Intensive Care Med (2019) 45:512–515
https://doi.org/10.1007/s00134-018-5363-x

WHAT'S NEW IN INTENSIVE CARE

What's new on emerging resistant *Candida* species

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Introduction

Accounting for more than 400,000 annual cases worldwide, with an incidence from 0.24 to 34.3 patients/1000 ICU admissions and mortality that approaches 40%, *Candida* spp. constitute the third or fourth most common cause of healthcare-related infections worldwide [1]. Although *C. albicans* remains the main causative pathogen, the increasing isolations of *non-albicans Candida* spp. resistant to first- and second-line antifungals (namely, fluconazole and echinocandins) in nosocomial infections is concerning. Resistance to azoles remains uncommon in *C. albicans* (< 5%), but it is more prevalent in *C. glabrata* (4–16%), *C. parapsilosis* (4–10%), and *C. tropicalis* (4–9%) [2]. Acquired resistance following echinocandin exposure appears to be on the rise, and the emergence of multi-resistant species among *Candida glabrata* and the novel pathogen *Candida auris* poses a serious threat to critically ill patients.

Echinocandin-resistant *Candida glabrata*

Variable rates of acquired echinocandin resistance among *Candida* spp. have been recorded in settings where these classes of antifungals are increasingly used [2]. The acquired resistance is reported for most of the clinically important *Candida* spp., remaining uncommon in *C. albicans* (< 1%), *C. tropicalis* (< 5%) and *C. krusei* (< 7%), with the exception for *C. glabrata*, which accounts for higher resistance rates (about 13% in some centers) [2, 3]. *C. glabrata* is the second most prevalent pathogen responsible for candidemia in different medical centers, mainly in USA, Canada and northern Europe [2]. Remarkably, echinocandin resistance is associated with cross-resistance to azoles [2]. A landmark study at Duke University Hospital reported an increase in echinocandin resistance from 4.9 to 12.3%, and to fluconazole from 18 to 30% in a 10-year period (2001–2010) [3], corroborating a growing trend of MDR lineage isolation. The SENTRY surveillance program [4] reported 8.0–9.3% resistance to echinocandins among *C. glabrata* bloodstream isolates collected between 2006 and 2010. In addition, a recent North American analysis attributed a 36% incidence of echinocandin resistance to fluconazole-resistant isolates of *C. glabrata* [5]. In contrast, echinocandin resistance among *C. glabrata* seems to be low in Europe (< 1%), Latin America (0.0%), and the Asia Pacific region (0.0%) [4, 6, 7]. Recent European studies analyzing echinocandin susceptibility among *C. glabrata* isolates found low-to-null resistance rates (0.7% in France, 0–2.1% in Italy, 0% in Spain, and 2.7% in Denmark) [8–10]. The antifungal susceptibility profiles of 210 *C. glabrata* Indian isolates showed the absence of echinocandin resistance [11]. Selection of echinocandin-resistant *C. glabrata* requires prolonged and recurrent exposure to echinocandins, with most cases occurring after 3–4 weeks of therapy [12]. However, resistance may develop even in shorter periods and in echinocandin-naive patients in high-incidence settings, suggesting intra-hospital transmission [13].

Hence, undetected infection sites may contribute to disease persistence, and resistance can evolve despite adequate therapies emphasizing the importance of routine susceptibility testing. Intra-abdominal infections create a particular microenvironment facilitating a strong selection pressure for MDR strains caused by biofilm

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production and limited drug penetration. Interestingly, in patients with *C. glabrata* invasive candidiasis, treatment failure was reported to range from 30% to more than 50%, based on prior echinocandin exposure and elevated minimum inhibitory concentrations (MICs) for echinocandins [14]. In *C. glabrata*, echinocandin resistance occurs due to mutations in the *FKS* gene (*FKS*1 and *FKS*2) sequences encoding for the glucan-synthase enzyme, which is the target of echinocandins. The presence of *FKS* mutations is the most important risk factor in predicting echinocandin therapeutic responses, being superior to MIC values, especially when caspofungin is used for testing. Recently, *MSH2* DNA mismatch repair (MMR) gene deletions in *C. glabrata* resulting in a mutator phenotype that facilitates rapid acquisition of fluconazole, echinocandins, and amphotericin B (AMB) resistance has been detected in different clinical isolates [11]. Moreover, resistance to fluconazole and/or amphotericin B may be present in > 25% of *FKS* mutant *C. glabrata,* especially in patients treated with multiple antifungals [14]. Thus, antifungal susceptibility testing and mutation analysis may provide important information, especially in patients previously exposed to echinocandins and exhibiting no response, or those with persistent infections. In cases of MDR *C. glabrata*, AMB lipid formulation is the main available option until new drugs become available. New glucan-synthase inhibitors (e.g., SCY-078), structurally different from echinocandins, have demonstrated promising primary results in in vitro preclinical studies against MDR *Candida* spp. with *FKS* mutations [15].

Candida auris global burden

"If you are already at death's door, which is often the case in ICU, then this is really bad news": this declaration was released by Prof. H. Pennington from Aberdeen University after the Royal Brompton Hospital ICUs in London in 2016 were forced to close for 2 weeks to contain the first European outbreak of 50 *C. auris* cases [16]. After the first isolation in Japan in 2009, *C. auris* infections have been reported from different countries in 5 continents (Fig. 1) [17]. From 2013 to 2017, the European Centre for Disease Control and Prevention (ECDC) reported 620 European cases of *C. auris* from several countries, with difficult-to-control outbreaks in the United Kingdom and Spain [16]. As of May 2018, 279 cases of *C. auris* isolations have been recorded by the Center for Disease Control and Prevention (CDC) in the US [18].

In-hospital mortality for *C. auris* candidemia ranges from 30 to 72%, and most of the infections occurred in critically ill adults, with only a few reported cases in pediatric patients [17]. Risk factors are similar to those associated with other *Candida* spp. infections, such as broad-spectrum antimicrobials, ICU stay, central venous catheters, immunosuppression, urinary catheter, and recent surgery [19]. Recent data of 54 patients from 3 continents demonstrated that the median time from admission to infection was 19 days, 61% of patients

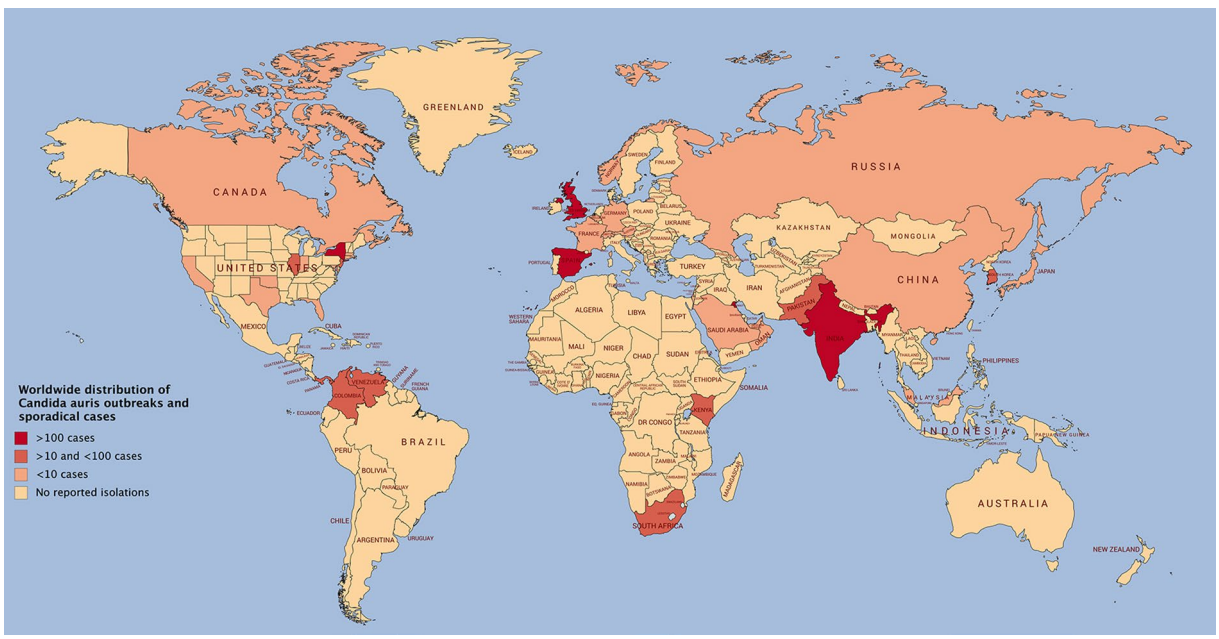

Fig. 1 Worldwide distribution of *Candida auris* isolations (reported in the literature) assessed up to 1 June 2018

had bloodstream infections, and approximately 41% of patients were receiving antifungal drugs when *C. auris* was isolated [19].

A high index of suspicion for *C. auris* infection should emerge when susceptibility testing shows resistance to antifungals. The species may remain unidentified or misidentified as *C. haemulonii* (most commonly) or some other rare *Candida* spp. by commercial biochemical identification systems. In fact, the true prevalence of *C. auris* infections remains unknown as misidentification is frequent using routine diagnostics [17]. MALDI-TOF (matrix-assisted laser desorption ionization–time of flight mass spectrometry) provides rapid and accurate identification. Also, molecular methods, such as sequencing of nuclear ribosomal RNA gene (*D1*/*D2* region) or the internal transcribed spacer domain (*ITS1* and *ITS2* region), provide correct microbial characterization [17].

Candida auris has high propensity for patient-to-patient transmission, and its spread is related to interpersonal contact and/or exposure to contaminated common surfaces and devices, where it can persist for days or even weeks due to virulence factors that are not completely understood [20]. Moreover, patients' colonization is difficult to eradicate and may persist for months. The majority of infected patients had a recent exposure to an indwelling device or underwent invasive procedures [19]. If feasible, removal of central catheters or other invasive devices may prevent persistent candidemia and recurrence. Healthcare organizations have released specific recommendations for patients' and contacts' isolation, and precautions such as cleaning of medical facilities and hospital environments in order to prevent and contain *C. auris* outbreaks [20]. Indeed, prevention and control measures are more relevant than antifungal treatment itself, or even than the antifungal resistance of the microorganism.

Antifungal susceptibility data of isolates from three continents has demonstrated that half were MDR, with strains being resistant to fluconazole (approximately 93%), amphotericin B (30–40%) and echinocandin (5–10%). Moreover, a small percentage was pandrug-resistant [19]. *C. auris* demonstrates a high propensity to develop resistance to multiple antifungals under selective pressure. The mechanisms of azoles, echinocandins and AMB resistance are under investigation. Recent studies have demonstrated that *C. auris* exhibits mutations in *ERG*11 (azole hotspot gene) and *FKS*1 genes which alter the drug binding [21, 22].

The best treatment for *C. auris* has not yet been defined. Echinocandins are the first-line therapy even in association with voriconazole, which seems to have a synergic effect [17]. Liposomial AMB should be prescribed in cases of unresponsiveness, and a synergistic effect is not excluded if associated with other antifungals (e.g., echinocandin). However, since resistance may develop while on therapy, periodical susceptibility testing is mandatory to confirm treatment effectiveness. Newer azoles (such as posaconazole and isavuconazole) have shown good in vitro activity against *C. auris*. The development of new antifungals against *C. auris* resistance are in the pipeline. The SCY-078 glucan-synthase inhibitor has demonstrated potent antifungal activity against *C. auris* and seems to be one of the best hopes for the near future [17]. Also, rezafungin (previously CD 101), a novel long-acting echinocandin, has shown excellent in vitro and in vivo activity against *C. auris* [23].

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Compliance with ethical standards

Conflicts of interest
The authors declare no conflict of interest.

Received: 6 July 2018 Accepted: 30 August 2018
Published online: 6 September 2018

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