ORIGINAL ARTICLE 10.1111/j.1469-0691.2012.03891.x

A non-compulsory stewardship programme for the management of antifungals in a university-affiliated hospital

F. López-Medrano[1], R. San Juan[1], M. Lizasoain[1], M. Catalán[2], J. M. Ferrari[3], F. Chaves[4], C. Lumbreras[1], J. C. Montejo[2], A. Herreros de Tejada[3] and J. M. Aguado[1]

1) *Infectious Diseases Unit,* 2) *Intensive Care Unit,* 3) *Department of Pharmacy and* 4) *Department of Microbiology, University Hospital 12 de Octubre, Madrid, Spain*

Abstract

Antimicrobial stewardship programmes promote excellence in the use of antimicrobials by selecting the appropriate antimicrobial agent and the correct dose, route of administration and duration of treatment. However, there is limited experience with such programmes targeting antifungal treatments. We present the results of a non-compulsory programme for the control of antifungals. For 12 months, prescriptions of oral voriconazole or intravenous voriconazole, caspofungin and liposomal amphotericin B were reviewed, and non-compulsory recommendations were made. The incidence and outcome of fungal infections were examined. The results for the dispensed defined daily doses (DDDs) and expenditure on antifungals were compared with those for the previous 12 months. The number of antifungal treatments reviewed was 662. A recommendation to change treatment was made in 29% of the cases, including a change from intravenous to oral treatment (15%), cessation of antifungal treatment (8%), and a change to fluconazole (6%). The DDDs of intravenous voriconazole and caspofungin were reduced by 31.4% and 20.2%, respectively. The DDDs of oral voriconazole and dispensed vials of liposomal amphotericin B were increased by 8.2% and 13.9%, respectively. Expenditure on antifungals was reduced by US$370681.78 (11.8% reduction). The programme was not related to significant increases in the incidence of candidaemia, percentage of persistent/relapsing candidaemia cases, percentage of fluconazole-resistant *Candida* species, incidence of infections by filamentous fungi, or 12-month mortality in patients with filamentous fungal infections. In conclusion, a stewardship programme targeting antifungals achieved a reduction in antifungal expenditure without reducing the quality of care provided.

Keywords: Antifungals, *Candida*, cost, resistance, stewardship
Original Submission: 26 September 2011; **Revised Submission:** 19 January 2012; **Accepted:** 31 March 2012
Editor: E. Roilides

Clin Microbiol Infect

Corresponding author: F. López-Medrano, Infectious Diseases Unit, University Hospital 12 de Octubre, Avenida de Córdoba s/n, Madrid 28041, Spain
E-mail: flmedrano@yahoo.es

Introduction

Inappropriate use of antifungals contributes to the global increase in antifungal resistance, and may lead to a variety of adverse outcomes, including unnecessary exposure to drugs and increased costs [1,2]. The prompt initiation of effective antifungal therapy reduces patient mortality. However, the indiscriminate application of risk factor-based prediction models leads to a massive increase in the number of unnecessarily treated patients [3]. New antifungals have slight differences in the spectrum of action, dose required, route of administration, and interactions with other drugs, which are difficult to manage by a non-fungal specialist [3]. Therefore, the need for stewardship programmes targeting antifungals has been raised [3,4].

Methods

Setting

The study was developed at the University Hospital 12 de Octubre, a 1300-bed hospital. A stewardship programme

focusing on antibiotics had been previously developed in our hospital [5]. The present study is an intervention study that used a non-randomized uncontrolled before–after methodology. The primary outcome of the study was a reduction in antifungal expenditure. No stewardship programme targeting antifungals existed in the hospital before the intervention. The protocol of this study was approved by the Clinical Investigation Ethics Committee. The study was supported by the hospital administration. The study was led by the Infectious Diseases Unit, and the Departments of Pharmacy, Microbiology and Intensive Care actively cooperated in study development. The intervention was developed in 2008–2009.

Programme description

The present programme was initiated in all departments of the hospital attending to adults. A member of the Infectious Diseases Unit (F.L.M.) was partially dedicated to this programme (*c.* 3 h every weekday). All prescriptions of antifungals were checked every working day. The following prescriptions were selected to be reviewed: (i) every new prescription; and (ii) prescriptions susceptible to modification or discontinuation according to the criteria of the investigator, taking into consideration the treatment indication. Antifungal treatments were identified by the computerized system of the Department of Pharmacy. The Infectious Diseases Unit and the Department of Microbiology held a meeting every day, at which every clinically relevant fungal isolate was reported. Furthermore, the treatment of the patients admitted to the Department of Haematology (22-bed ward), the Postsurgical Unit of the Department of Anaesthesiology (17-bed ward), and the Department of General Intensive Care Medicine (14-bed ward) was reviewed. Throughout the intervention period, every prescription of the following antifungals was reviewed: intravenous liposomal amphotericin B, intravenous caspofungin, and intravenous and oral voriconazole. The appropriateness of the antifungal treatment was personally discussed with the attending physician. Most of the cases resulted in oral recommendations. In cases where the responsible physician could not be contacted, a written recommendation could be left until personal contact could be made. Recommendations were made regarding the necessity for prescription of the antifungal drug, the route of administration, the dose of the drug, and the possibility of substitution with another antifungal drug. All of the recommendations were non-compulsory. The attitude of the physician in charge concerning the recommendation was checked 48 h later. Recommendations were based on the guidelines of the Infectious Diseases Society of America for the use of antimicrobial agents in neutropenic patients [6], for the treatment of intra-abdominal infections [7], and for diseases caused by *Aspergillus* [8] and *Candida* [9]. Only local antimicrobial prescription guidelines were available in the Postsurgical Unit. A special effort was made to substitute fluconazole for caspofungin or liposomal amphotericin B when fluconazole-sensitive *Candida* species were isolated, to stop the prescribed antifungal treatment when a *Candida* isolate was considered to be a colonizing organism (mainly isolates from respiratory samples), to change from intravenous to oral voriconazole when feasible, to stop empirical antifungal treatment when the patient was considered to no longer be at risk for this type of infection, and to stop prophylactic antifungal treatment when the patient was considered to be at low risk. The antifungal treatment of a single patient could be reviewed more than once.

Description of outcomes

The results of the intervention were compared with the results achieved in the hospital in the immediately preceding 12 months, which will be referred to hereafter as the pre-intervention period. The defined daily doses (DDDs) and antifungal expenses were provided by the Department of Pharmacy. A DDD of caspofungin was considered to be 50 mg, and a DDD of oral or parenteral voriconazole was considered to be 0.4 g [10]. As a DDD for liposomal amphotericin B has not been described [10], the 50-mg vial was taken as the unit. The expenses were based on the price paid by our hospital. This price may differ from the officially established price, owing to discounts negotiated with antifungal drug suppliers. All costs in Euros (Spanish currency) were converted to US dollars, taking into consideration the equivalence at the end of the intervention period (€1 = US$1.56). The antifungal expenditures 2 years and 3 years before the intervention period were also analysed. The Department of Microbiology provided the information about the number of blood cultures positive for *Candida*, and the percentage of *Candida* isolates resistant to fluconazole, during the intervention and the pre-intervention periods. Susceptibility to fluconazole was tested with a commercially prepared dried colorimetric microdilution panel (Sensititre YeastOne; Trek Diagnostic Systems Ltd., East Grinstead, UK). The yeast was considered to be susceptible when the MIC of fluconazole was ≤8 mg/L. Relapsing and persisting candidaemia were analysed together for the purpose of this study. The definition of this joint concept was the growth of the same type of *Candida* species in a blood culture after 48 h and within 30 days of the first positive blood culture. Data on the number of patients admitted to the hospital, in-hospital mortality, average length of stay and number of days of hospitalization were provided by the administration of the hospital. The following infections caused by filamentous fungi throughout the intervention and the pre-intervention periods were