Curr Fungal Infect Rep (2017) 11:197–202
https://doi.org/10.1007/s12281-017-0299-0

Candida auris: Antifungal Multi-Resistant Emerging Yeast

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Published online: 26 October 2017

Abstract
Purpose of Review The purpose of this review is to contribute to the knowledge about the existence of *Candida auris* as an emerging pathogenic fungus, multi-resistant to antifungal, and causing health care-associated infections (HCAI).
Recent Findings C. auris emerges as yeast with clonal transmission resistance to three families of commonly used antifungals, mainly azoles (fluconazole and voriconazole), diminishing therapeutic options for the treatment of fungal infections. In 2009, *C. auris* was isolated for the first time in Japan and by the time of this review, it has been reported in different countries in Africa, America, Asia, and Europe.
Summary It is important to identify yeasts of the *Candida* genus up to species, to perform susceptibility tests and to implement surveillance, prevention, and control measures, to minimize the global spread of this fungus, due to its impact on public health.

Keywords *Candida auris* · Outbreak · Healthcare-associated infections · Genotyping · Antifungal susceptibility · Fluconazole resistance

Topical Collection on *Clinical Mycology Lab Issues*

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Introduction

Candida auris appears as an emerging yeast fungus, pathogenic in humans and multi-resistant to antifungals, mainly to azoles (fluconazole and voriconazole), and to a lesser extent to amphotericin B and echinocandins. This fungus can cause candidemia and invasive infections associated with health care, and may increase mortality in susceptible populations who have risk factors for the development of an invasive fungal disease (IFD), such as immuno-compromised, oncologic, and transplant patients, exposed to broad spectrum antibiotics, with prolonged stay in intensive care units and hospitalization rooms, among others [1, 2, 3••]. It has been described that *C. auris* infections are present mainly in the bloodstream, wounds, auditory canal, and in minor proportion in the urinary and respiratory tract, isolating particularly in the hospital environment; however, it is still unknown whether its isolation from the last three sources corresponds to an infection or colonization [2]. It has also been reported to cause infection in association with other *Candida* species, even when the patient receives antifungal therapy [2]. The appearance of this yeast is a cause for worldwide alert, as it is capable of transmitting resistance to antifungal quickly and clonally, which would explain the lack of clinical response to the treatment, causing a great impact on global public health [4].

Molecular Identification

In 2009, the first case of *C. auris* was described worldwide, having been isolated from the external auditory canal of a patient in Japan; subsequently, in five South Korean hospitals, it was also reported as the causative agent of otitis media in 15 patients [3••, 4, 5]. In 2011, three cases of *C. auris* bloodstream infections were reported in South Korea, stating that this species of the *Candida* genus was capable of causing

invasive infections [3••, 5–7]. Afterwards, there have been reports of fungemia cases, due to this yeast, in several hospitals in India [8–10], South Africa [11], Kuwait [12], Venezuela, and Colombia [1, 13].

C. auris shows resistance to fluconazole and variable susceptibility to other azoles, amphotericin B and echinocandins. Its real prevalence is underestimated due to its misidentification as *C. famata*, *C. sake*, *C. haemulonii*, or *Rhodotorula glutinis*, when using conventional methods such as carbohydrate assimilation and commercial ones such as Vitek 2®, ID32C®, and API Auxacolor® in routine microbiology laboratories. It is phenotypically similar to the species that make up the *Candida haemulonii* Complex, and molecular methods are required to identify it properly [3, 14••]. *C. auris* and *C. pseudohaemulonii* are phylogenetically related to *C. haemulonii* in the Metschnikowiaceae clade, in which they have been grouped [3, 15••]. By the foregoing, *C. auris* represents a challenge at the time of its identification and subsequent treatment, especially when molecular methods are not available and access to antifungal other than fluconazole is limited [3, 14••, 15••].

Sequencing of the ITS regions, the major subunit of the rDNA D1/D2 domain and the region of the rDNA 28S gene is considered as the molecular reference method to correctly and definitively identify *C. auris* [1, 3••, 14••, 15••]. It is also possible to perform the identification by alternative techniques such as MALDI-TOF MS (Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry) which, in addition to allowing rapid and reliable identification, is also considered as a reference method for the identification of *C. auris* [1, 2, 3••, 13, 14••, 15••, 16–18].

Through the use of Amplified Fragment Length Polymorphism (AFLP) analysis technique, it was possible to differentiate *C. auris* from closely related species such as *C. haemulonii*, *C. pseudohaemulonii*, and *C. duobushaemulonii*. This technique also demonstrated the clonality of *C. auris* in each geographical region where outbreaks have been reported [3••, 13, 14••, 15••, 16–18, 19•]. Schelenz et al. using AFLP and subsequent analysis of whole genome sequencing (WGS) demonstrated the clonal relationship between *C. auris* isolates from four hospitals in India [20]. Meanwhile, Lockhart et al. from the whole genome sequencing of thousands of single nucleotide polymorphisms, which gathers unique clades by geographic region, found clonality among isolates that were part of each clade; additionally, they also detected mutations in the ERG11 gene that were associated with resistance to azoles in each geographic clade [14].

Virulence Factors

The *C. auris* genome has a size of 12.3 Mb, which possesses genes common to pathogenic species of the *Candida* genus that are crucial for adaptation to different environments, such as those that encode its metabolism [21, 22]. *C. auris* shares numerous virulence factors with *C. albicans*, for example, genes and pathways involved in cell wall modeling and nutrient acquisition, histidine kinase-2 systems, iron acquisition, tissue invasion, enzymatic secretion and efflux, and expulsion or ejection pumps [3••, 16, 21–24]. However, an in vitro study of multiple isolates of *C. auris* from different geographic regions showed that the production of enzymes was strain-dependent; in particular, the production of phospholipase and proteinase was detected in 37.5 and 64% of the evaluated isolates, respectively [25]. In general, tested strains of *C. auris* showed weak phospholipase activity, with most isolates not producing this enzyme [22].

A significant part of the *C. auris* genome codes for the two efflux pump systems of the ATP-binding cassette (ABC) family and the major facilitator superfamily (MFS). The joint action of both efflux pumps could explain the multiresistance of this pathogen to different antifungals [16, 22]. The ABC-type efflux pumps, which have a 6G Rhodamine transporter, were significantly higher for *C. auris* when compared to *C. glabrata*, a result that supports the intrinsic resistance of *C. auris* to azoles [21]. On the other hand, during the analysis of the whole genome sequence of *C. auris*, a close phylogenetic relationship was observed with *C. lusitaniae*, a species of *Candida* with recognized intrinsic antifungal resistance [16, 22].

A determinant virulence factor of *C. auris* is thermotolerance, since it develops well at 37 °C (98.6 °F) and is able to maintain its viability up to 42 °C (107.6 °F). Other factors such as tolerance to high concentrations of salt and cell aggregation, in large accumulations difficult to disperse, contribute to the persistence of the strains in the hospital environment [5, 23, 26]. The virulence of *C. auris* has also been demonstrated in murine models with invasive candidiasis where it was observed that the aggregation of yeasts in the animal's kidneys led to a lethal infection, suggesting that aggregation could be a mode of evasion of the immune response; thus, favoring the persistence in the tissue [27].

The ability of adhesion to inert surfaces, such as catheters, is another virulence factor of *C. auris*, as it allows it to form biofilms and resist the action of antifungal agents [28]. However, a recent study reported that biofilms in *C. auris* were significantly thinner, displaying 50% less thickness compared with those produced by *C. albicans* [25, 28]. On the other hand, it has been demonstrated that *C. auris* has a minimum adhesion capacity to the silicone elastomer (catheter material) with respect to *C. albicans* [25]. Therefore, the low adherence capacity of *C. auris* suggests that this factor is not determinant in catheter-associated candidiasis, in contrast to *C. albicans* and *C. parapsilosis*, which are frequently related to these infections [23, 25].

Candida auris in Hospital Outbreaks

Recent studies have reported the persistent colonization of *C. auris*, both in hospital environments and in multiple anatomical areas of patients, a condition that contributes to the increased transmissibility of this pathogen, to the contamination of the sanitary environment, and to the prolongation of outbreaks [14••, 19•, 20, 23, 29]. At a London cardiothoracic center, between April 2015 and July 2016, an outbreak occurred with 50 *C. auris* cases, in which AFLP technique demonstrated that isolates of this yeast from the hospital environment near the patients were the cause of the outbreak [3••, 19•]. In this same outbreak, a case of a health worker was described, who had under his care a patient highly colonized by *C. auris*, who presented a positive nasal swab for this pathogen [19•]. Vallabhaneni et al. indicated that between May 2013 and August 2016, the first seven cases of identified *C. auris* infection occurred in the USA [3••, 24, 30]. By analyzing the complete genome of *C. auris* isolates, it was shown that isolates of this yeast from patients entering a New Jersey hospital were almost identical to isolates obtained from patients admitted to an Illinois hospital; additionally, pathogen isolation was achieved in inert sites through samples taken from the mattress, bedside, eating table, and patient bed rail, proving that the *C. auris* present in the furniture and hospital setting was responsible for the outbreak, as in the London study [14••, 15••, 19•].

Several authors have emphasized that it is essential to apply strict measures for the control and prevention of infections in order to avoid the transmission of *C. auris* among contacts. The isolation of the patient and their contacts, the hand hygiene, use of protective clothing by health workers, decontamination of skin with chlorhexidine, cleaning of the environment with reagents based on chlorine, and final decontamination with hydrogen peroxide steam or ultraviolet (UV) light, as well as proper disposal of biological and non-biological waste, may be some of the measures to be implemented to prevent the spread of infection caused by this pathogen [3••, 19•, 20, 23, 24, 29, 30].

Emergence of *Candida auris* in Venezuela

The occurrence of *C. auris* in Venezuela was detected in 2016, during an outbreak in a third-level hospital located in the city of Maracaibo, where 18 episodes of candidemia were described, whose causative agents were initially identified as *C. haemulonii* [1]. This outbreak and its persistence over time were reported to the Mycology Department of the "Rafael Rangel" National Institute of Hygiene (RRNIH), requesting the verification of the identification of the isolates being sent. The isolates were again identified as *C. haemulonii* by conventional and automated methods such as the Vitek 2 Compact®, and susceptibility tests were also performed by the Etest® technique. These isolates, along with others received at the RRNIH from hospitals in the city of Caracas, including other isolates from the city of Maracaibo, were sent to the Centers for Disease Control and Prevention (CDC) located in Atlanta, USA, for confirmation of identification by the MALDI-TOF technique and performance of susceptibility tests.

From a total of 81 isolates, 71 (87.7%) were confirmed as *C. auris* (68 from Maracaibo), five were *C. haemulonii*, two were *C. haemulonii var.vulnera*, and the others were *C. duobushaemulonii*, *C. parapsilosis*, and *C. pseudohaemulonii* (one of each). In terms of phenotypic *C. auris* features, the highlight was that the 71 isolates (100%) developed at 42 °C (107.6 °F), only 70 (98.6%) showed blastoconidia without pseudohifas in corn flour agar and in chromogenic agar presented a cream color, 50 (70%) grew in 10% sodium chloride broth, and 58 (81.7%) grew on Mycosel® agar, similar to that described by other authors [21, 22, 24, 25].

Routine microbiology laboratories, as well as some reference laboratories, located in developing countries, have neither molecular methods nor mass spectrometry for the confirmatory identification of *C. auris*. On the other hand, conventional and commercial identification methods are not able to discriminate between the *C. haemulonii* Complex and *C. auris*, nor between cryptic and phylogenetically related species [32]. This situation creates a serious problem of worldwide underreporting. Therefore, in terms of *C. haemulonii* isolates or other species of the *Candida* genus described above, which in turn present resistance to azoles and possibly to amphotericin B, *C. auris* should be suspected [33, 34]; these isolates should be sent to reference laboratories that have the necessary methodology for their correct identification and should be preserved in culture collections for further studies.

Results of susceptibility testing, performed by the Etest® method at the RRNIH, *C. auris* isolates showed resistance to fluconazole, voriconazole, and echinocandins (100, 95.8, and 21%, respectively), and no resistance to amphotericin B was detected. These results were confirmed by the CDC using Etest® and the CLSI reference method [33, 34]. The resistance to the fluconazole of the Venezuelan strains, coincided with reports of *C. auris* isolates of fungemia cases resistant to the fluconazole, with minimal inhibitory concentrations (MIC) > 64 mg/L [3••, 14••, 15••, 17, 18, 22]. Voriconazole values differ to those published by other authors, where the percentage of resistance was lower [3••, 13, 14••, 15••]. According to the results obtained with the azoles, it is possible to predict that one of the mechanisms of resistance that the Venezuelan strains present are the CDR- and MDR-type efflux pumps and we cannot rule out the point mutations in the gene encoding the 14-α-dimethyl-anesterase enzyme; both mechanisms have been described for the *Candida* genus [3••, 14••, 15••, 23]. With respect to echinocandins, the

resistance percentage of Venezuelan strains was greater than that reported by Chowdhary et al. and Lockhart et al., and higher than the one reported in the study published by Kathuria et al. where they also reported resistance to amphotericin B [8, 14••, 15••].

Multi-Resistance to Antifungals

The emergence of this pathogen causing health care-associated infections (HCAI) is a cause for concern and alarm for all worldwide health service providers, since the transmission of resistance to the three antifungal families (azoles, polyenes, and echinocandins), frequently used for the treatment of patients with risk factors of developing invasive candidiasis, is of the clonal type [3••, 19•, 20–24, 29, 30, 35–38]. The investigations carried out so far, agree that *C. auris* infection represents a therapeutic challenge, and there is no consensus for the choice and application of an optimal treatment [23, 24].

Some studies have reported that MIC values > 32 μg/mL for fluconazole in *C. auris* isolates from a fungemia suggest intrinsic resistance against this drug [3••, 7–9]. Although there are no epidemiological cutoff values (ECV) or clinical cut-off points for *C. auris*, new azoles such as posaconazole, ranging from 0.06–1 μg/mL, and isavuconazole, with values < 0.015–0.5 μg/mL, have shown excellent in vitro activity against *C. auris* [4, 5, 7, 15••, 19•, 23, 24]. Variable susceptibility values for amphotericin B have been observed in 15 to 30% of *C. auris* isolates with MICs > 2 μg/mL [9, 15••] and poor resistance to echinocandins (2 to 8%) has been observed [9, 14••, 15••].

Nearly half of the isolates have multidrug-resistance (MDR) efflux pumps, which encode resistance to two kinds of antifungal families and a low percentage (4%) of resistance to all kinds of antifungal [2, 9, 12, 15••, 16, 19•, 23, 24]. Echinocandins remain the first-line therapeutic option for *C. auris* infections, as long as susceptibility testing is performed as soon as possible [24, 36, 38]. It has also been demonstrated that a novel oral bioavailable drug, SCY-078, which is the first inhibitor of 1,3-β-D-glucan synthesis, has a powerful activity against various *Candida* species, including *C. auris*; moreover, it showed anti-biofilms activity so it could be an important antifungal for the treatment of isolates with CDR- and MDR-type effluent pumps [3••, 20, 24, 25].

Currently, the mechanisms of resistance to the *C. auris* antifungal are not well defined. The recent genome project for this yeast revealed the presence of individual copies of the ERG3, ERG11, FKS1, FKS2, and FKS3 genes [3••, 15••, 16, 22, 23]. In the ERG11 mutation analysis, when comparing the *C. albicans* and *C. auris* sequences, nine amino acid substitutions were identified, which have been described in *C. albicans* non-wild-type resistant isolates. We further identified three additional amino acid substitutions that are decisive to significantly increase *C. albicans* resistance to fluconazole [21, 22]. These substitutions were strongly associated with each clade-specific geographic data by country; so we have F126T in South Africa, Y132F in Venezuela, and Y132F or K143R in India and Pakistan [14••]. Selective pressure for the indiscriminate use of antifungal drugs is likely to be the trigger for mutations leading to an early-stage antifungal resistance.

Final Comments

The authors of this review consider that the information generated so far about *C. auris* represents only the tip of a large iceberg. The debut of this yeast in the history of medical mycology raises many interesting questions that need to be answered in a short time, since the available information on the epidemiology and behavior of this pathogen is very recent. Research subsequent to the year 2009, held in a South Korean culture collection, detected the existence of *C. auris* since 1996 [3••, 7]. The obvious question that arises is whether this pathogen existed long before 1996 and simply could not be identified [3••]; however, the review of isolates preserved in culture collections from other global research centers showed no isolation of *C. auris* before 1996.

We do not know why *C. auris* emerged almost simultaneously in several countries of the world. It has been shown, at a phylogenetic level, that there are large genetic differences between geographic clades and a high clonality within them; however, a common feature is its high level of antifungal resistance, which is not frequent in other *Candida* species [3••, 14••, 19•, 22, 24].

C. auris is the only species in which several isolates with resistance to the four classes of antifungals have been identified [23, 24]. It is logical to think that the misuse or abuse of antifungals is one of the factors that favor resistance, without ruling out the intrinsic resistance, since there are still researches in development that seek to explain the *C. auris* behavior. Most of the revised publications have reported that environmental factors play an important role in outbreaks and infections associated with health care; these include the prolonged survival of the micro-organism by skin colonization, both in patients and asymptomatic carriers, as well as everything related to the environment for the operability of health centers. It is undoubtedly justified to continue investigating multiple aspects of *C. auris*, which apparently possess the typical characteristics of other well-known pathogens, also related to health care, such as gram-negative producers of carbapenemase, *Clostridium difficile*, *Enterococcus* resistant to vancomycin, and methicillin-resistant *Staphylococcus aureus* [37].

Knowing the behavior of the pathogens named above, it is expected, a greater spread of *C. auris* in the sanitary environments on a worldwide scale. In fact, the appearance of *C. auris*

has prompted the Centers for Disease Control and Prevention (CDC) (http://www.cdc.gov/fungal/diseases/candidiasis/candida-auris-alert.html), the executive agency of the UK Department of Health in London (Public Health England, PHE), (https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/534174/GuidanceCandidaauris.pdf), and the European Centre for Disease prevention and Control (ECDC) (http://ecdc.europa.eu/en/publications/Publications/Candida-in-healthcare-settings_19-Dec-2016.pdf), to issue health alerts for the strict monitoring of the *C. auris* cases [19•, 24].

Conclusions

Future research should focus on ecology, evolution, epidemiology, and mechanisms of resistance to antifungal agents, which will provide a clearer view on the clonal transmission of *C. auris* and its efficient global dissemination, as well as the knowledge to be able to offer an adequate and precocious treatment, in addition to implementing measures of containment, control and prevention of infection.

As an emerging fungal pathogen, *C. auris* could become the agent that motivates the inclusion of opportunistic mycoses, particularly fungemia, as notifiable diseases in all public health systems at local, regional, and global levels. The rapid increase in its incidence, as well as the increase in morbidity and mortality in populations at risk of acquiring an invasive fungal disease (IFD), seems to lead in that direction.

Compliance with Ethical Standards

Conflict of Interests The authors declare that they have no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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