Drug prices did not change significantly during the study.

often in elderly (mean age 66.2 years) male patients. Seven of the 157 patients examined were found to have endocarditis and excluded as management of treatment in these patients differed.² Fifteen (9.6%) patients were neutropenic and 61 (38.9%) were admitted to the ICU (45) and the intermediate care unit (16).

The incidence of candidaemia is higher in critically ill patients, mainly owing to the presence of many risk factors such as central venous catheters, total parenteral nutrition, broad-spectrum antibiotics, high APACHE (Acute Physiology and Chronic Health Evaluation) scores and previous surgery.² The mortality rate of candidaemia in our patients was 42.3%, in accordance with another study,¹¹ which showed a mortality rate of 45–50%. In most cases, candidaemia occurred during hospitalisation and was not the major cause of admission. This finding is supported by other studies in which candidaemia occurred in hospitalised

patients, such as elderly patients receiving corticosteroid treatment, patients with liver cirrhosis, with chronic obstructive pulmonary disease (COPD), patients receiving parenteral nutrition, or chemotherapy or monoclonal antibody treatment.^{12–13}

Cancer was found to be the most common comorbidity, in accordance with other studies in Europe^{14–15} and the findings of a Brazilian national surveillance programme.¹⁶ The Infectious Diseases Society of America (IDSA) guidelines emphasise the need for implementation of antifungal stewardship particularly in immunocompromised patients.¹⁷

In our study echinocandins were the most commonly used antifungal agents both in neutropenic and non-neutropenic patients, similar to the results published by Rajendran *et al.*^{18–19} The duration of treatment was 18 days, a finding confirmed by Pfaller *et al.*²⁰ *C. albicans* was the most common species. The second most common cause of candidaemia was *C. parapsilosis*, as reported by other investigators for South Europe and Turkey.^{21–22} This is mirrored by an increase in the use of echinocandins which leads to higher MICs for *C. parapsilosis*.²³ Quindós *et al.*²¹ found that the third most common cause was *C. glabrata*, whereas we found it to be *C. tropicalis*. Additionally, some rare *Candida* species, such as *C. intermedia*, *C. guilliermondii* and *C. kefyr* were isolated. This increase in uncommon species is due to the increasing resistance to antifungal drugs.²³ Another important point in this study was that *C. krusei* was the second most encountered *Candida* species in neutropenic patients, in accordance with the study by Arendrup and Perlin.⁴ Of the *Candida* species this leads to the highest mortality rates, while *C. parapsilosis* is less virulent than other *Candida* spp.²⁰

As in the study of Van der Geest, treatment can be safely and effectively de-escalated to fluconazole in critically ill patients with invasive, fluconazole-susceptible *C. albicans* infections⁶, and another study found no difference between the efficacy and safety of echinocandins and fluconazole for the treatment of patients with fungal infections. De-escalation is also recommended by most recent fungal infections management guidelines.^{12–24} In addition, fluconazole is a safe drug, which can be given orally with high bioavailability. It penetrates most body tissues, including the central nervous system (CNS) and urine,²⁵ while echinocandins are not distributed in the CNS.²⁶ In order

Figure 2 Study flow chart demonstrating the use of antifungal agents.

Figure 3 Estimated financial loss during the 6-year study.

to highlight the importance of de-escalation therapy, we must consider two important factors: (a) the emerging resistance to fluconazole and also to new potent antifungal agents such as echinocandins, and (b) the high cost of echinocandins or liposomal amphotericin B treatment.

Several studies, have indicated that resistance to echinocandins has increased.^{4 27 28} These findings are in accordance with our results. Two strains of *C. glabrata* resistant to micafungin and caspofungin were found, which were also resistant to fluconazole, so de-escalation was not possible and the patients continued treatment with liposomal amphotericin B. Moreover, a resistant strain of *C. albicans* was reported. The patient did not belong to the group of patients eligible for step-down because he had repeated positive cultures. Detection of the two *C. glabrata* strains resistant to echinocandins is probably associated with the extended use of echinocandins throughout the hospitalisation of the patients. In addition, resistance of *C. glabrata* has been associated with factors such as previous exposure to echinocandin, a previous episode of candidaemia and fluconazole resistance.²⁸

The resistance concerning *C. glabrata* is alarming, as it is a strain for which possible treatments are limited.

Resistance to *C. glabrata* was also found in a study conducted in Scotland,¹⁸ and by the study of Vallabhaneni *et al.*²⁸ Having found the resistant strains, we also compared the trend of the average MICs for each *Candida* species with consumption by using DDDs per 100 patient-days. We observed a corresponding shift in the trends of the DDDs per 100 patient-days and the MICs of caspofungin and micafungin for *C. parapsilosis*. Consequently, when use of echinocandins was reduced, the MICs for micafungin and caspofungin were also reduced. For liposomal amphotericin B, no correlation between MICs and DDDs per 100 patient-days was found. We should add that we found a clear increase in the MIC of fluconazole for *C. parapsilosis* (1.08 to 6.45). This can be explained by the use of fluconazole as empirical or prophylactic therapy or by a possible cross-resistance with echinocandins.²⁹

As mentioned above de-escalation of treatment is safe. In this study, we have found that 30.4% of the patients receiving echinocandins or liposomal amphotericin B could have been stepped down. Additionally, treatment was unjustifiably re-escalated in 9 (15.5%) patients. This can be attributed to three reasons. First, most of those patients were in an ICU or

or an intermediate care unit and the treating physician did not want to risk changing an effective drug in a clinically stable patient. Second, an infection control specialist was not part of the treating physician team and, finally, there was no multidisciplinary team (infection control specialist, clinical pharmacist) to control the de-escalation process. Not de-escalating from echinocandins or liposomal amphotericin B to fluconazole or unreasonably stepping-up led to significant costs for the hospital. A non-negligible annual cost of €35 306.05 was estimated and found to be statistically significant. The two following studies had similar findings. Bal *et al* calculated a significant cost of £1558.03 per episode in the university hospitals Crosshouse and Ayr of England.³⁰ This study was based on 37 patients for the years 2011–2013. Treatment for 19 of 27 patients was started with an echinocandin or voriconazole and changed to fluconazole. The second study was performed by Heimann *et al* at the University Hospital of Cologne, who found that the treatment with echinocandins resulted in excess costs of €15 690 per patient.³¹

In conclusion, our study, in accordance with the findings of other studies, indicates the need for antifungal stewardship as part of an antimicrobial stewardship programme in hospitals. The presence of a multidisciplinary team, including an infection control specialist and a clinical pharmacist, would result in limits being placed on prescription of advanced antifungal agents. Moreover, this team would control the de-escalation process, if applicable, which would reduce costs and probably decrease the emergence of resistant *Candida* species. Finally, it is very important to highlight that this is not an epidemiological study and the results are not conclusive owing to the limited number of patients and cultures. Multicentre studies are needed.

What this paper adds

What is already known on this subject

- Many articles have been published on the appropriate use of antifungal agents, but few refer to the implementation of antifungal stewardship as part of an antimicrobial stewardship programme and highlight specific points on which efforts should be focused.
- Use of echinocandins and liposomal amphotericin B is associated with high costs.

What this study adds

- Our data indicate that empirical antifungal therapy is appropriate. However, the de-escalation process for targeted antifungal therapy is not implemented according to the guidelines.
- The presence of a multidisciplinary team, including an infection control specialist and a clinical pharmacist, would limit prescription of advanced antifungal agents for empirical therapy. Moreover, this team would control the de-escalation process, where applicable, leading to cost reduction and probably a decrease the emergence of resistant *Candida* species.
- Adoption of antifungal stewardship programmes in hospitals is essential.

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