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Themed Issue: New challenges in antifungal therapy

Epidemiology of antifungal resistance in human pathogenic yeasts: current viewpoint and practical recommendations for management

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ABSTRACT

In this review, we describe the epidemiology and clinical significance of resistance in *Candida* spp. and other non-*Cryptococcus* yeasts. The rise in echinocandin resistance, azole resistance and cross-resistance to two or more antifungal classes [multidrug resistance (MDR)] has been a worrisome trend, mainly in US large tertiary and oncology centres, particularly as it relates to *Candida glabrata*. *Candida kefyr* is also a concern as it can be resistant to echinocandins and polyenes, especially in patients with haematological malignancies. Lately, *Candida auris* has drawn a lot of attention: this uncommon *Candida* spp. is the first globally emerging fungal pathogen that exhibits MDR and strong potential for nosocomial transmission. Its almost simultaneous spread in four continents could be indicative of increasing selection pressures from the use of antifungal agents. Echinocandin non-susceptibility is also common among non-*Candida*, non-*Cryptococcus* yeasts. As *Candida* resistance patterns reflect, in part, institutional practices of antifungal administration, the benefits of antifungal stewardship protocols are increasingly recognised and endorsed in recent guidelines. Development of rapid diagnostic methods for detecting or ruling out the presence of candidaemia and antifungal resistance, as well as discovery of novel antifungals, are key priorities in medical mycology research.

1. Introduction

Candidaemia is the most common invasive fungal infection in developed countries [1]. In one recent study, *Candida* spp. were identified as the most frequent cause of bloodstream infection in hospitalised patients [2]. Candidaemia is associated with a >40% in-hospital mortality rate and significant healthcare costs [1,3,4]. Since a delay in diagnosis of candidaemia can be detrimental [1,4], the threshold to start antifungal prophylaxis or empirical treatment in high-risk patients in intensive care or haematology units is low, leading to a marked increase in the use of antifungals over the last few years [5]. This increase has been associated with the development of antifungal resistance and multidrug resistance (MDR), i.e. resistance to two or more antifungal classes, among *Candida* spp. [6–10]. In this review, we describe the epidemiology and clinical significance of antifungal resistance in *Candida* spp. and other non-*Cryptococcus* yeasts, and highlight the need for antifungal stewardship.

2. Candida glabrata

Candida glabrata is one of the three most common *Candida* spp. causing invasive disease, along with *Candida albicans* and *Candida parapsilosis* [11]. It is the main species exhibiting resistance to azoles, echinocandins and MDR, presumably due to its haploid genome [12,13]. Specifically, *C. glabrata* has a known propensity for multi-azole non-susceptibility, but the frequency of echinocandin resistance is also increasing, at least in the USA: at least four separate reports showed echinocandin resistance in >10% of *C. glabrata* bloodstream isolates over the last years [6–8,10]. Moreover, although in US population-based registries the rates of MDR in *C. glabrata* clinical isolates are 1–2% [9,14], single-institution studies from centres with high antifungal consumption, such as transplantation centres and cancer hospitals, showed significantly higher rates of MDR: MDR was observed in 3.5% of *C. glabrata* bloodstream isolates at Duke University Hospital (Durham, NC) [7] and 7% at MD Anderson Cancer Center (Houston, TX) [8]. It should be noted that echinocandin-resistant *C. glabrata* strains in Europe [15,16], Asia [17] and Australia [18] are very rare (<2% of clinical isolates).

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Rather unexpectedly, two independent studies showed a strong association between azole resistance and echinocandin resistance in *C. glabrata* bloodstream isolates after adjustment for confounders, including prior exposure to antifungals [8,9]. Such results suggest that certain *C. glabrata* strains are predisposed to the development of cross-resistance to azoles and echinocandins, even though there are no known common pathways of resistance. One potential mechanism that could explain the observed independent association of azole with echinocandin non-susceptibility is the development of DNA mismatch-repair (MMR) gene mutations, which lead to 'hypermutable' clinical strains: disruption of the MMR gene *msh2* led to a 'mutator' phenotype (*msh*2Δ) and markedly increased the emergence of resistant strains to azoles, echinocandins and amphotericin B (AmB) both in vitro and in a mouse model of *C. glabrata* intestinal colonisation [12]. Such mutations were prevalent in 55% of clinical *C. glabrata* isolates [12]. However, in another recent study, antifungal exposure correlated with resistance better than *msh*2 mutations [16]. Therefore, it is likely that other mechanisms contribute to the propensity for MDR in *C. glabrata*, such as (i) upregulation of multiazole transporters in echinocandin-resistant isolates treated with echinocandins [13], (ii) single-gene mutations that confer MDR [19] and (iii) horizontal nosocomial transmission [20].

There is no definite association between antifungal resistance and virulence in *C. glabrata*: in the aforementioned study [12], *msh*2Δ strains had a modest fitness defect compared with wild-type *C. glabrata* when simultaneously infecting or colonising mice. However, isogenic mutant isolates were not less virulent, since both wild-type and *msh*2Δ strains exhibited the same degree of colonisation or infection when tested separately [12]. Other investigators observed compensatory changes that mitigated the fitness cost associated with resistance in the only series of sequential *C. glabrata* clinical isolates analysed by whole-genome sequencing (WGS) to date [13]. Furthermore, clinical studies demonstrated that infection with resistant *C. glabrata* was associated with worse outcomes compared with susceptible isolates, independent of confounders [6,8]. In summary, the rise in echinocandin resistance and MDR in *C. glabrata*, possibly with no virulence cost, is a worrisome trend, especially in large US cancer centres and transplantation hospitals.

3. Non-*albicans*, non-*glabrata Candida* spp.

Candida parapsilosis infections are frequently associated with echinocandin exposure [21] and this species has intrinsically higher minimum inhibitory concentrations (MICs) to echinocandins. However, this is due to natural *fks* polymorphisms rather than acquired mutations conferring resistance, and two recent studies showed comparable clinical outcomes between patients with *C. parapsilosis* fungaemia treated with an azole or an echinocandin [22,23]. Since *C. parapsilosis* is a frequent cause of intravascular catheter-related infections, central line removal is paramount [22]. We do not favour treatment of de novo *C. parapsilosis* candidaemia with an azole over an echinocandin; nevertheless, more data are needed regarding breakthrough infections.

Little is known about antifungal drug resistance in less common *Candida* spp. *Candida tropicalis* is a virulent pathogen causing bloodstream infections and is frequently resistant to fluconazole (up to 20% of clinical isolates [24]) and even pan-azole resistant [25]. In a recent hospital series involving patients with haematological malignancies, *Candida kefyr* (teleomorph: *Kluyveromyces marxianus*) has been recently reported as an emerging pathogen, with prominent summer seasonality [26] and frequent resistance to echinocandins and AmB and even MDR [3,5,26]. In one study of critically ill patients, infection with *C. kefyr* was associated with increased mortality [27]. High MICs to caspofungin [28], acquired echinocandin resistance [29] and therefore MDR have been described for *Candida krusei* (teleomorph: *Pichia kudriavzevii*), which is intrinsically fluconazole-resistant. *Yarrowia* (anamorph: *Candida*) *lipolytica* [28] and *Candida haemulonii* complex [30] have also been described as less susceptible to azoles and AmB. Another recent report described for the first time the development of pan-resistance in *Candida* (teleomorph: *Clavispora*) *lusitaniae* serial clinical isolates [31].

The significant differences in the distribution of *Candida* spp. and the prevalence of resistance among institutions are complex and multifactorial, in part reflecting differences in patient populations and institutional practices, including diagnostics and prophylactic, empirical, pre-emptive or targeted use of antifungals [1,3,21]: for example, in a tertiary care oncology centre that employs routine azole-based antifungal prophylaxis in patients with haematological malignancy or after haematopoietic stem cell transplantation (HSCT), and frequent use of echinocandins in all other scenarios of care, >97% of all bloodstream *Candida* isolates among patients with acute leukaemia were non-*albicans* spp. (Fig. 1) [3]. In one study, the frequency of uncommon, potentially echinocandin-resistant *Candida* spp. (such as *C. lusitaniae* and *C. kefyr*) rose in parallel with the increasing use of echinocandins [5]. It should be noted, however, that in that study caspofungin was used to test echinocandin susceptibility and, given significant interlaboratory variability, caspofungin MICs alone might not reflect true echinocandin resistance [32].

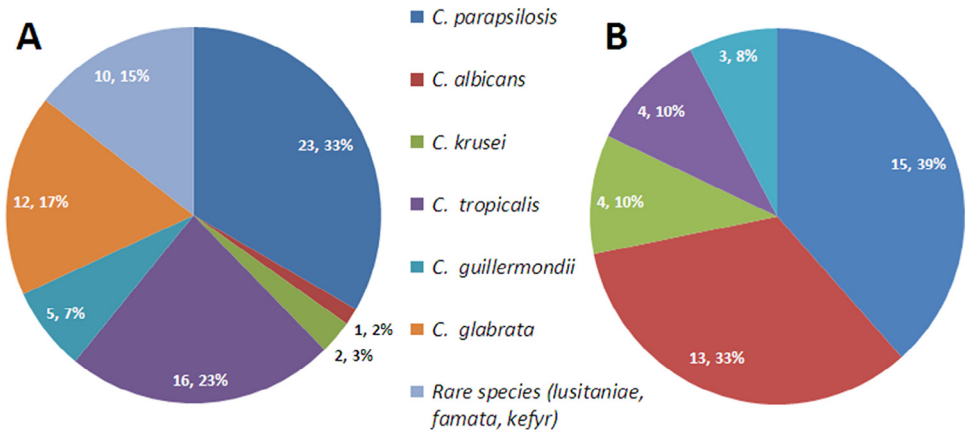

Fig. 1. Effect of antifungal practices on *Candida* spp. distribution in candidemic patients with acute leukaemia at two different US cancer hospitals: (A) use of triazole (voriconazole or posaconazole) prophylaxis ($n = 67$) was associated with a 98% predominance of non-*albicans Candida* spp., frequently *Candida glabrata*; (B) in the absence of routine antifungal prophylaxis ($n = 39$), with micafungin as the antifungal of choice for antibacterial-refractory neutropenic fever, most candidaemia episodes were due to *Candida parapsilosis*, followed by *Candida albicans*. No candidaemia episodes were caused by *C. glabrata*. Previously unpublished graph, adapted from references [3,21].