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Impact of antifungal prescription on relative distribution and susceptibility of *Candida* spp. — Trends over 10 years☆

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Summary *Introduction:* The incidence of *Candida* spp. infections is worrisome, particularly in critically ill patients. Previous reports suggested that increasing use of antifungal therapy might affect resistance profiles of invasive strains. The study objective was to describe the distribution resistance profile of *Candida* spp. strains, and to correlate it with antifungal consumptions within one ICU.
Method: Antifungal drug consumption was measured as the number of defined daily doses per 1000 hospital days. The distribution of *Candida* spp. over a 10 year period 2004—2013 and the

Abbreviations: ICU, intensive care unit; DDD, defined daily dose; HD, hospital days; MIC, minimum inhibitory concentration; SAT, systemic antifungal treatment; ARIMA, autoregressive integrated moving average; SD, standard deviation.

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Antifungal stewardship;
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Polyenes

MICs of antifungal drugs over 2007—2013 were determined. Time series analyses were performed.
Results: Of 2403 identified *Candida* spp. from 5360 patients, *Candida albicans* predominated (53.1%), followed by *Candida glabrata* (16.2%), *Candida parapsilosis* (7.9%) and *Candida tropicalis* (7.5%). *C. parapsilosis* increased from 5.7% in 2004 to 8.4% in 2013 ($P = 0.02$). The increase in caspofungin use is correlated with the increase in caspofungin MICs of *C. parapsilosis* ($P = 0.01$), *C. glabrata* ($P = 0.001$) and *C. albicans* ($P = 0.02$). Polyenes consumption correlated with an increase in amphotericin B MICs of *C. glabrata* ($P = 0.04$).
Conclusion: Previous history of antifungal prescription within an ICU influences *Candida* species distribution and susceptibility profile to antifungal agents. The significant selective pressure exerted by caspofungin and amphotericin B on *C. glabrata* is a concern.

Introduction

Candida spp. strains are the most common causes of fungal infections, and the incidence of *Candida* spp. infections has risen over the last two decades. They account for up to 17% of all ICU-acquired infections and are associated with a high and worrisome increasing trend in mortality rate.[1,2] This increase is partly explained by the increased exposure of ICU patients to multiple-site *Candida* colonization along with invasive procedures (promoted by severe underlying illness, renal replacement therapy, prolonged antibacterial therapy, complicated abdominal surgery, parenteral nutrition, urinary catheter, intravascular lines)[3] The diagnosis of infected patients still relies mainly on blood or sterile-site cultures, although their lack of sensitivity results in detrimental delay in initiating targeted antifungal therapy.[4,5]

In an attempt to limit *Candida*-related mortality, appropriate treatment of proven infection should be started as early as possible.[6] Empirical therapy was progressively extended to high risk patients with suspected candidiasis.[7,8] Systemic antifungal treatments (SAT) are now widely prescribed in ICU[9,10] despite the controversies about the actual benefits of this strategy.[11,12] Concerns about misuse of SAT in ICU patients include possible increase of adverse effects, drug interactions, and costs.[5] In addition, previous studies suggested that antifungal exposure may favor the selection of acquired resistance among isolates recovered from both colonization and infection.[5,13] Indeed, recent reports established the rise of clinical failures associated with acquired resistance.[4,14,15] Molecular resistance to echinocandin is mainly mediated by mutations in the *FKS* genes, which confer cross-resistance to all three echinocandins. *FKS* mutations are associated with clinical failure in patients receiving echinocandin treatments.[15]

Over the past 15 years, antifungal drugs have been increasingly prescribed. However, the commonly used antifungal armamentarium is poor and targets actually only two main fungal components, the membrane and the cell wall. Because global resistance emergence is a slower process on eukaryotes, ecological impact of drug pressure has to be monitored on longer periods than for bacteria. Ecological changes over a wide period can be multifactorial. We previously reported limited data suggesting that antifungal use predisposes to select some *Candida* species and to increase their minimum inhibitory concentrations (MICs).[13]

The objective of this study was to describe both the distribution and the antifungal susceptibility profiles of *Candida* spp. isolates recovered from colonized and infected sites in ICU patients during a 10-year period. The correlation between antifungal consumptions and both *Candida* spp. distribution and susceptibility profiles was assessed using autoregressive integrated moving average (ARIMA) models and a transfer function. This method is well adapted to demonstrate temporal relationship between two time series such as consumption modifications and ecological changes.

Methods

This is a retrospective study which was carried out in the Grenoble University Hospital ICU, France, between January 2004 and December 2013. This 18-bed ICU serves medical and surgical adult patients, including transplant recipients and patients with hematological and solid malignancies. It was an observational study based on anonymous monthly data. It was not necessary to obtain patient's consent and ethic approval.

Antifungal drug use

Data on antifungal drug use were extracted from the electronic database of the hospital pharmacy. Targeted antifungal drugs were polyenes (including amphotericin B and liposomal amphotericin B), caspofungin, micafungin, voriconazole and fluconazole. Regarding itraconazole, posaconazole, 5-fluorocytosine and anidulafungin, the levels of use in our ICU was considered too low during the study period to exert major effects.

We converted antifungal drug doses from milligrams to defined daily dose per 1000 hospital days (DDDs/1000HD), in accordance with the Guidelines for ATC classification and DDD assignment (WHO collaborating Centre for Drug Statistic Methodology; www.whocc.no). The DDDs were 70 mg for amphotericin B, 210 mg for liposomal amphotericin B, 50 mg for caspofungin, 100 mg for micafungin, 400 mg for voriconazole and fluconazole. In a second step, we pooled the data for amphotericin B and liposomal amphotericin B to define overall polyene use.