Candida auris and other phylogenetically related species – a mini-review of the literature

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Abstract

The lesser-known non-*albicans* *Candida* species are often overlooked and difficult to diagnose in most microbiology laboratories. *Candida auris*, a relatively newly discovered species, is responsible for outbreaks in various geographical regions. Because of its increased resistance to antifungal drugs, *C. auris* is responsible for hard-to-treat infections and its pathogenicity is still incompletely elucidated. Non-*albicans* species phylogenetically related to *C. auris*, like the *C. haemulonii* complex might also play a role in human pathology. The current summary of the literature presents the emergence, virulence, laboratory identification, and molecular mechanisms responsible for antifungal resistance of emergent rare non-*albicans* *Candida* species.

Keywords *C. auris*, *C. haemulonii*, *C. ruelliae*

Introduction

Candida genus is polyphyletic and many members of the genus have been reassigned in recent taxonomic studies. The revised taxonomy better reflects the resistance profiles of clinically important species like *Nakaseomyces glabrata* (previously *Candida glabrata*), *Pichia kudriavzevii* (previously *Candida krusei*) or *Debaryomyces hansenii* (formerly known as *Candida famata*).¹

Until recently, *Candida albicans* was the most commonly encountered species of the *Candida* genus. *C. albicans* is ubiquitous, it can cause infections mainly in immunocompromised hosts and almost any microbiology laboratory can easily identify it. Non-*albicans* species, on the other hand, have received scant attention, despite their

newly emergent nature. With an increased pool of immunocompromised patients, more prone to fungal infections, non-*albicans* species have increasing importance and the lack of species identification is often considered inadequate.

Conventional methods of identification for fungi, used by most laboratories, fail to identify the lesser encountered *Candida* spp., as they are relatively unreactive and insufficiently studied. Although rare, some non-*albicans* species pose not only diagnostic challenges but are also harder to treat, as they exhibit increased resistance to antifungal drugs.²

Recent studies have proven that *C. auris* can be part of the microbiome, raising questions about how this fungus emerged just recently,

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causing hard-to-treat infections. Various theories aim at explaining the rise of *C. auris* including the use of antifungal drugs, environmental changes, and human activities that permitted the fungus to escape its specialized niche and to colonize larger areas of skin. It is now known that *C. auris* can be a colonizer, but screening programs, where needed, are still difficult to draft. A single screening test proved to be imperfectly sensitive and more research is needed for discovering an effective screening strategy.³

Emergence

In 2009, a novel species of *Candida* isolated from the external ear canal of a Japanese patient was first described. The strain was named “*Candida auris*” and it resembles *C. ruelliae* and *C. haemulonii* complex at a phylogenetic level.⁴ In 2011, *C. auris* was incidentally found in a stored bloodstream isolate from 1996, in South Korea.⁵ In Europe, the first case of an infection with *C. auris* was imported from India, in 2009.⁶

C. auris belongs to the Clavispora clade of the Metschnikowiaceae family of the order Saccharomycetales⁷ and it might have previously existed as a plant saprophyte. Because of its salinity tolerance and thermal tolerance, some authors are considering its emergence to be linked with global warming.⁸

Independent different clonal populations (clades separated by thousands of single-nucleotide polymorphisms) have been identified on 3 continents.⁹ Although it is commonly accepted that there are four major clades: the South Asian (I), Asian (II), African (III), and South American (IV), a potential fifth clade of *C. auris* has been reported in Iran, in 2018.¹⁰ *C. auris* strains isolated from different geographical areas tend to be phylogenetically distinct, whereas *C. haemulonii* strains are more interrelated.¹¹ Analysis of *C. auris* genome showed a 40% genetic share with *C. lusitanae*, especially related to genes that provide multiple antifungal resistance. Moreover, *C. auris* harbors virulence genes that are present in *C. albicans*.¹²

To date, cases of infections have been reported all around the globe (Figure 1).¹³⁻²⁷ However, the real global distribution remains

unknown, mainly because the current commercial methods used in the microbiology laboratory are often misidentifying as other non-*albicans*.²⁸

C. haemulonii (*Torulopsis haemulonii*) was first isolated from the gut of a blue-striped grunt (*Haemulon sciurus*) in 1962,²⁹ found in the Western Atlantic, Gulf of Mexico, and the Caribbean.⁷ The *C. haemulonii* complex includes *C. haemulonii* (*C. haemulonii* group I), *duobushaemulonii* sp. nov. (*C. haemulonii* group II), and *C. haemulonii* var. *vulnera* var. nov.³⁰ In 2016, Sugita et al. isolated a strain named *Candida pseudohaemulonii* sp. nov. from the blood of a patient in Mae Sot Hospital, Thailand.³¹

At a genetic level, *C. haemulonii* resembles *Debaryomyces hansenii*, *C. guilliermondii* and *C. auris*.^{2,11} Although rare, its prevalence is increasing, especially from patients with deep-seated infections³² and it can be transmitted within healthcare facilities.³³

C. haemulonii is an opportunist fungus capable of causing fungemia outbreaks.^{2,34} The disease is not clinically distinct from other common nosocomial infections: the patients present high fever and leukocytosis. Risk factors include malignancy, mechanical ventilation, and central venous catheter insertion.³⁵ In 2021, a case of liver abscess caused by *C. haemulonii* var. *vulnera* was reported in Peru.³⁶

C. duobushaemulonii, first reported in 2016, causes vulvovaginal candidiasis, onychomycosis, fungemia, and chronically infected wounds of lower extremities, mainly in patients with diabetes mellitus. *C. haemulonii* var. *vulnera* causes fungemia, ulcers of the feet, and onychomycosis in adult patients with preexisting conditions like sickle-cell anemia, B-cell lymphoma, or other malignancies.^{37,38}

C. ruelliae has been isolated from the *Rouellia* sp. (*Acanthaceae*) flowers in India, in 2008 and it is different from *C. haemulonii* by a 14% nucleotide sequence divergence.³⁹ Its role in human pathology is yet to be discovered.

Virulence

Because of the high genetic diversity exerted by *C. auris*, there are conflicting reports about its

Figure 1. Countries with reported cases of *C. auris* infections¹³⁻²⁷

virulence. The virulence-associated genes in *C. auris* encode predominantly hydrolases, mannosyl transferases, hemolysins, oxidoreductases, oligopeptide transporters, aspartyl-secreted proteases (Saps), lipases, phospholipases. The lytic enzymes (lipases and proteinases) are produced in a strain-dependent manner, and the level of Saps is similar to those of *C. albicans*, and even more, highly expressed even at 42°C, ensuring pathogenicity at high temperatures.^{12,40}

However, the genes encoding adhesins and integrins seem to be poorly represented. In terms of biofilm formation, *C. auris* has 686 biofilm-related proteins (ribosomal proteins, transporters, several enzymes, transcription factors). The biofilms are composed mainly of yeast cells, engulfed in a limited amount of extracellular matrix. Mannosyl transferases are known for maintaining the cell wall architecture in *C. albicans*, and also for influencing the recognition of the fungus by the immune system, and for facilitating the adherence to the host cells. Moreover, because it possesses transporters that

act like efflux pumps, this might explain its resistance to different antifungal drugs.^{7,24,40,41}

C. auris express a greater ability to form biofilms while compared with species from the *C. haemulonii* complex⁴² and the biofilm eradication concentration (MBEC) of antifungal agents proved to be 512-fold higher than the minimal inhibitory concentration (MIC), proving that sessile cells exhibit increased resistance to antifungal drugs compared with planktonic cells.⁴³

Immune response

Neutrophils, key cells for the control of invasive *Candida* infections seem to fail to release neutrophil extracellular traps (NETs) or to phagocytose *C. auris* cells. This impaired innate immune response might explain the high mortality rates associated with *C. auris* infections, but the underlying mechanisms that can explain this phenomenon are still incompletely elucidated.⁴⁴ Also, while compared with other *Candida* spp., *C. auris* proved to have a unique stress resistance profile: it has a high tolerance to

cationic stress and it is less resistant to the superoxide-generating drug menadione and the organic peroxide *tert*-butyl hydroperoxide. The stress response is important, as different niches within the human hosts are dynamic microenvironments and the ability of a microorganism to quickly respond and adapt is an important virulence trait.⁴⁵

C. auris has a cell wall rich in chitin and is differentially phagocytosed by macrophages, as compared with other *Candida* spp. and it barely stimulated the production of IL-1 β , IL-6, IL-10, and TNF α .⁴⁶ In the initial phase (4 hours), the immune response induced by *C. auris* is largely similar to the immune response induced by *C. albicans*, probably because they have a similar β -glucans structure. At 24 hours, the late transcriptomic response induced in peripheral blood mononuclear cells by *C. auris* is distinctive and is largely mediated by the structural mannoproteins.⁴⁷

Laboratory identification

From blood culture bottles, *C. auris* is usually detected after 33.9 hours of incubation. In subcultures, on Sabouraud dextrose agar, it forms white-cream-colored smooth colonies.²⁵ The growth pattern is similar to *C. albicans*, as *C. auris* can reach the stationary phase within approximately 20 hours.⁴⁰ Some strains grow in clumps, with aggregated daughter-cells after budding, and reduced pathogenicity compared to the non-aggregating variants.¹²

Because of the high risk of misdiagnosing these strains, some authors recommend the usage of PCR and electrophoretic karyotyping for etiologically diagnosing fungemia.⁴¹ Vitek 2 YST[®] (bioMérieux, France) is widely used for the diagnosis of *C. auris*, but *C. auris* is frequently misdiagnosed as *C. haemulonii*, *C. duobushaemulonii*, *C. haemulonii* var. *vulnera*, *C. lusitanae*, *C. famata*, *C. albicans* or *C. tropicalis*. When suspecting *C. auris*, follow-up cultures on cornmeal agar are recommended. If the fungus grows without hyphae or pseudohyphae (lack of candida lysin ECE1 and hyphal cell wall protein HWP1 genes which are highly expressed in *C. albicans*), the culture is most likely *C. auris*. This

presumptive identification is also flawed, as some strains of *C. auris* can form hyphae and pseudohyphae.^{12,28,48} Compared with *C. haemulonii*, *C. auris* has a higher thermotolerance (can grow at 42°C), and a higher ATP-dependent drug efflux activity,^{11,49} which translates into an increased virulence. Similarly, *C. rouelliae* can grow at 42°C, and it can assimilate galactose, l-sorbose, cellobiose, ethanol, l-arabinose, salicin, glycerol, and citrate.⁷

Kumar et al. described an affordable and rapid method for differentiating *C. auris* and *C. haemulonii* by using CHROMagar supplemented with Pal's agar: *C. auris* forms white-cream smooth colonies at 37-42°C in 24-48 hours of incubation, while *C. haemulonii* forms light-pink smooth colonies in 24-48 hours of incubation and does not grow at 42°C. However, automated identification systems are still necessary to rule out other non-*albicans* species that can form pink colonies on CHROMagar Candida medium.^{26,50} Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) analysis is a quick and accurate method that can be used to identify *C. auris*, *C. haemulonii*, *C. duobushaemulonii*, *C. haemulonii* var. *vulnera* and to test their susceptibility to antifungal drugs.²⁸

Moreover, Arendrup et al. evaluated the susceptibility of 123 isolates of *C. auris* to eight antifungal drugs and interpreted the results accordingly to EUCAST and CLSI standards, with similar results.⁵¹

Resistance

The significance of *C. auris* resides in the fact that it can be resistant to multiple classes of antifungal agents, hence the infections are associated with high rates of mortality.⁴⁰ The cases of *C. auris* infections have initially caught the attention because of its high mortality, but in a study for North India, *C. auris* was not just more commonly isolated than expected (with a prevalence of 5.3%, ranked as the fifth pathogen among the candidemia cases in Indian ICUs), but was also associated with lower mortality.⁵²

Most *C. auris* isolates show resistance to the main classes of antifungal drugs. While a reduced susceptibility to fluconazole is often reported,

amphotericin B, 5-flucytosine, and even echinocandins might sometimes fail to eradicate the infection.⁵³

The resistance of *C. auris* to azole is due to mutations in *ERG11*, *TAC1b*, *Y132F*, *K143R*, and *F126L* genes and also, due to the ABC-binding cassette (ABC) and major facilitator superfamily transporters.⁵³⁻⁵⁵ While compared with *C. albicans*, the *Erg11* amino acid sequences in *C. auris* contain nine hot spot amino acid substitutions, which may be responsible for its increased resistance to fluconazole. The mutations in *ERG11* are different in each geographic clade,⁹ but the high resistance levels cannot be fully explained only by the *ERG11* mutations. Rhodamine 6G, a substrate for the ABC type efflux pumps is significantly higher in *C. auris* strains, as compared with *N. glabrata* and *C. haemulonii*.¹¹

Gain-of-function (GOF) mutations in genes that encode zinc-cluster transcription factors are well-known mechanisms that induce azole resistance in *C. albicans* strains. A large proportion of the fluconazole-resistant *C. auris* strains has mutations in *TAC1b* gene (a gene with a high homology with *CaTAC1*, described in *C. albicans*). Mutations that occur in *TAC1b* gene have been shown to increase the resistance to azoles drugs in *C. auris* strains from different clades. Some authors showed that these mutations induce resistance by a CDR1-independent mechanism (CDR1 encodes an ABC transporter),^{55,56} while others contradicted their research by showing an increase in the CDR1 expression related to the *TAC1b* mutations.⁵⁷

The resistance to flucytosine, a nucleoside analog, might occur due to an F211I amino acid substitution in the *FUR1* gene.⁵⁸ Also, mutations in *MEC3* increase the MIC for polyene,⁵⁹ and caspofungin, a drug effective against *C. albicans* biofilms, is inactive against *C. auris* biofilms.⁶⁰

The mainstay of treatment for *C. auris* infections includes using an echinocandin such as micafungin and, if no clinical improvement is observed, amphotericin B can be prescribed.⁴⁸ Resistance to echinocandins is rare, and when it occurs it is due to mutations in the *FKS1* gene

that encoded a subunit of the β -D glucan synthase. The mutation occurs at a single amino acid, S639.^{33,54} The incidence of *C. auris* candidemia might be higher in patients who have been pre-exposed to fluconazole or echinocandin, suggesting that the exposure to antifungal agents exerts a selective pressure that favors the *C. auris* infections.⁵²

C. haemulonii has decreased susceptibility to amphotericin B and azoles.^{2,35} Echinocandins or newer triazoles may be reliable antifungal choices for invasive infections with *C. haemulonii*.³⁵ The molecular mechanisms responsible for antifungal resistance might consist of mutation in the *ERG11* gene (e.g., Y132F substitution), efflux pumps, or chromosomal duplications.^{32,33} As compared with *N. glabrata*, *C. haemulonii* showed an increase rhodamine 6G efflux activity.¹¹ *Candida pseudohaemulonii* sp. nov. showed in vitro resistance to fluconazole, miconazole, itraconazole, and amphotericin B.³¹ Clinical isolates of *C. duobushaemulonii* showed increased resistance to fluconazole, voriconazole and amphotericin B.⁶¹

Conclusions

Because of the onerous identification process, the lesser encountered *Candida* species like *C. auris* and *C. haemulonii* complex are often overlooked. Nowadays, we know that the non-*albicans* group is sufficiently genetically divergent for justifying the laboratory identification at a species level, in selected cases and rare species are emerging in various geographical regions. *C. auris* outbreaks are particularly worrisome, because of their increased resistance to antifungal drugs, and because of the lack of proper, accessible identification tools, their identification is challenging for numerous laboratories.

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CNC. All authors read and approved the final version of the manuscript.

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