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Candida auris: the new fungal threat

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SUMMARY

Candida auris is an emergent fungal pathogen of particular concern. Since its first identification in Japan in 2009, it rapidly spread all over the world, including Italy. The main concern related to the diffusion of this fungus is its antifungal resistance. It is speculated that about 90% of isolates are resistant to fluconazole, 30% to amphotericin B and 5% to echinocandins; furthermore, some cases of pan-antifungal resistance have been described. Critically ill patients are particularly at risk of being colonized by this yeast and person-to-person transmission may generate hospital outbreaks. In fact, *C. auris* can survive on inanimate surfaces for a long time and commonly used disinfectants are not effective. Additionally, devices such as central venous catheters (CVCs) or urinary catheters are particularly at risk of being colonized, representing a possible source for the development of bloodstream infections caused by *C. auris*, which carries a high mortality rate. Given its capability to spread in the hospital setting and the limited therapeutic options it is of outmost importance to promptly identify *C. auris*. However, commonly used biochemical tests frequently misidentify *C. auris* as other *Candida* species; currently the best identification techniques are MALDI-TOF and molecular methods, such as PCR of the ITS and D1/D2 regions of the 28s ribosomal DNA. Whole genome sequencing remains the gold standard for the phylogenetic investigation of outbreaks. The majority of cases of colonization by *C. albicans* will not cause bloodstream infections and contact precautions and surveillance of contacts will be sufficient. When invasive fungal infections occur, echinocandins still represent the first therapeutic choice. A combination therapy or the use of novel antifungals (such as ibrexafungerp or fosmanogepix) would be required for echinocandin resistant strains. In conclusion, *C. auris* represents a growing threat because of its antifungal resistance characteristics, its difficult identification and its easy spread from person to person. The aim of this mini-review is to summarize the main aspects concerning this pathogen.

Key words: Candida auris, epidemiology, antifungal resistance, novel therapies.

INTRODUCTION

On October 2022 World Health Organization published the fungal priority pathogen list. One of the fungi in the critical priority group is *Candida auris*, a pathogen that emerged in recent years. It was first isolated by Satoh et al. in 2009 from the external auricular canal of a Japanese patient and since then several other reports from all over the world has been published and today *C. auris* has been isolated from all continents except Antarctica. Circulating strains of *C. auris* has been categorized into five clades: I (southern Asia), II (eastern Asia), III (Africa), IV (south America), and V (Iran) [1, 2].

The origin of this pathogen is yet unknown: some hypothesize that global warming may have played a role in the emergence of this species and then birds, in which *C. auris* has an ideal habitat given their high body temperature, could have spread this fungus all over the world [3].

C. auris infections, represented primarily by candidemia, usually follow colonization of the skin of

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patients, which may also lead to person-to-person transmission in the hospital setting. This ability to spread from a patient to another together with the ability to survive on inanimate surfaces makes *C. auris* responsible of hospital outbreaks, especially in intensive care units (ICU) [4, 5].
Another important concern is that *C. auris* frequently manifests resistance to common antifungals agents, with some cases of pan-drug resistance [6].
These problems lead to the necessity to quickly identify *C. auris* to prevent its diffusion in the hospital ward and to begin a surveillance of other patients. However, using common diagnostic techniques, *C. auris* can be often misidentified with other *Candida* species [7].
C. auris is an urgent health threat due to its global and rapid emergence, challenging microbiological identification, high mortality, and persistent transmissions. The aim of this mini-review is to summarize the main aspects concerning this pathogen.

Origin and diffusion of Candida auris
Since its first identification, *C. auris* rapidly spread to all continents almost simultaneously. There could be several explanation to this phenomenon. One hypothesis is that *C. auris* was always been present but it was not identified. This is supported by some retrospective analyses of *Candida* collections: for example, some isolates of *Candida haemulonii* in the series of Kim et al. were retrospectively identified as *C. auris* [8]. However, other studies didn't confirm this observation and in the SENTRY antifungal surveillance program, which covered twenty years and collected isolates from 39 different countries, *C. auris* was not isolated until 2009 [9].
Another possible explanation of the sudden diffusion of *C. auris* is the extensive use of antifungals in the hospitals and in the agricultural field which could have driven the emergence of this yeast that frequently exhibits resistance to commonly used antifungals. A confirmation of this can be seen in the emergence of other species of fungi with antifungal resistance, such as the shift toward non-*albicans Candida* species and azole-resistant *Aspergillus fumigatus.* In particular, the rising number of cases of infections caused by fluconazole-resistant *C. parapsilosis* and by echinocandin-resistant *C. glabrata* represents a great concern [10].
Lastly, another possibility is that global warming may have helped the diffusion of *C. auris* given its ability of growth at high temperatures. Then *C. auris* could have spread from its original habitat to all over the world carried by migratory birds. In fact, birds have a greater body temperature than other animals, representing an ideal vector for growth and diffusion of this yeast [3].
In Europe it was first detected in the United Kingdom and in Spain, but soon it was isolated in other countries, including Italy [5]. According to ECDC, from 2013 to 2021 cases of *C. auris* were reported in 15 different countries with a nearly doubled number of cases observed between 2020 and 2021.
In the years 2019-2021, 5 European countries (Denmark, France, Germany, Greece, and Italy) reported 14 outbreaks of *C. auris*, defined as more than 2 cases with an epidemiological link [11].
The first isolation of *C. auris* in Italy occurred in 2019 in Genoa [12]. Since then, this yeast was isolated also in other regions (Piedmont, Emilia-Romagna and Veneto) [13]. Between July 2019 and December 2022, a total of 361 cases were detected in Italy, the majority of which were located in Liguria region. Interestingly, about one third of the patients were SARS-CoV-2 positive and it could be assumed that the COVID-19 pandemic played a role in the spread of this fungus [14]. A possible explanation could be the overload of the health system with a great number of patients that required admission to ICUs, where most of the cases of *C. auris* were found. Other possible factors that could explain the association between the COVID-19 pandemic and the rise of cases of *C. auris* are the frequent use (and misuse) of antibiotics in such patients, the increased length of stay in hospitals, the overcrowding in ICU units, the need of mechanical ventilation and the use of central venous catheters (CVCs) or other devices which could be colonized by *C. auris,* leading to the development of candidemia.

Characteristics of Candida auris
Species belonging to the genus *Candida* are between the main agents of bloodstream infections (BSIs) and a mortality exceeding 35% has been described in several studies. The mortality of systemic infections caused by C. *auris* does not differ from that described for infections caused by other *Candida* species [15]. All the species be-

longing to this genus expresses several virulence factors which are responsible of the pathogenicity of these fungi in the human host. Some of the main virulence factors include the synthesis of enzymes, such as phospholipases and aspartic-proteases, and the possibility to express a phenotypic switch to a filamentous phenotype. Although virulence factors of *C. auris* are not yet completely understood, some experimental studies show that the pathogenetic factors of this yeast are like that of *Candida albicans* [16].

One of the greatest challenge in clinical practice is the ability of *C. auris* to form biofilm thanks to the production of adhesins [17]. The biofilm production allows *C. auris* to colonize the skin of the patients, particularly at axillary and groin levels, and a great number of health devices, such as urinary catheters or CVCs. Colonization of skin or other body sites proved to be a risk factor for the development of *C. auris* BSIs [4]. Also, the presence of CVCs is reported to be linked to an increased probability of candidemia due to *C. auris* and it is described as one of the main source of infection in several studies [18].

Furthermore, biofilm enables *C. auris* to persist also in the hospital environment for a long period of time (i.e.: the UK outbreak of *C. auris* originating from axillary thermometers colonized from this yeast) [19]. Additionally, biofilm produced by *C. auris* is able to resist to commonly used disinfectants, including quaternary ammonia compounds; for this reason currently CDC recommends the use of chemical agents that are also effective against *Clostridioides difficile* spores to prevent transmission of *C. auris* [17].

Lastly, biofilm can result in a decreased susceptibility to antifungals agents because of low penetration and sequestration of the antifungal in the matrix. However, *C. auris* manifests resistance to antifungals even in the planktonic state with the highest rates of multidrug resistance being described in clade I isolates from United Kingdom, India and Pakistan, with around 97% isolates resistant to fluconazole and 50% resistant to polyenes [20]. Triazole resistance is generally linked to point mutations in the gene ERG11, which codes for lanosterol demethylase enzyme being responsible for the production of ergosterol. The precise mechanism of resistance to amphotericin B in not known, but it is speculated that a reduction in the ergosterol composition of the membrane could be implicated. Less frequently, mutations in the gene FKS1 (which codes for 1,3-beta-D-glucane synthase) have been shown to be responsible for echinocandin resistance [21]. Multiple resistance mechanisms can be also expressed in the same strain, thus yielding a pan-resistant isolate. These characteristics together with the ability to spread from person to person in the hospital setting makes *C. auris* a terrible enemy to face, with the need to identify it promptly and with limited therapeutic options.

Identification of Candida auris

The correct identification of *C. auris* is of outmost importance because of the need to establish contact precautions and to start a surveillance within a given ward/hospital. However, serum biomarker of fungal infection such as 1,3-beta-D-glucane show a lower sensitivity in identifying BSI caused by *C. auris* compared to those caused by *C. albicans* and common laboratory techniques frequently misidentify *C. auris* with other *Candida* species thus leading to a delay in the application of infection prevention strategies [22].

Culture alone cannot be used to distinguish between *C. auris* and other *Candida* species, even with the recently developed formulations of chromogenic media, such as CHROMagar *Candida* Plus (CHROMagar, France) [23]. On this media, *C. auris* forms white colonies with blue-green halos, more evident after 72 hours of incubation at 35°C than after 48 hours. However, the only colour of the colonies cannot allow to distinguish between *C. auris* and other closely related species, such as *C. haemulonii*, *C. pseudohaemulonii* and *C. duobushaemulonii*.

Also, other commonly utilized biochemical laboratory techniques, such as VITEK (bioMérieux, Marcy l'Étoile, France) and API 20C AUX (bioMérieux), frequently can misidentify *C. auris* with other species. This misidentification may be related to overlapping biochemical profiles between *C. auris* and other yeasts. In Table 1 are reported some of the possible species that could be confounded with *C. auris* [24].

Therefore, cultural and biochemical methods are not precise enough to identify *C. auris*, yielding a risk of a consistent delay in the establishment of infection control practices. On the other hand, Matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS)

Table 1 - Possible errors in the identification of Candida auris using common biochemical methods.

VITEK MS	*C. albicans*
	C. lusitaniae
	C. haemulonii
VITEK 2 YST	*C. haemulonii*
	C. duobushaemulonii
API 20C AUX	*Rhodotorula glutinis*
	C. sake
	Saccharomyces cerevisiae
	Saccharomyces kluyveri
API ID 32 C	*C. intermedia*
	C. sake
	Saccharomyces kluyveri
BD Phoenix	*C. haemulonii*
	C. catenulate
MicroScan	*C. famata*
	C. guillermondii
	C. lusitaniae
	C. parapsilosis
RapID Yeast Plus	*C. parapsilosis*

can identify *C. auris* in a more accurate way once the specific spectra have been included in the databases [25]. MicrobeNet, a database provided by CDC, includes *C. auris* spectra and is freely available for the supplementation of the FDA-cleared Bruker Biotyper (Bruker-Daltonics).
Other molecular methods, such as multilocus sequence typing and whole genome sequencing, can be used to identify *C. auris*. A set of genetic loci that is reported to be highly discriminatory between *C. auris* and *C. haemulonii* can be amplified via conventional PCR methods. These genes include the internal transcribe spacer (ITS) and the D1/D2 region of the 28s ribosomal DNA. Many commercial tests with a rapid turnaround time have been developed. These assays proved to be highly sensitive and specific for the identification of *C. auris*. On the contrary, whole genome sequencing remains the gold standard for the determination of the phylogenetic analysis of the isolates to investigate nosocomial outbreaks [7, 24]. The main disadvantage of these methods is their high cost, so it would be useful the development of less expensive kit that would allow the correct identification of *Candida* spp. isolates in all kind of samples in the routine practice, enabling infection surveillance strategies.

Susceptibility testing and therapeutic options
Both the Clinical Laboratory Standard Institute (CLSI) and the European Committee for Antimicrobial Susceptibility Testing (EUCAST) provide indication on the broth microdilution method that allow to identify antifungal MICs for yeasts. However, none of these organizations has set yet an interpretative clinical breakpoint for isolates of *C. auris*. Tentative breakpoints for antifungal resistance have been provided by CDC using the CLSI method: fluconazole resistance is defined by an MIC ≥32 µg/ml (CDC also suggest to use fluconazole susceptibility as a surrogate for susceptibility assessment of others triazoles, although occasionally isolates resistant to fluconazole may respond to voriconazole), while resistances to amphotericin B, anidulafungin, caspofungin and micafungin are defined by MICs ≥2 µg/ml, ≥4 µg/ml, ≥2 µg/ml and ≥4 µg/ml, respectively.
Using these tentative breakpoints, about 90% of *C. auris* isolates are resistant to fluconazole, 30% to amphotericin B and 5% to echinocandins [20]. Given the lower rates of resistance expected, echinocandins remains the mainstay of therapy according to CDC indication [26]. However, the site of infection may represent a barrier for an effective treatment with echinocandins, for example in urinary tract infections. In these cases, amphotericin B with or without 5-fluorocytosine may be an option.
However, some pan-antifungal resistant *C. auris* has been reported [6]. Little in vitro studies are available to guide therapeutic decisions in such cases, some of them describing an efficacy of the combination therapy of an echinocandin plus voriconazole [27], but reports of the efficacy of such combination therapy are scarce.
New antifungal agents are currently being evaluated for the treatment of invasive candidiasis caused by *C. auris*. Rezafungin is a novel echinocandin characterized by a long half-life that can be administer once weekly instead of the daily administration required by other member of this class. Some reports show promising in vitro activity of rezafungin against *C. auris* [28], however the main drowback of this drug is that being an echinocandin makes it ineffective against isolates presenting FKS1 mutations.
A new antifungal agent that proved efficacy even

against *C. auris* with echinocandin resistance is ibrexafungerp [29]. In fact, even if this drug inhibits the 1,3-β-D-glucan synthase, it is structurally different from standard echinocandins and retain activity even against isolates with FKS1 mutations. An open label study evaluating the efficacy of ibrexafungerp for infection caused by *C. auris* is ongoing.
Lastly, fosmanogepix (which is a prodrug of its active moiety, manogepix) belongs to a new class of antifungals: it inhibits Gwt1, an enzyme involved in the synthesis of glycosylphosfatidylinositol, required for the anchorage of mannoproteins to the cell wall and membrane, altering their integrity and slowing fungal growth. Several reports showed its potent in vitro efficacy against *C. auris* in a recent phase II study (MIC range 0.008 to 0.015 µg/ml) [30].
However, there is a paucity of report that assess the efficacy of this novel antifungals and the majority of evidences come from in vitro studies. For this reason further real life studies and randomized control trial would be required to define what is the best treatment option for *C. auris* infections.

CONCLUSIONS

Given its antifungal resistance profile and its ability to generate hospital outbreaks, *C. auris* represents an emerging global health threat.
In many cases, colonization will not result in the development of invasive fungal disease, so that the only contact surveillance would be sufficient. However, invasive candidiasis, such as BSIs, necessitate a prompt diagnosis and adequate antifungal treatment. Diagnosis at the species level is still challenging in many laboratories and accurate and easy-to-use microbiological tools should be implemented. When invasive fungal infections occur, echinocandins still represent the first therapeutic choice. However, limited therapeutic options exists for echinocandin resistant strains. In such cases, a combination therapy or the use of novel antifungals (such as ibrexafungerp or fosmanogepix) would be required.

Conflict of interest
The authors declare no conflict of interest.

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