Candida auris

Subjects: Infectious Diseases

Contributor: Nicholas Geremia, Pierluigi Brugnaro, Maria Solinas, Claudio Scarparo, Sandro Panese

Candida auris is considered to be an emerging fungal pathogen and is related to high mortality rates, persistent candidemia, inconsistencies in susceptibility testing results and misidentification by available commercial identification systems. Multidrug-resistant (MDR) and pandrug-resistant (PDR) strains are increasingly detected. In Europe, hospital outbreaks caused by *C. auris* have been reported in the United Kingdom (UK), Italy and Spain.

Keywords: Candida auris ; emerging fungal disease ; public health promotion

1. Introduction

From 2009, *Candida auris* has been considered to be a rising healthcare emergency worldwide. *C. auris* infections are related to high mortality rates, persistent candidemia, inconsistencies in susceptibility testing results and misidentification by available commercial identification systems. All this must be considered alongside a high risk of treatment failure, which complicates its management [1].

In 2009, *C. auris* was initially found in Japan [2][3]. However, a retrospective review of the *Candida* strain found *C. auris* in South Korea in 1996 [4]. Studies have suggested that *C. auris* emerged simultaneously and independently in four global regions (South Asia, East Asia, Africa and South America; also named clades I, II, III and IV, respectively). These four clades are genetically distinct [5]. Most recently, a new potential V clade was identified that was isolated from Iran [6]. In the last few years, *C. auris* infections have increased worldwide [1][7]. In many parts of Africa and Asia, *C. auris* is now considered to be endemic [8]. In addition, several outbreaks have been reported in European countries such as the United Kingdom (UK), Spain and Italy [1][8][9][10].

Multidrug-resistant (MDR) and pandrug-resistant (PDR) *C. auris* strains are increasingly detected worldwide. The most frequent resistance is to fluconazole (FLC), followed by amphotericin B (AMB) and voriconazole (VRC). Echinocandin remains the treatment of choice, but resistance can also affect this class of antifungal drugs [1][11].

2. Identification

C. auris was first detected in the external ear canal of a 70-year-old Japanese woman. A 26S ribosomal DNA (rDNA) D1/D2 domain analysis, 18S internal transcribed spacer (ITS) rDNA region sequences and chemotaxonomic studies showed that the newly discovered *Candida* species (spp.) had a close phylogenetic relationship to the *Metschnikowiaceae* clade, particularly with *C. ruelliae* and *C. haemulonii* [3]. A retrospective study on historical Korean isolates revealed that *C. auris* strains were initially misidentified as *C. haemulonii* [12]. A genetic analysis based on ITS 1/2 and D1/D2 sequences showed that *C. auris* belongs to the *Metschnikowiaceae* family within the *Candida*/*Clavispora* clade such as *C. albicans*, *C. tropicalis*, *C. haemulonii* and *C. lusitaniae* [3].

The misidentification of *C. auris* as another yeast species using conventional phenotypic and biochemical methods can be common (**Table 1**) [2][3]. The thermal tolerance property of growth at temperatures up to 42 °C on CHROMagarTM Candida Plus (CHROMagar, France) has been used to differentiate *C. auris* from other *Candida* spp. [13][14]. The diagnosis of *C. auris* infections includes biochemical-based tests such as analytical profile index strips, VITEK 2, BD Phoenix yeast identification and MicroScan. Nevertheless, these tests lack a comprehensive database for yeast identification [13]. **Figure 1** shows *C. auris* identification.

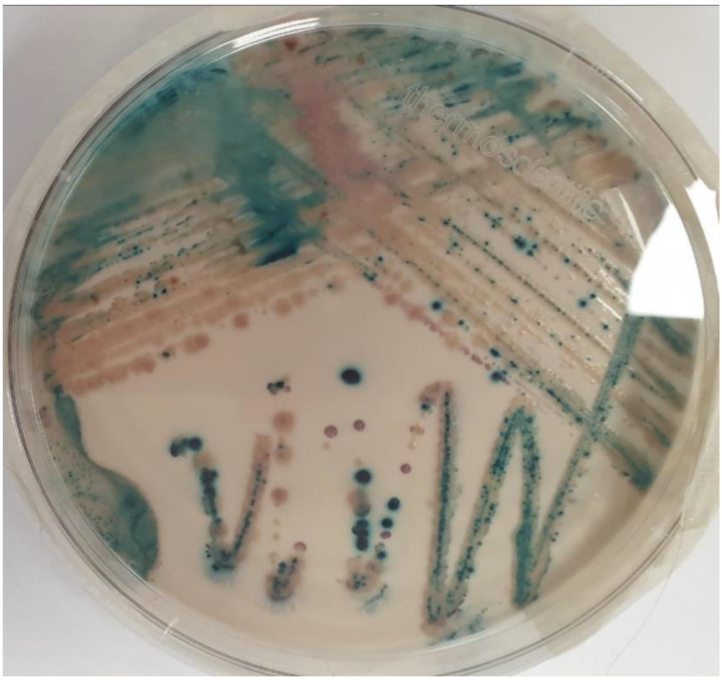

Figure 1. *Candida* isolates from Brilliance™ Candida Agar Base (Thermo Fisher Scientific™, Waltham, MA, USA). *C. auris* (light blue with blue halo colonies), *C. krusei* (pink and fuzzy colonies) and *C. albicans* (green–blue colonies).

The identification of yeasts by matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) analyses has the potential to quickly identify *C. auris*. However, initial attempts to identify *C. auris* using this tool were unsuccessful. Following this *C. auris* isolation across many countries, MALDI-TOF MS added isolates from all four major clades to their FDA-cleared databases [12][13]. In addition, DNA sequencing techniques such as polymerase chain reaction (PCR) have also been used for the identification of *C. auris*. For example, the PCR amplification of the D1/D2 region and ITS rDNA can be used to differentiate the principal phylogeographic clades of this species, but a further delineation of local hospital clusters required higher resolution methods, including amplified fragment length polymorphism (AFLP) and whole genome sequencing (WGS) analyses [14].

3. Virulence Factors

C. auris can express several virulence factors, including saps and lipases [15]. However, *C. auris* is less virulent than *C. albicans*. That characteristic was shown in murine and invertebrate *G. mellonella* infection models. In murine models, it was demonstrated that *C. auris* was much more virulent than *C. glabrata* and *C. haemulonii* [2][16]. This difference, compared with *C. albicans*, depended on the inability of *C. auris* to develop virulence factors such as hyphae or pseudohyphae, which play a critical role in tissue invasion [14]. Furthermore, *C. auris* is a haploid yeast whereas natural *C. albicans* isolates are diploid. This could have an essential role in the intrinsically low virulence of *C. auris*. In FLC-induced haploids, the *C. albicans* strain reduced their virulence compared with the diploid form [2][17]. The filamentous cells of *C. auris* are poorly implicated in its virulence during systemic infections, but could play a role in skin and environmental surface colonization [2].

4. Antifungal Resistance

FLC and echinocandins are the most used antifungal drugs to treat candidemia. Unfortunately, FLC (or other azole) resistance is common. A recent meta-analysis from Sekyere et al. showed that the most frequent resistance was to FLC (44.29%), followed by AMB (15.46%), VRC (12.67%), caspofungin (CAS) (3.48%), flucytosine (FC) (1.95%), itraconazole (ITZ) (1.81%), isavuconazole (ISA) (1.53%), posaconazole (POS) (1.39%), anidulafungin (AFG) (1.25%) and micafungin (MFG) (1.25%) [11][12]. MDR *C. auris* strains have been reported in several cases, showing resistance phenotypes to FLC and AMB [18]. Resistance to echinocandins is not so frequent. Chen et al. found that the resistance rates to CAS, MFG and AFG were 12.1%, 0.8% and 1.1%, respectively. However, almost all isolates resistant to CAS were from India (23.6%) [19].

The molecular mechanism for azole resistance in *C. auris* is mainly related to alterations in the lanosterol demethylase enzyme, which is encoded by the ERG11 gene. *C. auris* can also encode ATP-binding cassette (ABC) and major facilitator superfamily (MFS) efflux pumps, which are essential mechanisms of antifungal resistance, especially during the initial stages of biofilm development. When resistance to echinocandins; occur, it is due to mutations in FKS genes that

encode a subunit of the β-D-glucan synthase. Moreover, changes to the cell membrane sterol and/or a given point mutation are potential mechanisms of AMB resistance [13][20].

Unfortunately, no antifungal susceptibility breakpoints for *C. auris* are currently standardized for the Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST). Therefore, the Centers for Disease Control and Prevention (CDC) defined a *C. auris*-specific antifungal susceptibility interpretation based on a close phylogenetic relationship to other *Candida* spp. The correlation between the microbiologic breakpoints and clinical outcomes is not known. The current breakpoints are summarized in **Table 1** [21].

Table 1. *C. auris*-specific antifungal susceptibility interpretation according to CDC [21].

Antifungal	MIC	Interpretation
Fluconazole	**≥32**	**Isolates with MIC ≥ 32 were shown to have a mutation of the Erg11 gene**
Voriconazole	**NA**	**Consider using fluconazole susceptibility as a surrogate for other azoles. Occasionally, isolates that are resistant to fluconazole may respond to voriconazole**
Amphotericin B	**≥2**	**Isolates with a MIC of ≥2 should be considered to be resistant**
Anidulafungin	**≥4**	**Breakpoints are based on the distribution of echinocandin MICs of approximately 100 isolates from diverse geographic locations**
Caspofungin	**≥2**	
Voriconazole	**≥4**	

5. Risk Factors and Mortality Rates

Most *C. auris* cases have escalated within the last few years. The reported isolates were mainly isolated in males (64.76%). No reason has been given for the *C. auris* distribution by gender. Local variables and the health diversity of countries could play a role in the increase in *C. auris* male case rates. Patients with *C. auris* infections frequently presented several other underlying health comorbidities such as diabetes, sepsis, pulmonary diseases, bacterial pneumonia, renal diseases, transplants, immunosuppression, solid tumors, cardiovascular diseases, chronic otitis media and liver diseases [1].

The risk factors for *C. auris* infections are similar to other *Candida* spp. generic risk factors. Most frequently, infections occur in hospitalized patients, especially those admitted to the intensive care unit (ICU) or those who underwent surgery in the previous 30 days. Moreover, central venous catheters, hemodialysis catheters and permanent urinary catheters could be related to invasive *C. auris* infections [1][20][22].

Even with an appropriate antifungal treatment, invasive candidiasis has a mortality rate of up to 30–40%. Currently, there is limited information on specific *C. auris*-case fatality rates. However, several authors have suggested that the mortality rate of invasive *C. auris* infections is comparatively higher than that of *Candida* spp. For *C. auris*, the crude mortality rate was estimated to be 30% to 72% [1][18][23][24].

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