

## Candida auris: a literature review

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### Abstract

**Background:** Emerging pathogen *Candida auris* has been associated with nosocomial outbreaks demonstrating widespread antifungal resistance. This microorganism is associated with systemic infections with a high mortality rate, and studies that contribute to a better understanding of this agent are important.

**Objectives:** The present article aimed to carry out bibliographic research on *Candida auris*. Therefore, a literature search was carried out between January 2018 and January 2022, applying the following: *C. auris*; *Candida auris* and Infection, in Portuguese, English and Spanish. This review considers the available literature on *C. auris* and highlights key unknowns, which will guide future work in this field.

**Results:** The data collected in the present review allowed us to divide the theme into topics on Pathophysiology, Epidemiology/clinical and drug resistance mechanisms, so that the understanding of *Candida auris* can be better detailed and understood.

**Conclusion:** The predilection of *C. auris* by the most vulnerable and immunosuppressed patients or with comorbidities and with the potential to cause invasive and bloodstream infections with a propensity to cause outbreaks and concerns regarding resistance to antifungal agents, the fungus *Candida auris*, is of increasing clinical relevance. The increase in the number of detected cases and the occurrence of strains with multiple drug resistance prove to be worrisome, and applied research is essential to contribute to the knowledge of this strain and effective therapy.

**Keywords:** *Candida*; revision; resistance, *auris*.

### Background

*Candida auris* belongs to the *Saccharomycetaceae* family, which is a diploid yeast. This oval-shaped yeast multiplies by budding and, under certain conditions, produces a germ tube and forms the filamentous unit, such as hyphae or pseudohyphae (Figure 01). This species was initially reported in 2009 in Japan, being collected in the ear canal of a patient, and is considered an emerging pathogen (Belkin et al., 2017; Jeffery et al., 2018).

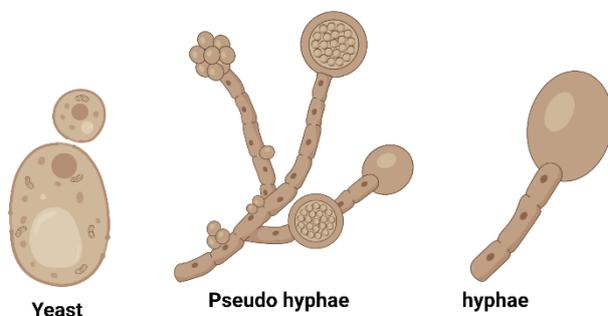


Figure 01: Structure of *Candida auris* (Yeast, Pseudo Hypha; Hypha). Source: Own authorship. Created with: [www.biorender.com](http://www.biorender.com).

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*C. auris*, unlike other *Candida* species, is easy to spread in different environments, enabling nosocomial outbreaks. Furthermore, it can persist in areas of the human body such as inanimate objects for long periods. When the conditions of the environment/human body become favourable, proliferation, tissue invasion and dissemination occur, triggering systemic candidiasis (Heath et al., 2019; Pappas et al., 2018). This fungus has presented multiple resistance to antifungal agents and difficulties in its diagnosis, facts that complicate the treatment of infections and control of their dissemination.

One theory for the growth of unconventional fungal infections, such as that caused by *C. auris*, would be driven by the inordinate use of antifungals such as fluconazole. In this sense, invasive candidiasis caused by non-albicans *Candida* species has become a clinical challenge, given the emergence of multidrug-resistant strains (Ruiz & Lorenz, 2021).

As for the initial body region of colonization, *C. auris* prefers the skin, unlike other species, which had tropism for the intestine. When disturbances of the mucosal microbiota and/or weakening of the host's immunity occur, a transition from commensalism to opportunism is observed, and there may be dissemination to internal organs (liver, brain, lungs, bones, kidneys and urinary tract) through the bloodstream - candidemia (Jeffery et al., 2018; Rhodes et al., 2019; Viera & Santos, 2021; Durante et al., 2018).

Among the factors that may favor this spread are antibiotic-induced loss of the local microbiota, skin lesions induced by cytotoxic chemotherapy, infectious processes and iatrogenic immunosuppression (Jeffery et al., 2018; De Groot et al., 2021). Because it is an emerging strain and has a high mortality rate for candidemia, it is important to produce technical review material on the subject. In this sense, the present article aimed to discuss the different aspects of *C. auris* presented in the scientific literature through bibliographic research involving.

## **Methods**

The present study was characterized as a bibliographic study, with a search in the literature of the Scielo and Science direct databases, considering the period from January 2018 to January 2022, with the application of the described: *C. auris*; *Candida auris* and Infection, in Portuguese, English and Spanish. Abstracts were analyzed and used insofar as they were correlated with the topic, and duplicates were discarded.

## **Results**

### **Pathophysiology**

*Candida auris* has high transmissibility and a high level of resistance to antifungal agents, which differentiates it from other species and can remain on inanimate surfaces for long periods, and can be transmitted to the host by contact. On the body surface, in the form of yeast, the initial adhesion will occur mediated by fungal cell wall glycoproteins and adhesins, which interact with specific ligands of the host cell (De Groot et al., 2021; Chow et al., 2019).

This interaction can be influenced by temperature, pH, nutrients, secretory IgA and cellular surface hydrophobicity. When disturbances of the mucosal microbiota and/or weakening of the host's immunity occur, the yeast proliferates and establishes local colonization (De Groot et al., 2021; Chow et al., 2019; Viera & Santos, 2021; Cavalheiro; Teixeira, 2018).

Subsequently, the presence of secretion of extracellular enzymes that destroy the cell membranes of the host is observed. One of these is phospholipases that use host cell membrane phospholipids as substrates. Proteinases, on the other hand, have proteolytic action by degrading collagen, keratin and peptides. These enzymes favor the formation of hyphae and invasion of host tissues (De Groot et al., 2021; Heath et al., 2019).

When reaching the blood vessels, the hyphae release yeasts into the bloodstream (CANDIDEMIA), favoring their dispersion to other organs such as the liver, spleen, kidneys, heart and brain. The invasion process can be favored by low host immunity, as in cases of cancers, AIDS,

autoimmune diseases and the prolonged use of antibiotics (Heath et al., 2019, Viera & Santos, 2021). The pathophysiology described in this topic is illustrated in Figure 02.

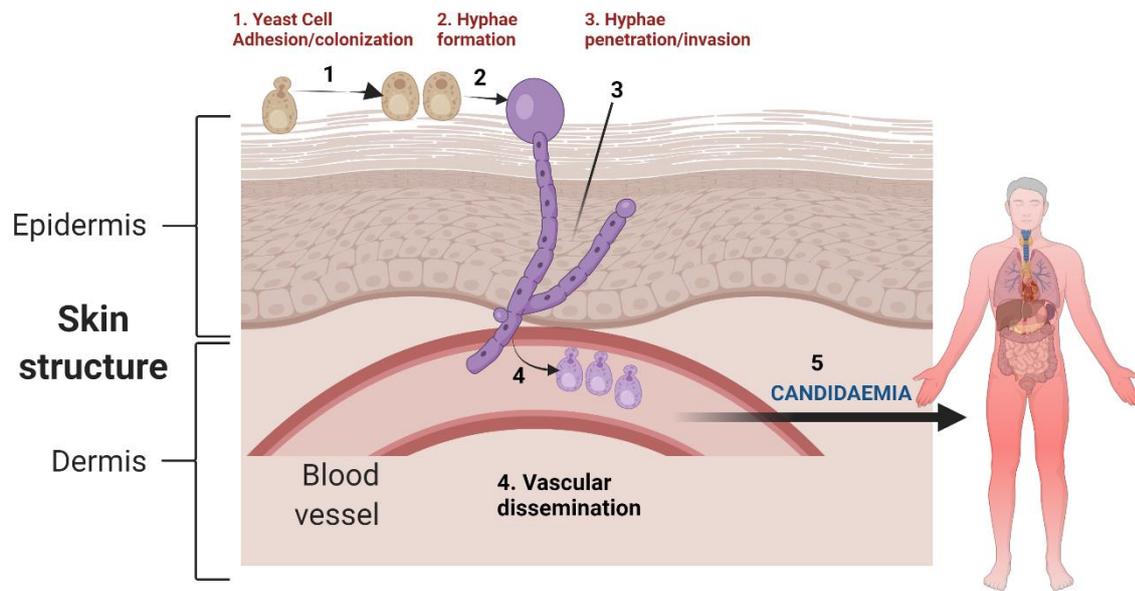


Figure 02: Pathophysiology of *Candida auris*. Source: Own authorship. Created with: [www.biorender.com](http://www.biorender.com).

The yeast emits extended filaments (hyphae) towards the deep tissues in search of more nutritious zones, this phenomenon is known as thigmotropism. In cases of abrasions or skin wounds, host invasion may be facilitated. The release of hydrolytic enzymes, as mentioned above, favors the destruction of tissues that contribute to fungal invasion and the supply of nutrients to *C. auris* (Belkin et al., 2017; Heath et al., 2019; Chow et al., 2019).

### Epidemiology and clinical

The *Candida auris* species received this name because it was initially isolated in one of the ear canals of a Japanese patient in 2009, being isolated in the following periods on several continents. This strain is classified as opportunistic, as it mainly affects immunocompromised patients or those in intensive care (Cavalheiro & Teixeira, 2018; Vieira & Santos, 2021).

Information about the patients from which *C. auris* was isolated has now been reported globally, with more than 5,000 cases worldwide in more than 47 countries, among them Brazil (18 cases), the United States (1156), Israel, Chile, Canada, Italy, Netherlands, Venezuela, Pakistan, Kenya, Kuwait, Mexico, United Kingdom and Spain (Vieira & Santos, 2021; Chow et al., 2019; Kordalewska; Perlin, 2019).

The clinical features of candidiasis are quite varied and may present as cutaneous mucosa (intertriginous candidiasis, onychomycosis, oral candidiasis and vulvovaginitis) and invasive/systemic candidiasis that spreads via the blood (candidemia). The symptoms vary according to the affected organ, such as the heart, digestive, respiratory, renal, ocular, hepatic and central nervous system (Cavalheiro & Teixeira, 2018; Vieira & Santos, 2021).

### Drug resistance mechanisms

*Candida auris* is an emerging fungus that represents a great interest and a serious threat to global health and that has shown multiple drug resistance, which has contributed to the high mortality rate among infected patients, reaching 70% in some regions. of mortality (Kordalewska & Perlin, 2019; Rhodes & Fisher, 2019). Table 01 presents the main groups of antifungals used in the treatment of invasive candidiasis, including triazoles, polyene derivatives and echinocandins.

**Table 01: Antifungals used in invasive candidemia**

Group	Mechanism of action	drugs
Polyenes	Acts on ergosterol by destabilizing the cell membrane;	Amphotericin B
Triazoles	They act by inhibiting the enzyme lanoline-14a-demethylase, interfering with the production of ergosterol; They act on the fungal cytochrome P-450, affecting fungal metabolism; They compromise the detoxication of hydrogen peroxide, producing its accumulation and toxic effect.	Fluconazole; Itraconazole; Voriconazole
Echinocandins	They act by inhibiting the synthesis of b-glucan in the fungal cell wall, compromising cell development.	casprofungin

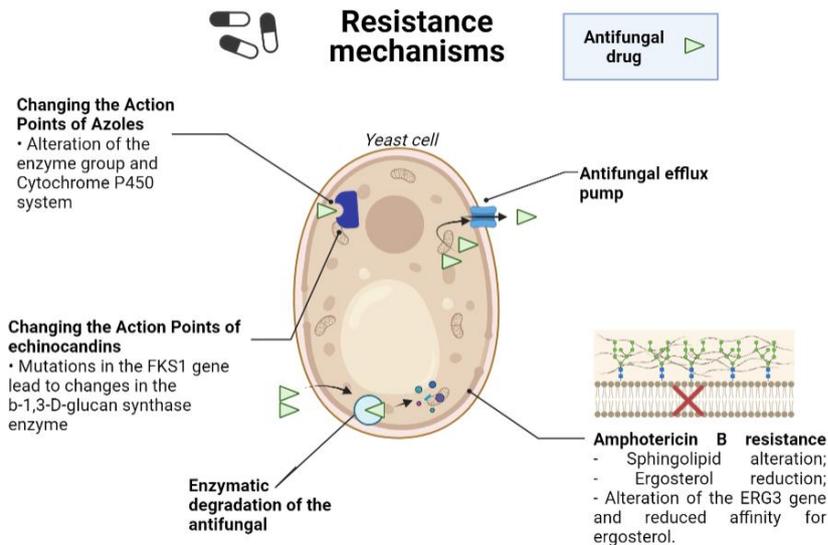
Source: Viera;Santos (2021); Kordalewska; Perlin (2019); Brunton (2018).

The main resistance factor, common to most *Candidas*, refers to the production of biofilm, which is constituted by a polymeric network, with microorganisms adhered to it. The biofilm allows the fungal colony to adhere to inert surfaces (intravascular catheters, prosthetic heart valves and joint replacements) and living tissue, contributing to persistent colonization and infections. In addition, they present greater protection to antifungals, and yeasts inside the colony (De Groot et al., 2021; Cavalheiro & Teixeira, 2018).

Another known mechanism refers to efflux pumps, which are characterized by transmembrane proteins, and their action would be associated with mutations in genes that lead to their overexpression, favoring the removal of the antifungal from the interior of the cell. In addition, several genes can lead to the production of antifungal degradation enzymes, reducing their time of intracellular activity and consequent compromised therapeutic effect, examples of affected drugs are: amphotericin B and fluconazole (De Groot et al., 2021; Vieira & Santos, 2021).

As for the mechanism of resistance to polyenes, specifically Amphotericin B, there is an alteration in the fungal membrane, with changes in the amounts of sphingolipids and a reduction in ergosterol. The latter may still have its affinity reduced to amphotericin by altering the ERG3 gene, which leads to the formation of sterols with lower binding affinity for amphotericin B (De Groot et al., 2021; Vieira & Santos, 2021).

In turn, Azos or Azolic agents are a group of synthetic fungistatic agents, with a broad spectrum of antifungal activity, which may be associated with resistance, alteration of the group of enzymes and Cytochrome P450 system, in which they act, reducing their antimicrobial activity. A fact similar to that observed for Echinocandins in which mutations in the FKS1 gene lead to alterations in the b-1,3-D-glucan-synthase enzyme, thus reducing the antifungal effect of casprofungin (De Groot et al., 2021; Vieira & Santos, 2021). These aforementioned mechanisms are illustrated in Figure 03.



**Figure 03: Antifungal resistance mechanism. Source: Own authorship. Creating with: [www.biorender.com](http://www.biorender.com).**

Concerns about resistance to triazole antifungals and amphotericin B led to the recommendation to use echinocandins as an empirical treatment before specific susceptibility test results become available, as in invasive candidiasis in some regions. However, as the use of echinocandin is becoming more widespread, the emergence of strains of *C. auris* with reduced susceptibility has been reported (Kordalewska & Perlin, 2019; Vieira & Santos, 2021).

The site of infection plays a critical role in choosing the antifungal agent for invasive infections. Echinocandins have limited penetration into several sites, including the cerebrospinal fluid, due to their high molecular weight. Therefore, other drugs should be used for the central nervous system (CNS) or renal tract infections with *C. auris*-associated infections. The use of amphotericin B preparations with the possible addition of 5-flucytosine has been suggested for urinary tract infections. For CNS infection, as with other infections by *Candida auris* species, empirical amphotericin B and 5-flucytosine have had some success, with optimization of therapy as reported by sensitivity tests (Kordalewska & Perlin, 2019; Brunton et al., 2018; Vieira & Santos, 2021).

### Discussion and conclusion

Based on the consulted literature, it was possible to verify the clinical relevance of *Candida auris*, having possibilities of contacts in inanimate objects and surfaces. In contact with susceptible people, the fungus can settle and later spread an infectious process. Therefore, health education programs aimed at personal hygiene measures, areas and objects should be reinforced, especially in health units and susceptible groups, mitigating the transmission of this agent.

Regarding the diagnostic approach and clinical epidemiology, early and accurate diagnosis of the infection is important, so that the correct medication, combined or not can be efficient, mitigating impacts on the patient's health, costs to the system of health and induction of fungal drug resistance. As stated by Jeffery-smithi et al (2018), this occurs in different parts of the world due to the lack of professional preparation and adequate infrastructure.

Thus, the implementation of prevention and control actions is urgent, encompassing decontamination and cleaning measures, investment in professional qualification on the subject, health education programs, mainly for the most vulnerable population and infrastructure for the correct diagnosis and treatment. This will favor the reduction of hospitalization time and hospital costs, damage to the patient's health, as well as the proliferation of multiresistant strains of antifungals.

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