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Infection caused by *Candida auris*: state of the art

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Abstract

Candida auris, a new emerging yeast that was isolated for the first time in 2009 in the ear canal of a Japanese patient, are increasingly been associated with outbreaks, threatening the whole world. As a highly lethal and contagious microorganism, *C. auris* can be considered a threat to public health, mainly due to the high death rate in hospital environments and ability to resist to the main first-line antifungal agents (echinocandins, azoles and polyenes), which limits its treatment and infection control. As it is a microorganism with little scientific and clinical knowledge, controlling its infection is still a great challenge. Faced with the worrying situation, this review presents important information concerning the morphology and biology of *C. auris*, as well as resistance mechanisms, updated epidemiology, virulence, immune response escape mechanisms, pathogenesis and processor involved in the pathogenesis mechanism, clinical manifestations, laboratory diagnosis and sample collection methods, molecular diagnostics, treatment of infection (main drugs used and future therapies) and prophylactic methods, with the objective not only of clarifying doubts of the scientific and medical population, but also of helping to control new outbreaks of *C. auris* worldwide.

Keywords – antifungal therapy – candidemia – emerging fungus – infectious diseases – resistance

Introduction

Fungal infections are becoming more and more frequent. The main factors that influence fungus infections increase are population rise, displacement between regions/travels, growth of human habitats and the uncontrolled use of medicines (Guarner & Brandt 2011). In short, these infections have moved from diseases caused by obscure agents rarely studied, to highly lethal and complex infections that affect the entire vulnerable population (Ostrosky-Zeichner & Sobel 2016). Among the most prevalent fungal infections, those caused by *Candida* species stand out. Single-celled yeasts of this genus are commonly found in the human microbiota (30 to 50% of

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individuals), as in the skin, lower gastro tract and genitourinary system. However, physiological disorders cause an imbalance in the body and promotes infections by these microorganisms such as superficial diseases, dermatitis, vulvovaginal candidiasis and candidemia (Evans 2010). Therefore, *Candida* species are opportunistic microorganisms, mainly affecting people with compromised immune systems, with chronic diseases (like diabetes, cirrhosis, pneumonia, kidney failure) and transplant patients. Since under these conditions the organism is limited in defending itself from attacks, *Candida* species finds a favourable environment for its development and dissemination, changing from a commensal to a pathogenic (highly lethal) condition (Mba & Nweze 2020). Another factor that has caused the increase in *Candida* ssp. infections is the COVID 19, a pandemic of global concern that has affected billions of people worldwide. Immune imbalance, increased length of stay in intensive care units, use of central venous catheters for extended times and broad-spectrum antimicrobial therapy may be the main factors of COVID 19 related to the increase in *Candida* infection (Arastehfar et al. 2020, Pemán et al. 2020). Infections in mucous membranes can affect the skin, being more common in the mouth, genitourinary system, ear, nails and skin. However, these infections can vary from superficial to deeper and systemic infections, reaching deep tissues and organs, such as kidneys, liver and brain, presenting mortality rates that can reach 60% (Sobel 2007, Das et al. 2011, Smeekens et al. 2013, Du et al. 2020). Among the most frequently isolated species, *C. albicans* is the most prevalent among fungal infections, affecting about 75% of women at least once in their lives. However, other non-*albicans* species are increasingly frequent, such as *C. glabrata*, *C. kruseis*, *C. tropicalis* and *C. parapsilosis*. Furthermore, the uncontrolled use of antifungal agents and climatic change may favor new species emergence, that are even more resistant, such as *C. auris* (Poulain 2015).

Candida auris, an emerging pathogen, was first reported in the ear canal of a Japanese patient in 2009. The Center for Disease Control and Prevention (CDC 2021) reports that clones of *C. auris* exist in different regions of the world, but they are different lineages. This new *Candida* species may have emerged due to changes in the environment and appeared simultaneously in different regions, with different characteristics, followed by subsequent transmission in hospital environments. When isolated and identified, resistance profiles after exposure to the antifungal were observed. However, its identification is hampered by the lack of scientific knowledge. Furthermore, the unknown prevalence of the population, uncertain environmental niches and unclear mechanisms of dissemination have made its control difficult (Vallabhaneni et al. 2017, Jeffery-Smith et al. 2018, De Oliveira et al. 2019). In addition to changes in the environment, the uncontrolled use of drugs such as echinocandins, amphotericin B and fluconazole may have contributed to the emergence of these new species of pathogenic fungus (Lockhart et al. 2017, Marena et al. 2022a). Studies report that this uncontrolled use is related to the widespread use of these drugs, resulting in the isolation of other even more resistant *Candida* species. In addition, other circumstances such as prolonged treatment, repeated therapy in episodes of candidiasis or candidemia, use of single doses of oral and topical azoles are related to uncontrolled use of drugs, isolation of new resistant species and increased deaths around the world (Azoulay et al. 2012, Sujana et al. 2016).

Studies report the involvement of *C. auris* infection in the blood with high morbidity mortality in the world. This gets worse every year, mainly due to its ease dissemination, survival in the environment, ability to colonize very quickly on the patient's skin and greater transmissibility within the hospital environment, leading to severe and prolonged outbreaks. In addition, an alarming feature is its ability to persist on dry and wet surfaces, floors, sinks, air conditioning, skin, beds, nasal cavities and internal tissues of infected patients, being persistent on average for 7 days in these locations. It is estimated that approximately 4 hours is the minimum contact period for the acquisition of *C. auris* contamination Furthermore, it can colonize and be expelled from the skin at a rate of approximately 10^6 cells/hours (Schelenz et al. 2016, Piedrahita et al. 2017, Osei Sekyere 2018, Abastabar et al. 2019).

Owning to the increased infections caused by *C. auris* and the difficulty of diagnosis and resistance, this review presents information that can contribute to the clinical scope with updated

information about this new microorganism and what measures should be taken for a better diagnosis and therapy in order to address this major public health concern.

Epidemiology

With the first case of *C. auris* infection in 2009, researchers conducted a retrospective case study and found that *C. auris* had already been isolated and misidentified as *C. haemulonii*, where the first case was in 1996. Two yeasts have similarities and even today they can be confused if not correctly diagnosed (Cortegiani et al. 2018, Du et al. 2020). Since then, this species has spread throughout the world. Patients with *C. auris* have risks similar to those with other *Candida* species with mortality associated with 30-70% of cases with prolonged illness, facilitating the spread in the hospital environment. Over time, many types of research have been carried out on this species, since it presents multi-resistance to the main classes of antifungal drugs, being therefore called today "Super fungus" (Chowdhary et al., 2016; Cortegiani et al., 2018).

Clade of South Asia (clade I), clade of East Asian (clade II), clade of South African (clade III), clade of South American (clade IV), and clade of Iranian (clade V) (Chow et al. 2019, Vila et al. 2020). The fifth Iranian clade was recently detected and has approximately 200,000 nucleotide polymorphisms distinct from the other clades. Its emergence in different geographic locations is still debatable, but the hypotheses include: animals as a reservoir and climate change that leads to these microorganisms modifying themselves to adapt and maintain their species (Chow et al. 2019, Forsberg et al. 2019, Ahmad & Alfouzan 2021).

Each clade of *C. auris* has variable characteristics, such as aggregative forms, virulence, resistance, growth time in culture medium and yeast size (Naicker et al. 2021). South American and South Asian clades are responsible for the greatest cause of bloodstream infections (between 47 and 76%). The South African clade can affect urinary tract infections/colonization (about 38%) (Tian et al. 2021). Clade II has isolates with a slower growth rate than the other clades. Clade I and Clade III present aggregated yeasts while Clade II species present in a non-aggregative form (Ruiz-Gaitán et al. 2018). One study reported variability between clades I, II and IV exposed to UV radiation, and the results showed that non-aggregative species were more susceptible to UV radiation when compared to aggregative species (Chatterjee et al. 2020). The virulence factor was more evident for the South American side (Clado IV), the results of infection in mice show (Forgács et al. 2020). Another study points out that Clado II is more susceptible environmental stress and treatment with azoles and other antifungals. However, almost all Clade I, III isolates and approximately half of the Clade IV isolates are resistant to azoles (Muñoz et al. 2018). Furthermore, the isolates of Clades I and IV present genomic modifications that give them the characteristic of fluconazole resistance in the transcriptional factor TAC1b that regulates the CDR1 efflux pump. Finally, approximately 7% of the isolates of Clades I, III and IV show resistance to the echinocandin group (Muñoz et al. 2018). n view of this, *C. auris* has been reported in 44 countries (Vila et al., 2020) (Fig. 1).

The United States and a part of Europe in 2015 and 2016. In 2016, the Pan American Health Organization/World Health Organization (PAHO / WHO) launched an epidemiological alert about ways to prevent and control contamination by *C. auris* (Ahmad & Alfouzan 2021).

Cases of *C. auris* in the United States have increased dramatically in recent months. According to the CDC, this increase is related to local spread within health facilities. Among the states with the most cases of infection, New York, California, Illinois and Florida stand out with 285, 245, 242 and 135 cases, respectively. In 2017, New York, California, IIIinois, and Florida had 99, 1, 11, and 2 cases of *C. auris* infection, respectively. Observe a large increase in a short time. Also, in North America, between 2012 and 2019, Canada reported 24 cases of colonization on infection caused by *C. auris* (CDC 2022a).

According to data from the European Center for Disease Prevention and Control (ECDC), 29 out of 30 EU/EEA countries diagnosed cases of *C. auris* as of May 2019. A total of 349 cases were reported and the countries with the most cases were: Spain (n = 291), England (n = 48), Germany (n = 3) and Holland (n = 2). Bloodstream infection was the most prevalent 24% of reported cases. Among the cases, 92.8% were acquired in the local region and 5.4% were considered imported

because they had a history of hospitalizations in countries with reported cases. In another 1.7% of cases, the location of the possible acquisition of the infection is unknown (Plachouras et al. 2020).

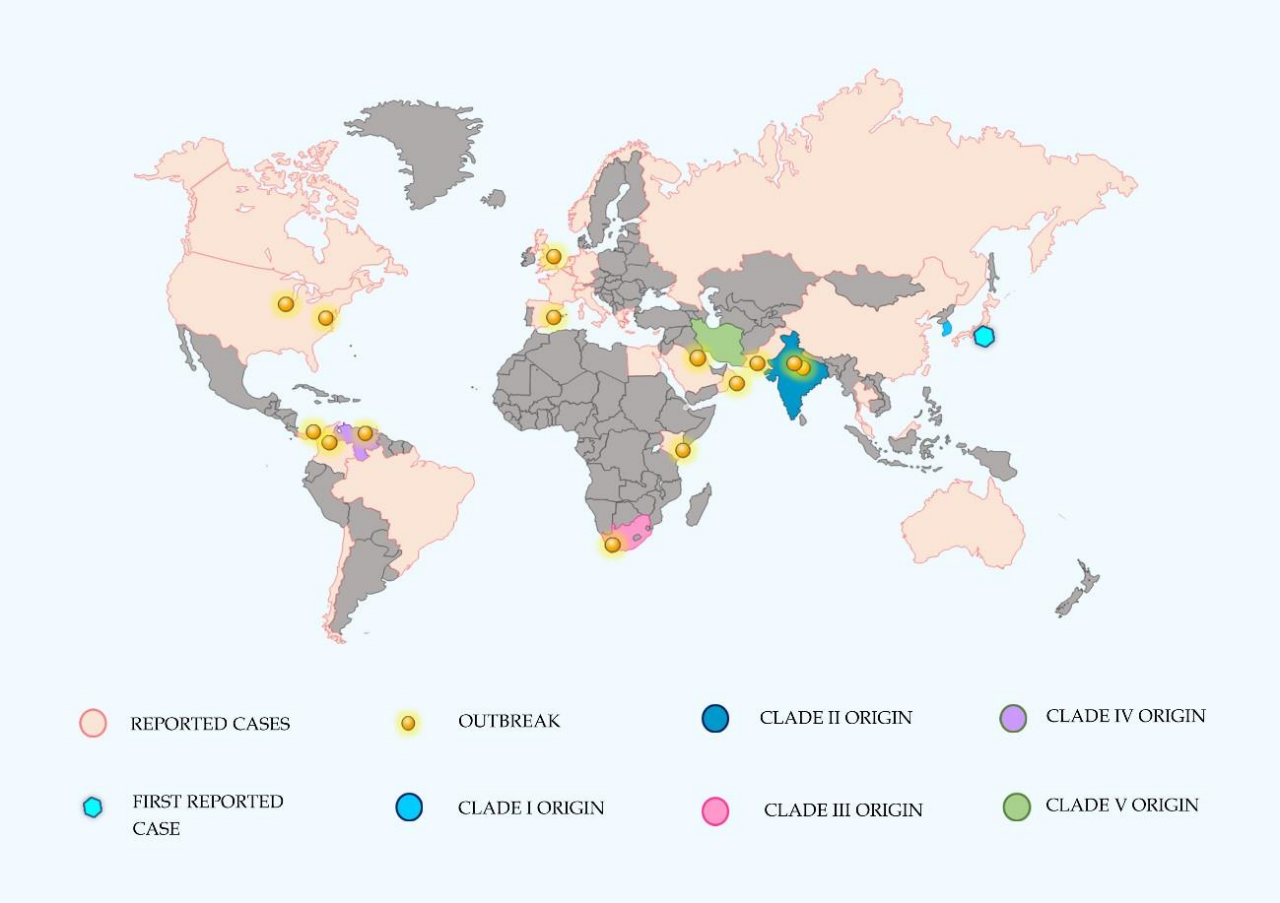

Figure 1 – Reported cases of *Candida auris* around the world. Outbreaks of *C. auris* occurred in India, South Africa, Pakistan, Japan, Spain.

On the Asian continent, the first case of *C. auris* in China was reported in 2018 in bronchoalveolar lavage (Wang et al. 2018a). As of 2021, another 38 cases have been reported in China (Tian et al. 2021). Singapore (Tan & Tan 2018) and Malaysia (Mohd Tap et al. 2018) also reported the first cases. In India, the first case was reported in 2013 (Chowdhary et al. 2013), however the numbers of reported cases increased in 2020 (15 cases in New Delhi), mainly due to the pandemic caused by COVID 19 (Chowdhary et al. 2020). In Japan, more than 300 strains were isolated from bloodstream between 2002 to 2013 (Ishikane et al. 2016). In total, 1787 cases of *C. auris* (Sekizuka et al. 2019). Kuwait, South Korea, Israel, Qatar Oman, Saudi Arabia, United Arab Emirates have also reported cases of *C. auris* (Kim et al. 2009, Alfouzan et al. 2019).

The African continent had the first reported case of *C. auris* in 2009. However, this notification was only confirmed in 2014 as the infection was initially misidentified as *C. haemulonii* (a closely related yeast). South Africa has a clade separate from other clades around the world, with thousands of distinct nucleotide polymorphisms. This feature suggests that *C. auris* African arose independently of other clades and simultaneously on other continents (Lockhart et al. 2017, Ahmad & Alfouzan 2021). By the year 2016, more than 1600 cases of *C. auris* were reported in South Africa (Ahmad & Alfouzan 2021). Between the years 2016–2017, candidemia was the third most common cause in South Africa (Naicker et al. 2021).

In Oceania, the first case of *C. auris* reported in Australia was in 2018 (Lane et al. 2020), four cases were identified in Victoria and three in Sydney (Biswas et al. 2020). However, another study reports a case reported in 2015 in a 65-year-old visiting patient from Kenya with sternal osteomyelitis (Heath et al. 2019).

The first cases caused by *C. auris* in South America occurred between 2012 and 2016, and the first outbreak reached about 18 people in Venezuela, of which 13 were pediatric patients and all had previously uninvasive medical procedures, antibiotic therapy and was in the Intensive Care Unit (ICU). Yeast was found in clinical specimens of peritoneal fluid, cerebrospinal fluid, bone, urine, in addition to being responsible for causing fungemia in a percentage of infected patients (Santos et al. 2017).

In Colombia, cases were misdiagnosed at baseline and correctly diagnosed 28 days later. There were 17 isolates from 17 patients in 6 different hospitals, most samples were obtained from blood, and the rest from peritoneal fluid, cerebrospinal fluid, bone, or urine. Patients had a catheter and risk factors for candidemia. All had been treated before the diagnosis of *C. auris* with antibiotic and antifungal therapy, but the 30-day mortality rate was 35.2% (Morales-López et al. 2017).

Brazil presented three of the most recent reported cases of *C. auris* infection, both patients were hospitalized in the same intensive care unit due to complications of COVID-19, and curiously both isolated species were related to clade I (South Asia) (De Almeida et al. 2021).

Resistence and virulence

Resistance

The emergence of new highly pathogenic and multidrug-resistant microorganisms represents a global threat, causing disorder in the fight against infectious diseases (Fisher et al. 2018). Worrying consequences are observed in the area of health and economy, causing several world organizations such as the European Commission, Center for Disease Control and Prevention (CDC), World Health Organization (WHO), among others, recognize the alarming situation of the emergence of a new resistant fungus and the need for new studies and development of surveillance and control. The European Commission, for example, created the European Antimicrobial Resistance Surveillance System (EARSS), a national surveillance organization with the aim of collecting comparable information and reliable tools with the aim of collecting variations in antimicrobial resistance over time, locating and provide the basis for evaluating the effectiveness of prevention programs and policy decisions (Bronzwaer et al. 2002).

The diagnosis of *C. auris* has increased over the years. New outbreaks of this new species have been reported in several regions and this is of extreme concern. This increase in outbreaks is related to the high resistance of this microorganism to antifungal therapy. Studies report the resistance of clinical isolates tested against all available antifungals (Spivak & Hanson 2018).

The resistance presented by *C. auris* is very worrying, mainly due to the small number of isolated clinical strains that present sensitivity to conventional therapy. Studies indicate that *C. auris* has greater antimicrobial resistance when compared to other strains of the same species. Furthermore, clinical isolates from different regions have already shown low sensitivity to first-line antifungal agents. Among the factors related to resistance, there are genetic modifications, enzymatic activity and drug inhibition, biofilm and efflux pump (Kean & Ramage 2019).

Many clinical samples of *C. auris* were isolated throughout the world and these clinical isolates showed multi-resistance to azoles, amphotericin B and echinocandins (Chowdhary et al. 2018). Some genes found in *C. auris* genome are targeted by antifungal agents, such as the lanosterol 14 α-demethylase gene (ERG11) which is targeted by azoles, the 1.3-beta-glucan synthase gene (FKS1) target of the echinocandins group and the uracil phosphoribosyl-transferase (FUR1) gene that is a target of flucytosine. Genes, such as ERG11, mutate randomly and resistant genotypes (Y132F and K143R) are selected and maintained by other generations (Healey et al. 2018). These mutations were enough to modify the antifungal target site. 54 clinical isolates of *C. auris* and treated with antifungal agents were evaluated. The results showed that *C auris* showed a resistance of 93, 54, 35, 7 and 6% to fluconazole, voriconazole, amphotericin B, echinocandins group and flucytosine, respectively (Chow et al. 2018, Muñoz et al. 2018).

Important mutations were evidenced in ERG11 in *C. auris* resistant to the azoles groups. Amino acid substitutions at position Y132 and K143 were detected in the ERG11 sequence. Studies

have shown that after heterologous overexpression of *C. auris* ERG11 -Y132 and ERG11 -K143 alleles (variant strains) in *Saccharomyces cerevisiae* showed high resistance to fluconazole and voriconazole (Lockhart et al. 2017).

Ergosterol is an abundant component present in the fungal membrane and is important in cell development. The enzyme Lanosterol 14-alpha-demethylase (encoded by the ERG11 gene) is responsible for its synthesis by converting lanosterol into ergosterol (Chaabane et al. 2019). Some antifungals, like polyenes, act by inactivating this enzyme and preventing ergosterol biosynthesis and avoiding the development of fungal cells. However, some mutations located in the ERG11 gene (between amino acids 105-165, 266-287 and 405-488) promote less sensitivity to polyenes with activity against the ergosterol-forming enzyme, making the strains resistant to therapy (Vandeputte et al. 2012). Genetic modifications in the ERG11 gene were detected in clinical isolates of Indian (Chowdhary et al. 2018) and Colombian (Healey et al. 2018) *C. auris*. Both isolated showed greater resistance to antifungal agents with enzymatic action of ergosterol inhibition (Chaabane et al. 2019).

Modifications in the FKS1 gene are related to resistance to the echinocandin group, since the mutations promote changes in the drug's binding site. Thus, the inhibition of the 1-3-β-glucan synthase enzyme does not occur (Schelenz et al. 2016). Four isolates showed resistance to panechinocandin by amino acid substitution S639F at position S645 of the FKS1 gene, which is associated with echinocandin resistance by *C. albicans* (Bidaud et al. 2018).

One of the main resistance mechanisms acquired by fungi is the efflux pump, since this resistance feature allows the microorganism to transport drugs from the interior of the cell to the outside, reducing the concentration of the drug inside the cell and the antimicrobial action, increasing fungal survival. Two types of efflux pumps can be highlighted: ATP Binding Cassette (ABC) and Major Facilitator Superfamily (MFS) transporters (Chaabane et al. 2019). Furthermore, about 2.4% of *C. auris* genes encode ABC and MFS along with other resistance factors such as iron transporters and oligopeptide transporters (Chatterjee et al. 2015).

The MFS are proteins embedded in the plasma membrane and act as H^+ anti-carriers (Vu & wasi 2018). Among the MFS superfamily there are two subfamilies of transporters, the transmembrane spans (TMS), within the TMD: DHA1 (drug: H^+ antiporter 1; 12 TMS), and the DHA2 (14 TMS) (Cannon et al. 2009). ABC are proteins found in prokaryotic and eukaryotic cells, being important exporters of multiple drugs from inside the cells to the outside, thus, an important mechanism of microbial resistance. They are promiscuous exporters and have the potential to structure a wide variety of substrates, metals, drugs, lipids and xenobiotics. Study indicated that the *C. auris* clinical isolated (CBS 10913T) recovered in 2009 from a Japanese patient presented 28 putative ABC proteins and that the presence of drugs promoted an overexpression of a wide variety of modified ABC transporters, suggesting a potential resistance mechanism of this strain (Wasi et al. 2019).

Molecular study show that the presence of proteins anchored by glycophosphatidylinositol (GPI), such as PLB3, IFF4, PGA52, PGA26, CSA1, HYR3, and PGA7 were observed in *C. auris* and which are also conserved in *C. haemulonii*, *C. duobushaemulonii* and *C. pseudohaemulonii*. These proteins were regulated by clinical strains of *C. auris* in biofilm formation and may be associated with the resistance mechanism (Muñoz et al. 2018). Zinc cluster transcription (TAC1) and protein kinases have also been identified in clinical strains of *C. auris*. These protein kinases are found in microbial stress, increasing the fungi tolerance against antifungal agents (Sharma et al. 2016).

In view of this, the speed that *C. auris* has in acquiring drug resistance are worrying. The low availability of antifungals and few therapeutic discoveries in recent years is even more alarming. All these factors contribute to the increase in outbreaks and new cases of infection caused by *C. auris*.

Virulence

Several clinical isolates from bloodstream showed high percentage of virulence and mortality

in *in vivo* models (60 to 70% mortality) (Xin et al. 2019). The continuous increase in outbreaks related to systemic infection of *C. auris* is directly related to virulence factors, since these characteristics are responsible for the dissemination, persistence, resistance and maintenance of the species in several different geographic locations at the same time. The filamentation factors, enzymatic hydrolysis, biofilms, tolerance to temperature changes, osmo-tolerance and phenotypic exchange stand out as the main virulence mechanisms present in *C. auris* (Billamboz et al. 2021).

At first, it was believed that *C. auris* did not have the ability to form filaments. However, further studies discard this information, showing that this species has a filamentous character. Initial studies also demonstrated that this potential is present in systemic infections in a mammalian host, indicating that *C. auris* did not have filaments. In addition, three different types of *C. auris* were identified: typical cells, filament-competent cells and filamentous cells (Yue et al. 2018, Billamboz et al. 2021, Garcia-Bustos et al. 2021).

Another important virulence factor in *C. auris* is its ability to survive in environments with high concentration of salt, allowing this species to grow in places such as swimming pools, sea water and even in human skin. Studies indicate the ability of *C. auris* to resist disinfectants (Satoh et al. 2009, Jackson et al. 2019). The literature informs that the high concentration of salt can promote morphological alteration in this fungus as an adaptation method to stress (Wang et al. 2018).

Most microorganisms that live on planet Earth are unable to survive at temperatures similar to those of the human organism. However, a virulence factor to be highlighted is *C. auris* survival at temperatures above 40ºC. In fact, high temperatures caused by global warming may have contributed to the emergence and evolution of *this fungus* as a microorganism capable to survive at similar temperatures to the human body, especially in stress, causing infections (Casadevall et al. 2019).

The enzymes produced by *C. auris* are capable of causing degradation of infected tissues to capture nutrients, favouring its spread. Furthermore, hydrolytic enzymes act by inhibiting the action of antimicrobials and the immune response, activating inflammatory mediators and provoking cell lysis. Among the main enzymes, proteinases, hemolysins, lipases and phospholipases can be emphasized (Chaffin 2008, Billamboz et al. 2021).

Morphological plasticity is a very common strategic factor used by microorganisms to quickly adapt to climate change. These transitions are part of the virulence mechanism of *Candida* sp as well as *C. auris*. These microorganisms can spontaneously undergo morphological changes in response to weather signals, being important in the maintenance of the species (Du et al. 2020). Study indicate that *C. auris* can be in the form of single cells or in aggregated cells of the pseudo-hyphae type. In most cases, aggregated yeasts are more resistant to antifungal agents when compared to isolated cells. However, isolated cells have a significantly higher level of virulence (Singh et al. 2019).

Another important virulence factor is the evasion of the host's immune system, being observed that neutrophils are not as efficient for phagocytosis of *C. auris* compared to other *Candida* sp. It is not yet known what factors influence this condition (Bruno et al. 2020).

Biofilm

Biofilms are structures formed by a community of microorganisms, which may be composed of more than one species of microorganism (bacteria and fungus in a symbiotic association) aggregated on a biotic or abiotic surface and protected by an extracellular polymeric matrix (EPS). This matrix has the ability to protect microorganisms from the external environment, against immune response or drug attacks (Burmølle et al. 2014, Ramos et al. 2018).

Fig. 2 shows the yeast biofilm formation scheme. In general, biofilm formation begins with the adhesion of planktonic yeast cells to surface and recognition of the location for the formation of a basal layer (A). After adhesion, cells begin to proliferate over the entire surface in a reversible manner (B). The cells continue to proliferate and the production of EPS begins in an irreversible way (C). The amount of EPS increases with the development of mature biofilm (D). Finally, the

amount of nutrients and toxins lead part of this biofilm to disintegrate, forming small groups of cell clusters or individual cells that deposit on another surface and originate a new cycle of biofilm formation (Burmølle et al. 2014, Tsui et al. 2016).

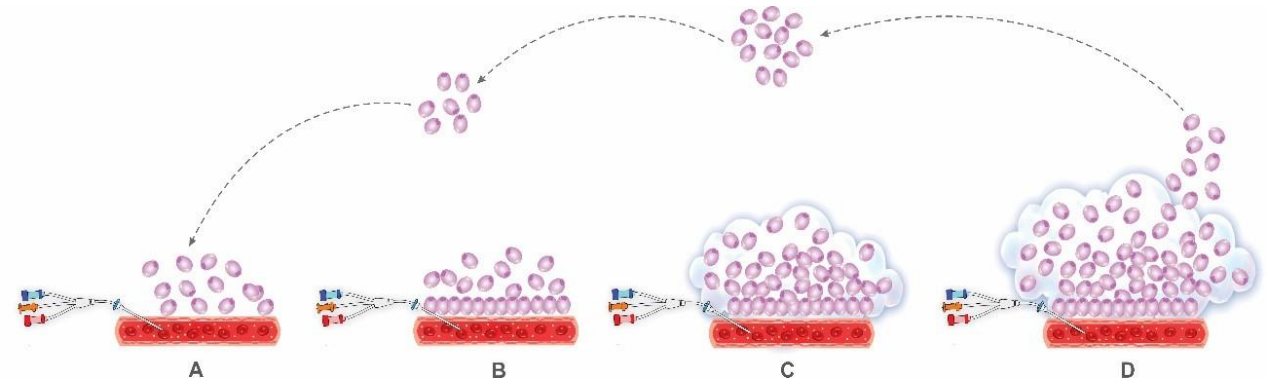

Figure 2 – Biofilm formed on intravenous catheter tip.

Initially, there was not enough evidence that *C. auris* was able to form biofilms. However, years later, in several clinical materials, such as line ends catheters, neurological shunts, as well as in fomite materials in nosocomial environment and in probes, suggesting that *C. auris* can form biofilms in both, hosts and surfaces. Furthermore, more sophisticated multi-omic techniques proves the formation of biofilms with high antifungal tolerance (Eyre et al. 2018, Kean & Ramage 2019).

Other study show the alarming capacity of *C. auris* to form biofilms on hospital surfaces, favoring transmission between patients or environments (bedroom and intensive care unit), being considered an important factor in its installation and persistence in the environment of healthcare facilities (Uppuluri 2020).

C. auris biofilm has a large amount of blastoconidia and, occasionally, pseudo-hypha composing a limited EPS. They are characterized by low susceptibility to antifungal agents, including azoles, polyenes and echinocandins (Billamboz et al. 2021). This fungus biofilm has the ability to resist antifungal agents that have effective activity against their planktonic counterparts (Sherry et al. 2017). Studies indicate that antifungals have activities in planktonic cells, however, the results are not satisfactory compared to treatment in biofilms and requiring higher concentrations. Voriconazole had a Minimum Inhibitory Concentration (MIC) ranging from 8 to 32 µg /mL in planktonic cells, however, in biofilm it did not show effective activity up to 32 µg/mL. Micafungin MICs ranged from 0.5 to 0.0062 µg/mL, however, most testate strains showed resistance up to 32 ug/mL in biofilms (Pierce et al. 2006, Sherry et al. 2017).

Finally, the biofilm is an extremely important defence mechanism for *Candida* sp, especially *C. auris*, which can defend itself from drug attack during treatment. Considered an intelligent adaptation and protection mechanism, biofilms have become a threat in hospital environments, especially in the ICU. Associated with the biofilm, the mechanisms of virulence make this microorganism a global threat and a serious public health problem.

Pathogenesis and pathology

The clinical features of infection can be nonspecific and difficult to interpret in most cases since other systemic infections can present similar clinical presentations (Osei Sekyere 2018). However, what can facilitate the correct identification of a disease caused by *C. auris* are the signs and symptoms at the site of isolation of *C. auris*, differentiating from a colonization of infection. Having reports of patients with culture-positive results in the skin, oropharynx, ear canal, respiratory and urinary tract without clinical signs, in which isolated in non-sterile areas of the body are probable to be more associated with colonization than infections (Chowdhary et al. 2016, Cortegiani et al. 2018, Jung et al. 2020).

Colonization by *C. auris* was detected, for example, in the nostrils, groin, armpit and rectum, and isolated for 3 months or longer after first detection, despite treatment in the intermediate period. In health services, these findings suggest the need for continuous isolation of the patient after treatment and on readmission, as they act as sources of contamination for other patients and for the environment (Vallabhaneni et al. 2016, Jeffery-Smith et al. 2018).

Invasive infections have increased, especially candidemia associated with invasive procedures (Kean et al. 2020, Osei Sekyere 2018). In fact, patients undergoing invasive procedures and devices are at greater risk of acquiring bloodstream infection, as catheters, for example, provide the fungus with easy access to the hematogenous route (Rudramurthy et al. 2017, Cortegiani et al. 2018). Other infections associated with urinary tract, respiratory tract, pericarditis, myocarditis, meningitis, skin abscesses, bone and wound infections have been related to *C. auris*, but is still poorly elucidated (Chowdhary et al. 2016, Rudramurthy et al. 2017, Jeffery-Smith et al. 2018).

The ability of *C. auris* to cause infection is attributed to several factors related to adhesion in host cells, biofilm formation, secretion of extracellular enzymes as phospholipases and proteinases. Pathogenicity processes have been elucidated *in vivo* in invertebrate, fish and murine models (Kean et al. 2020). Study by Fakhim et al. (2018) in murine observed that *C. auris* was able to produce lethal infections in immunocompetent mice, revealing in the histopathological examination a high fungal load in kidneys followed by spleen, liver and lungs, thus causing a disseminated infection, in which only yeast cells without pseudo-hyphae formation were observed. However, Ben-Ami et al. (Ben-ami et al. 2018) in a research observed cell aggregates in mouse kidneys, suggesting that aggregation may be a mode of immune evasion and tissue persistence.

According to Forgács et al. (2020), also carried out in murine model, the heart and kidneys were the most affected organs and the fungal load results showed a correlation with lethality, that is, *C. auris* isolates with higher lethality produced high fungal loads, with the increase observed between the second and sixth day of infection. The presence of pseudo-hyphae in the tissues was not evidenced, however all the isolates produced large cell aggregates in the organs, except the spleen. In the histopathological findings, there were multiple foci of yeasts between the myofibers of the sub-endocardial myocardium and in the pericardium in the late stages of the infection, with the presence of coagulative necrosis of myocytes and loss of cross-striations of myocardial fibers. In the kidneys, there was multifocal infiltration in the parenchyma with destruction of the tubules and frequent areas of necrosis. In the liver large multifocal lesions were observed with central necrosis of the lobes and the presence of the fungi spread radially in the liver parenchyma. Unlike such organs, only yeast cells were seen in the spleen (Forgács et al. 2020).

The kidney, heart and brain were the organs with the highest fungal loads of *C. auris* in neutropenic and immunocompetent mice, in a study carried out by Torres et al. (Torres et al. 2020). In other organs such as bladder, uterus, spleen, intestines, stomach and lungs, the fungal load produced was modest. Histology revealed abscesses with necrotic cores in the kidneys expanding to the renal capsule and inflammatory foci with numerous neutrophils infiltrating the interstitium between renal tubules. Large abscesses also occurred in the heart with extensive inflammation spreading to the pericardium, with numerous intact yeasts in such abscesses and inflammatory infiltrate rich in macrophages. In the brain, microabscesses with isolated and agglomerated yeasts were observed. The results also revealed viable *C. auris* cells shed in mice urine and feces (Torres et al. 2020).

It is known that hyphae are responsible for tissue penetration and mucosal infection by *C. albicans*, but the presence of such structures in *C. auris* is not identified, thus clinical disease in the oral cavity, for example, is not expected. However, the complete incapacity of *C. auris* to colonize the oral tissue was reported, and the elimination of this fungus was observed after 4 hours of inoculation in mice oral mucosa. This fact may be associated with a lack of key adhesins, although the host immune response must also be considered. In contrast, *C. auris* persisted much longer (7 days) when compared to *C. albicans* (2 to 4 days). Infection was observed in the peritoneal cavity and kidneys, and in the kidneys, there was a recuperation of the infection for up to 7 days (Villa et al. 2020).

Clinical manifestations

Candidemia

Around the world, *C. auris* infection is associated with severe invasive infection and candidemia. However, although few, non-invasive clinical isolates were detected in other locations, such as urinary tract, respiratory tract, skin, etc (Eyre et al. 2018).

The concern of *C. auris* to spread within the hospital environment exists all over the world. As well as other infections, *C. auris* can be acquired in the hospital, and the infection manifests itself within several weeks of patient admission. As a suggestion, there is an exogenous source, lack of control in the norms for fighting infection and inappropriate use of personal protective equipment. There is already a strong hypothesis that central venous catheter (CVC), urinary catheter and surgical procedure act as entry points that result in introduction or reinfection, in which removal of catheters resolved several candidemia (Lee et al. 2011, Chowdhary et al. 2013, Lockhart et al. 2017).

Among the factors that may favor infection by *C. auris*, we can highlight the presence of catheters (central, venous and urinary), parenteral nutrition, surgical procedures, invasive medical devices, prolonged hospitalizations or hospitalizations in the intensive care unit, mechanical ventilation, previous or ongoing exposure to broad-spectrum antimicrobial therapy, immunosuppressive therapies. In addition to comorbidities such as diabetes mellitus, human immunodeficiency virus (HIV/AIDS), cancer and transplants (Osei Sekyere 2018).

The first three *C. auris* isolates from the bloodstream are from South Korea. One of the isolates was recovered from a blood culture on the 51st day of hospitalization of a pediatric patient who underwent surgery, as well as central catheterization and mechanical ventilation due to aspiration pneumonia and encephalopathy hypoxic, in which the patient was previously under treatment for candidemia caused by *C. albicans.* In another case, *C. auris* fungemia was diagnosed on the 53rd day of admission of a patient undergoing total laryngectomy who developed complications of aspiration pneumonia and lower gastrointestinal requiring antibiotics, central catheterization and angiographic embolization. In this patient, fungemia persisted until his death due to septic shock and multiple organ failure after seventy-one days of hospitalization. The third isolate came from a pediatric patient on her 12th day of hospitalization, who was undergoing chemotherapy with a recent history of colectomy after colitis perforation, the patient had a clinical picture of disseminated intravascular coagulation and the cause of death was reported as septic shock due to persistent fungemia (Lee et al. 2011).

Cases of candidemia by *C. auris* in a hospital in India were associated with some risk factors such as the use of indwelling urinary catheter, CVC, parenteral nutrition, admission to the intensive care unit and use of broad-spectrum antimicrobials. In addition to conditions more closely related to immunosuppression such as diabetes mellitus, chronic kidney disease, chronic obstructive pulmonary disease, cancer chemotherapy, HIV infection, neutropenia, and hematologic malignancies. The main source in these infections was attributed to urogenital colonization by yeast, as most patients used an indwelling urinary catheter, although no urine sample had been cultured. Most of these patients had persistent candidemia and in some of them sepsis and septic shock was present (Chowdhary et al. 2013).

Sepsis and septic shock were also present in cases of fungemia caused by *C. auris* in Venezuela. The affected patients had been admitted to intensive care units prior to *C. auris* isolation in blood culture, so they were already seriously ill and had been previously exposed to antibiotics and various invasive medical procedures such as CVC and surgery (Calvo et al. 2016). In some cases of fungemia, in addition to blood culture, *C. auris* was isolated from other sites such as peritoneal fluid, catheter tip, urine, pharyngeal and rectal surveillance cultures (Ruiz Gaitán et al. 2017). There is even a report of persistence of fungemia up to 3 weeks after starting antifungal treatment (Chowdhary et al. 2013).

Urinary tract infection

There are several reports that describe patients with proven or suspected candiduria of *C. auris* associated with candidemia (Vallabhaneni et al. 2016, Ruiz-Gaitán et al. 2019). Furthermore, episodes of recurrent candidiasis are likely features of persistent colonization (Vallabhaneni et al. 2016, Al-Siyabi et al. 2017, Ruiz-Gaitán et al. 2019).

Clinical conditions such as diarrhea and gastrointestinal decompression were associated with increased susceptibility to infection or colonization by *C. auris* in the urinary tract, acting as risk factors. In these cases, it is inferred that the source of *C. auris* could be the intestine, a region colonized by some *Candida* sp. Thus, it is believed that *C. auris* could migrate from the intestinal region to the urinary tract, resulting in an infection or colonization; however, this hypothesis needs further investigation (Tian et al. 2018). Another study in mice showed that *C. auris* can easily aggregate in the kidneys, indicating that the possible cause of the invasive infection is due to the aggregation (Schelenz et al. 2016).

Patient with a history of ICU admission and diagnosed with obstructive ureteral stones, perirenal inflammatory changes, and moderate hydronephrosis, underwent ureteral stent and central venous catheter placement, obtained positive blood cultures and urocultures for *C. auris*. It is also worth mentioning that the presence of *C. auris* was observed in cultures from the skin, armpit and groin one week after the end of antifungal treatment, confirming colonization. After discharge, the patient was advised to continue with hygiene care and hand washing in order to avoid recurrence (Anwar et al. 2020).

Incomplete identification and interpretation of *C. auris* presence in urine results in treatment difficulties is reported by Biagi et al. (Biagi et al. 2019). In this case, the patient was a nursing home resident, with comorbidities, such as quadriplegia, multiple chronic wounds, hip osteomyelitis with abscess formation and deep vein thrombosis in the upper limb. In addition to having chronic tracheostomy, chronic indwelling urinary catheter, enteral feeding tube and colostomy. Initially, this patient was admitted to the hospital, with positive blood cultures for bacteria (coagulase-negative *Staphylococcus* sp. and carbapenem-resistant *Klebsiella pneumoniae*) and positive urine cultures for *Candida* sp. which was considered by the medical staff as colonization, although imaging tests revealed a thickening of the bladder wall suggestive of cystitis. After treatment with antibiotics, blood cultures became negative, but urine cultures remained positive for yeast, then, on the 27th day yeast was also isolated in the blood. However, the yeast was only identified as *C. auris* a few days later (Biagi et al. 2019).

Respiratory tract infection

Patients with cystic fibrosis can acquire pulmonary infections, causing greater limitations to the lung and worsening of the clinical prognosis. These patients often have *Pseudomonas aeruginosa* infections that progress to a chronic phase. In a report, *C. auris* was isolated from the upper airways of a patient with cystic fibrosis associated with chronic *P. aeruginosa* infection without exacerbation for two years. In the case of this patient, due to the presence of excessive coughing with sputum production, a diagnosis of pulmonary exacerbation with subsequent deterioration of 30% in pulmonary function was made. At first, sputum cultures were positive for *Aspergillus fumigatus*, *Aspergillus terreus* and for *Candida* non-*albicans*, which was not identified at the specie level. After four months, a new culture repetition, using a throat smear, revealed the presence of *C. auris*, but it was not possible to determine whether the previously isolated *Candida* non-*albicans* was already *C. auris*. This was the first report of *C. auris* isolated in a patient with cystic fibrosis, highlighting the importance of correctly identifying the isolated yeasts at the species level. In addition, these patients go through periods of hospitalization and are followed up in outpatient clinics, in which colonization by *C. auris* can contribute to the spread of the fungus not only in the healthcare environment but also to other patients (Stathi et al. 2021).

C. auris was also isolated from bronchoalveolar lavage (BAL) from a patient hospitalized for nephritic syndrome, which is the first report of the identification of this *Candida* species in China. In complementary tests, this isolate was susceptible to all antifungals tested, including amphotericin

B, fluconazole and caspofungin (Wang et al. 2018). In another report, *C. auris* was isolated in BAL from a newly transplanted lung. In the pre-implantation culture *P. aeruginosa* and *Candida haemulonii* growth was observed, additionally Gram coloring reveled abundant yeast. Five days after the transplant, the patient developed pneumothorax due to complications from ventricular tachycardia, hypotension and respiratory arrest, requiring tubular thoracotomy and endotracheal intubation. Chest X-ray imaging revealed retrocardiac opacification and laboratory tests showed peripheral leukocyte counts of 28.000 cells / μL. The isolated yeast was submitted to the CDC for definitive identification and three days later the patient died. The CDC confirmed the identification of *C. auris*. This is another example of incorrect initial identification of *C. auris* (Azar et al. 2017).

Otitis

In a case of bilateral acute otomastoiditis caused by *C. auris*, secretions of a sanguinolent nature were observed in the ear canal on physical examination. The samples were sent for laboratory tests where the total white blood cell count (total of 54.600/μL) and C-reactive protein of 4.16 mg/dL were performed. Tomographic findings of the temporal bone showed fluid in both mastoid air cells, this fact was reversed after treatment with antifungal in which the tomography revealed good aeration of the temporal bone and tympanic cavities without any finding related to inflammation. However, before the patient improves, a ventilation tube was inserted, as well as surgical debridement for infection control. In this case, *C. auris* was isolated from a culture of ear secretion and a surgical specimen from the site of infection (Choi et al. 2017).

In another case, *C. auris* was isolated from a patient with recurrent complaints of otalgia and a history of treatment for clinically diagnosed otomycosis nine months ago. This patient underwent oral surgery which resulted in an odontogenic brain abscess requiring hospitalization. During hospitalization, a computed tomography scan of the temporal bone showed chronic otitis media with mastoiditis and mastoid osteomyelitis, being treated with antibiotics. On a new admission for treatment of a left frontal brain abscess, the patient underwent tympanostomy with drainage of clear fluid and an ear drainage swab of *C. auris* was isolated. The fungus also grew in four repeated smears of secretion from the same ear, over a period of six weeks, also showing evidence of meningitis and external otitis with the presence of moist white debris and clear secretion (Schwartz & Hammond 2017).

Study conducted by Jung et al. (2020) in a medical center in South Korea, observed that most patients, 87%, with positive culture for *C. auris* presented a clinical condition of chronic otitis media and had previously attended the otolaryngology clinic for complaints of otorrhea, ear fullness, dizziness, earache, hearing difficulty or itchy feeling. Few patients had suspected invasive infection when they had skull base osteomyelitis and surgical site infection after kidney transplantation.

Ear pain, intense itching, hearing loss and creamy white secretion in the ear canal were also clinical manifestations associated with *C. auris* infection. In the studies of Abastabar et al. (2019), physical examination showed signs of inflammation, tympanic membrane perforation even without known trauma, and redness, the patient only reported that used to swim in a public pool three times a week before the signs and symptoms appeared. The patient had repeated positive cultures for *C. auris* from the ear secretion, but in other areas such as the groin, armpits, oropharynx, rectum, respiratory and urinary tract the cultures were negative. Furthermore, environmental samples from areas of contact with the patient in home negative cultures were also obtained (Abastabar et al. 2019).

Ophthalmitis

In rare report, *C. auris* was isolated from a case of pan-ophthalmitis, in which it was observed that this fungus is able to contribute to fulminant infection in an immunocompromised patient without a history of trauma, which resulted in loss of vision and structural eye integrity. In this case, the patient had HIV infection and syphilis, and initially presented fatigue, irritation and central blind spot in the visual field of the right eye. It then progressed to total vision loss in the

right eye and difficulty in opening both eyes. Physical examination revealed periorbital edema, proptosis, chemosis and purulent discharge with the right pupil fixed and non-reactive to light. Magnetic resonance imaging revealed thrombosis of the cavernous sinus and orbit computed tomography suggested the occurrence of endogenous pan-ophthalmitis with orbital cellulitis, as there was no history of trauma, surgery or corneal ulceration. In vitreous cultures, *Pseudomonas aeruginosa* and yeast were isolated, which the support laboratory confirmed to be *C. auris* (Shenoy et al. 2019).

Pericarditis

C. auris was associated with a rare case of fungal pericarditis, the patient had several comorbidities such as chronic alcoholism, chronic liver disease, ascites and grade II hepatic encephalopathy. Initially her hospitalization, blood, sputum and ascitic fluid cultures were negative, but two weeks later she started with dyspnea, cough and sputum. Imaging examinations revealed gross bilateral crackles in the lower lung fields, interstitial edema and gross cardiomegaly, and pericardial effusion with tamponade. The patient was placed on ventilatory support and pericardiocentesis was performed with drainage of hemorrhagic fluid. In the growth of fungi was observed, which were identified as *Candida haemulonii*. Initial laboratory tests diagnosed an infection caused by *C. haemulonii*. Later, urine, blood and bronchoalveolar lavage were collected. The isolates were sent for molecular identification that showed 99% similarity with a Korean isolate of *C. auris*. So, the yeast was mistakenly identified as *Candida haemulonii* by the commercial identification system VITEK2 and later confirmed as *C. auris* by molecular methods (Khillan et al. 2014). In conclusion, this study shows the importance of correctly identifying the agent causing the infection for an effective and safe treatment.

Finally, the knowledge of the clinical manifestations as well as the pathology caused by the infection of *C. auris* is of crucial importance to the clinical environment, since it allows greater security in the decision making about the clinical condition of the patient. Furthermore, knowing the clinical features of an infection avoids possible misdiagnosis.

Immune response to *C. auris* infection

One of the reasons for the increase in the incidence of disease caused by fungi is the increase in the number of immunosuppressed patients. Among the main related factors are biological immunomodulatory agents for the treatment of autoimmune diseases, HIV transmission, viral hepatitis, chemotherapies, immunosuppressive therapies, internal medical devices such as intravenous catheters, prolonged hospitalization, especially in the use of broad-spectrum antibiotics (Oliveira et al. 2021).

Microorganisms, including fungi, have co-evolved with their mammalian hosts over the course of millions of years of existence. This fact is related to the emergence of mechanisms complex of immune surveillance in the host with the sophisticated strategies of fungi to antagonize the immune response (Romani 2011).

Considered a fast and conserved mechanism, the innate immune response of hosts has the function of protecting the organism from the attack of pathogens and preventing the spread and infection. The defence mechanism established by the skin barrier, mucosal cells of the superficial epithelium, as well as defensins, collectins and microbial antagonism, recognize and control the entry of pathogenic fungi and possible infections. In addition, other cells contribute to the attack and control of infection, as well as phagocytic cells (monocytes, macrophages and neutrophils) and even non-phagocytic cells (endothelial and epithelial cells), which act by helping the innate response to fungi through the process of phagocytosis and direct killing of microorganisms (Johnson et al. 2018).

For optimal activation of the antigen-specific adaptive immune defence system to occur, activation of the innate immune system's pathogen detection mechanism must first occur. In the event of a fungal infection in a host, several pattern recognition receptors (PRRs) can be stimulated by molecular patterns associated with fungal pathogens (PAMPs) by different combinations. This

combination will depend on the type of fungal species and the types of cells involved. For example, the contribution of individual Toll-like receptors (TLRs) may vary depending on the fungal species, route of infection, fungal morphotypes, and receptor cooperativity (Romani 2011).

The adaptive immune response mechanism of dendritic cells (DC) against a fungus will depend on cooperation and specialization between DC subsets. It is known that the immune response mechanism of dominant TH1 cells is correlated with the protective response against fungi. The important function of TH1 cells is to activate phagocytic cells (phagocytes) at the site of infection. Therefore, any failure of activation of phagocytes by T cells can cause serious damage to the body, causing overwhelming infections, limiting antifungal therapy, and favouring the persistence of fungal infection. This infectious persistence can cause the death of the patient. In addition, another important defence mechanism is the cytokines IL-4 and IL-13. These cytokines have the potent action of providing proximal signals for the commitment of naive T cells to the TH2 cell lineage, for dampen the protective responses of TH1 cells and promoting the alternative pathway of macrophage activation, can cause allergic responses related to fungi and inhibition of the infection (Romani 2011).

To ensure their survival inside the host, in relation to fungi, they have mechanisms that can "dribble" or "cheat" the host's immune system, known as regulatory factors of the inflammatory response. By masking the detection signals performed by the host's immune system, fungi can prevent the inflammatory response, favouring the spread, growth and opportunism of the fungus at the site. The fungal structure is also a very important factor in this stage of infection and inflammatory inactivation. The fungal cell wall is an important dynamic structure that is constantly changing over time and during morphological changes. External stresses, cell growth and hyphae also affect the cell wall. These factors contribute to the decrease in the recognition of the host's defence cells, inactivating the inflammatory response and favouring the infection (Romani 2011, Oliveira et al. 2021).

In general, the interaction between the fungus and the host's immune system can determine whether this microorganism will be considered commensal or threat to the organism, classified as a pathogen, and this factor can continually change (Romani 2011).

Among the fungi, *Candida* spp. stands out, where a small part of these species can commonly colonize the human microbiota, however, any physiological imbalance caused by immunosuppression or another underlying disease can make this microorganism pathogenic and cause infection. Among the most common species in invasive human infections are *C. albicans* and non-*albicans* species (Oliveira et al. 2021).

The immune defense mechanism against *Candida* spp. depends directly on an adjusted interaction between the innate immune response and the adaptive immune response. The first defense response against *Candida* spp. is the skin and mucosa, which act as a physical barrier. Fungi may not be recognized by innate immune defense cells, however, these cells can recognize through PAMPs in the fungal wall by various PRRs located on the surface of immune defense cells, for example: C-type lectin receptors such as dectin-1, dectin-2, macrophage mannose receptor, non-integrin dendritic cell-specific intercellular adhesion (DC-SIGN), TLR2 and TLR4, which can activate mechanisms of microbial elimination such as phagocytosis, production of pro- and anti-inflammatory cytokines, and release of reactive oxygen species (ROS) (Bruno et al. 2020).

The emergence of *C. auris* is well discussed earlier in this article, reporting its worrying transmission and severe invasive infection. The pathogenicity mechanism is still debatable and new information emerges over time. *C. auris* has some similarities with other species of *Candida* sp., however, neutropenia has not been diagnosed for *C. auris*. In this case, the absence of neutropenia in infections suggests that the neutrophil response may not be adequate to control the invasive infection of *C. auris* in the host (Nett 2019).

Neutrophils are leukocytes of the innate immune system with a fundamental role in the control of systemic candidiasis, fighting the fungus by phagocytosis or by trapping extracellular neutrophils (NETs), which are structures of genetic material, proteins and histone. The phagocytosis mechanism practiced by neutrophils has more action against single yeasts, while NET

has action against hyphae. However, one study reports that *C. auris* can elude the neutrophil response, causing neutrophils to be unable to phagocytose or release NETs effectively (Johnson et al. 2018, Dominguez et al. 2019, Horton & Nett 2020). Research study using an alternative *in vivo* model infected Zebrafish showed that neutrophil recruitment in *C. auris* infected groups was approximately 50% lower when compared to *C. albicans*. This result reinforces the worrying situation of *C. auris* eluding the immune response (Johnson et al. 2018). Furthermore, this information suggests that the innate defense cell cannot be activated in the face of a *C. auris* infection, justifying the high mortality rates (Rossato & Colombo 2018).

The opposite is observed in mouse models where the immune response of these rodents acts more effectively. One study report that the response against *C. auris* was better when compared to *C. albicans*, with *C. auris* being less virulent. It is not clearly explained why the rodent immune system responds more effectively when compared to human neutrophils. What can be justified is the difference in neutrophil receptors between species. Furthermore, the virulence and resistance of *C. auris* can vary between species. (Johnson et al., 2018). An *in vivo* study reported that several clinical isolates, as well as clades of *C. auris*, with the exception of clade V, show greater intensity of immune response when compared to *C. albicans*. Using a mouse model with systemic infection, the authors report that phagocytes acted more effectively against *C. auris* infection when compared to *C. albicans*. In this study, the authors report that the level of macrophage lysis and virulence of *C. auris* was lower (Bruno et al. 2020).

The way in which *C. auris* can activate/stimulate host defense cells is associated with the sequential involvement of the different components present in the fungal wall. The early (4 h) immune response is induced by β-glucans. This component, as well as mannans, were crucial in the recognition by defense cells (Bruno et al. 2020).

Neutrophils coordinate their recruitment against pathogens, cooperating in increasing antimicrobial activity. Swarming is a very important process in the containment of *C. albicans* and this process involves LTB4, myeloperoxidase (MPO), ROS and NETs. Although the clusters were identical in size, the swarms formed by *C. auris* and *C. glabrata* were smaller when compared to the swarms formed by *C. albicans*, (Alex et al. 2020).

Among the most important mechanisms in swarming and restriction of fungal growth are ROS, MPO and NETs. In addition, the cytokines GM-CSF and GCSF have the function of acting as mediators in swarming and increasing antifungal function (Alex et al. 2020).

One study reported a distinct stimulation of cytokine production in peripheral blood mononuclear cells (PBMCs) between *Candida* species compared *C. auris*. The results showed that *C. auris* induces robust transcriptional modifications in PBMCs in the human organism. This leads to include not only common pathways induced by *C. albicans*, but also by more robust specific IFN-dependent transcription programs and explicit cytokine responses. A study reports the strong link between *C. auris* mannans with serum IgG and the mannose binding lectin, and this opsonization in human serum is necessary for the production of cytokines induced by *C. auris* mannan. This amount of cytokines is correlated with the specific properties of each clade of *C. auris*. Furthermore, this difference can influence colonization and persistence in the infected organism (Bruno et al. 2020).

One study used mice infected with *C. auris* and *C. albicans* and evaluated the immunological profile against these pathogens. According to the data, innate and adaptive immune system cytokine production against *C. auris* is fully functional in an immunocompetent host. *C. auris* has genes that provide mechanisms of virulence and resistance, as well as genes for the development of biofilms, aspartyl proteinases, phospholipases, lipases and secreted transporters (Rossato & Colombo 2018). All these factors justify virulence, antifungal resistance and survival in natural niches and hosts (Du et al. 2020).

As previously discussed, yeast aggregation is associated with the mechanism of tissue invasion and the persistence of infection in the host. The aggregation mechanism practiced by *C. auris* hinders the immune response, developing a barrier preventing the action of defence cells. This barrier protects the pathogen from immune attack and contributes to its persistence in the

body. Furthermore, this characteristic allows greater resistance of *C. auris* against the main antifungal agents (Rossato & Colombo 2018, Du et al. 2020).

It is known that biofilms act as a protective mechanism for *C. auris* against the antifungal, making it resistant. However, the mechanism of immune response influenced by biofilms is still unknown (Nett 2019). A study reports that *C. auris* clade III, related to invasive infection, induces a higher proportion of cytokines when compared to other clades and this higher production of cytokines is related to the ability to form aggregates (Bruno et al. 2020).

According to the information obtained, it is concluded that the body's immune response against *C. auris* can be considered as a classic antifungal mechanism. However, some specific responses are triggered by structures present in *C. auris* cells. It is important to emphasize that more information about the immunological profile and defense mechanisms needs to be further investigated.

Diagnosis

Once the infection confirmation and the etiological agent identification are essential to ensure that there is a correct and effective treatment *C. auris* diagnosis is of fundamental importance, being generally carried out by combining the clinical condition with laboratorial exams (Hani et al. 2015).

The clinical samples collected are processed firstly for direct assay where it is possible to observe the feasible etiological agent. Next, the culture is carried out, by placing the isolate in substances favorable for the yeast growth, making it able to visualize its macroscopic characteristics and proceed with the diagnosis for the specie identification, where each one develops specific structures, different biochemical characteristics, enabling identify them and deal with most appropriate way. Therefore, it is worth mentioning that the correct diagnosis of the species involved in fungal infections is not only of epidemiological but also clinical interest. The great difficulty in diagnosis is related to the lack of sensitivity or specificity in laboratory techniques. These limiting factors make treatment difficult and worsen the patient’s prognosis, where many end up dying due to incorrect diagnoses and ineffective treatment (Anane & Khalfallah 2007, Zhang & Izadjoo 2015).

Laboratory Diagnosis of *C. auris*

It is extremely important that infections caused by fungi or bacteria are detected as soon as possible, being a crucial step in effective antimicrobial treatment. Unfortunately, most mycology laboratories which use conventional phenotypic tests are not prepared to identify with the necessary speed and accuracy this important pathogen. In developing countries there is a lack of technology where *C. auris* is still unknown and even the most common *Candida* species are not identified at the species level (Saris et al. 2018).

In the past, the diagnosis of infection caused by species of the *Candida* sp. was performed using the classic laboratory approaches: microbiological, immunological and histopathological. However, the identification of *C. auris* requires specialized laboratory methods, since the conventional biochemical methods (manual and some automated systems) and those with based on morphological analysis (direct mycological examinations and microculture on slide) cannot identify it (McCarty & Pappas 2016).

Classic microbiological methods (direct mycological examinations and culture) generally allow the identification of *Candida* sp. but do not identify *C. auris* (Pappas et al. 2018). Routine laboratory tests, especially in developing countries, can lead to delays in diagnosis of diseases caused by this yeast (Arastehfar et al. 2018).

Candida auris isolates were identified in different biological samples, including urine, blood, organs, eschar, bronchoalveolar lavage, abdominal pus, purulent exudate and central venous catheter tips (Ruiz-Gaitán et al. 2018, Almaghrabi et al. 2020). The emergence of *C. auris* has brought great concern to the development of new protocols for diagnostic (Keighley et al. 2021).

The collection of clinical samples for the isolation and detection of *C. auris* depends on the anatomical site involved and is done in the same way for the diagnosis of candidiasis caused by other *Candida* sp. The collection can be made using rayon tip swabs, nylon flocked swabs or by using sponge sticks and placed in a zip-top bag containing 45 mL of phosphate-buffered saline (PBS) with 0.02% Tween 80 (Welsh et al. 2017, CDC 2022b). It is worth mentioning that the semi-solid transport medium is the most advisable for dry swabs, as they preserve the viability of the microorganism (Chowdhary et al. 2017, Mulet Bayona et al. 2020, Keighley et al. 2021).

C. auris has been isolated from surveillance samples, including patient swabs from nose, skin, oropharyngeal nasopharynx, rectum, axilla, groin, vulva, tracheostomy, and wounds (Welsh et al. 2017, Chowdhary et al. 2017, Eyre et al. 2018, Leach et al. 2018). It has also been isolated from environmental samples as reusable equipment, including axillary temperature probes and pulse oximeters (Eyre et al. 2018, Leach et al. 2018). The effective method and gold standard in the diagnosis of candidemia remain blood culture (21-75% in bloodstream infection, ~5-20% in abdominal candidiasis). Furthermore, the blood culture time in an oven can last up to 7 days (Clancy & Nguyen 2017, Pappas et al. 2018, Pitarch et al. 2018). Table 1 presents information on the type of infection, biological samples usually collected and sample collection methods in patients infected with *C. auris*.

Table 1 Characteristics and method of collecting samples infected by *C. auris*.

Desases	**Biological samples (n)**	**Collection method**	**Reference**
Otitis	Purulent exudate	Ear exudate collection	Satoh et al. (2009), Pekard-Amenitsch et al. 2018)
Candidemia	Blood	Aseptic venipuncture or catheter tip (central venous catheter)	Lee et al. (2011), Emara et al. (2015), Das et al. (2018), Noginskiy et al. (2018), Parra-Giraldo et al. (2018), Castro et al. (2019)
Vulvovaginitis	Exudate	Aseptic collection of two high vaginal swabs	Kumar et al. (2015)
Otomastoiditis	Bloody exudate	Ear exudate collection	Choi et al. (2017), Schwartz & Hammond (2017)
Preseptal cellulitis	Purulent exudate	Swab exudate collection	Parra-Giraldo et al. (2018)
Urinary tract infection	Urine or Bedsore ulcer and urine	Urinary cateter or biopsy	Tian et al. 2018, Almaghrabi et al. (2020)
Intra-abdominal infection	Abdominal washout surgical cultures	aspirate	Almaghrabi et al. (2020)
Postoperative wound	purulent exudate	swab exudate collection	Almaghrabi et al. (2020)
Lung	Bronchoalveolar fluid	Bronchoalveolar lavage	Wang et al. 2018, Almaghrabi et al. (2020)
Osteomielitis	Borne tissue	Biopsy	Fernández-Chagüendo et al. (2020)
Spondylodiscitis	Tissue	Tissue collected during discectomy and curettage of the lumbar spine	Supreeth et al. (2020)

Routine laboratory test

Direct mycological examination and staining techniques used in mycology laboratory routine do not differentiate *C. auris* from other *Candida* sp. However, they can be the laboratory's first step forward to identify species in the clinical sample (Mahmoudi et al. 2019). Although still widely used, conventional methods of diagnosis, such as microscopy and culture are essential in many investigations but lack sensitivity and can delay diagnosis (Avni et al. 2011). On microscopy, *C. auris* present spherical morphology, with many oval-elongated buds (single or aggregated), smooth surface and a size of approximately 2.0–3.0 x 2.5 –5.0 μm (Fig. 3) (Satoh et al. 2009, Kathuria et al. 2015).

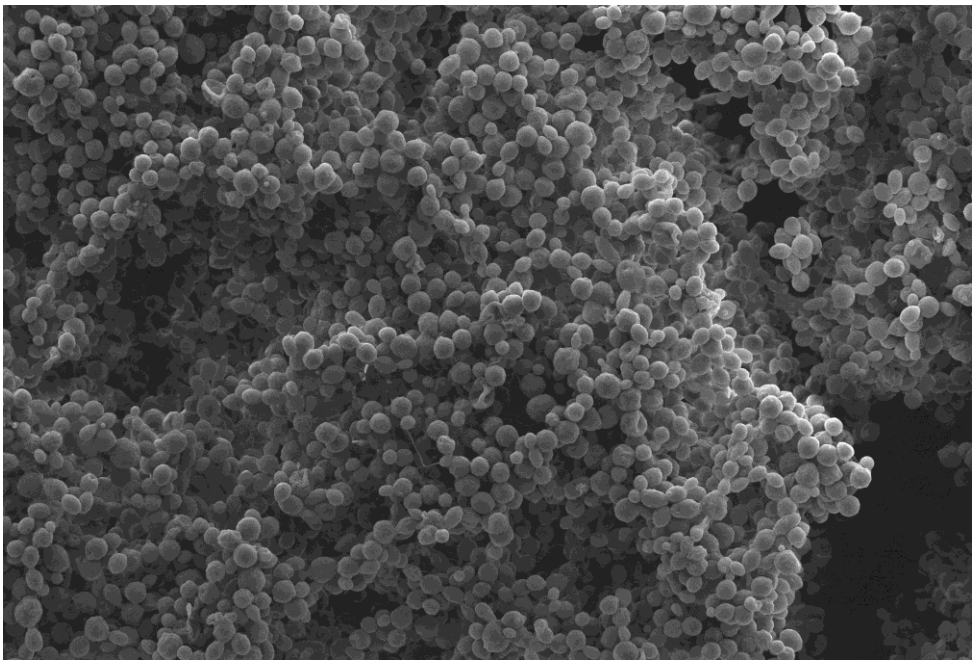

Figure 3 – Biofilms were analyzed using a Jeol JSM-6610LV scanning electron microscope 1000X increase *C. auris* morphology in scanning electron microscopy (SEM).

C. auris grows at temperature range of 25 to 42°C (Arastehfar et al. 2018, Almaghrabi et al. 2020) and has an ideal growth temperature of 37-40°C (Prakash et al. 2016, Welsh et al. 2017 Ahmad et al. 2019). *C. auris* grows well in culture media used in routine laboratories such as Sabouraud Dextrose Agar (SDA), Glucose Yeast Extract Peptone Agar, and chromogenic agar after 2 to 5 days of incubation. In fact, 48 h of incubation after enrichment may be enough for its growth (Ruiz-Gaitán et al. 2018). It should be mentioned that this fungus does not grow on medium containing 0.1%-0.01% cycloheximide (Satoh et al. 2009, Khillan et al. 2014).

The performance of culture and identification tests varies according to each laboratory's protocols. The use of selective enrichment broth optimized the growth of *C. auris* growth providing a faster result (lower time) in clinical specimens, with greater sensitivity and specificity (Adams et al. 2018). Welsh et al. (2017) observed that different to other *Candida* sp, *C. auris* grows well in salinity (10%wt/vol) in the sabouraud (with 10% Dulcitol with chloramphenicol and gentamicin), salt sabouraud dulcitol enrichment broth, Yeast Nitrogen Base (YNB) broths with dulcitol or mannitol as carbon sources.

As for the visual aspects, *C. auris* colonies on SDA are smooth, from white to cream (Satoh et al. 2009, Kathuria et al. 2015, Chew et al. 2018) as also observed in other *Candida* species of medical interest (Keighley et al. 2021). Clinical specimens can be processed for isolation of *C. auris* by direct plating on CHROMagar or using the Salt SAB Dex enrichment method (Welsh et al. 2017). Chromogenic methods such as CHROMagar® *Candida* despite being useful, as they allow a relatively rapid presumptive identification (incubation time of 24–48 h and 40–42ºC), does not specifically differentiate *C. auris* (Mulet Bayona et al. 2021). According to the CDC, confirmation must be made by other more specific methods that will be mentioned during this review (CDC 2021).

It is worth mentioning that on chromogenic agar plates, *C. auris* colonies' texture is smooth and glossy. On the Brilliance^{TM} Candida Agar (Oxoid, UK) presents beige to pink colonies (Satoh et al. 2009, Chew et al. 2018, Keighley et al. 2021), pale pink colonies on *Candida* CHROMagarTM (Becton Dickinson, Heidelberg, Germany) (Chew et al. 2018), and on CHROMIDR *Candida* (BioMerieux, France). *C. auris* can be seen as pale pink colonies (Satoh et al. 2009, Kathuria et al. 2015, Chew et al. 2018, Bentz et al. 2019, Borman et al. 2021, Keighley et al. 2021, Mulet Bayona et al. 2021). The color variation problem appears to have been solved on

the new chromogenic agar, CHROMagar Candida Plus (CHROMagar, France) which presents a new specific color for this species: light blue with a blue halo at 36 h of incubation (with a sensitivity and specificity of 100%). This medium can be a good alternative for use in clinical laboratories to a rapid presumptive identification and differentiation of *C. auris* from other *Candida* species (Borman et al. 2021, Keighley et al. 2021, Mulet Bayona et al. 2021).

Although desirable in order to identify microorganisms in less time, automation and easy execution (Carvalho et al. 2020a), phenotypic methods such as: VITEK 2 YST, API 20C, API ID 32C, MicroScan, RapID Yeast Plus, GenMark ePlex BCID-FP Panel, BD Phoenix, bioMérieux VITEK MS MALDITOF and Bruker Biotyper MALDI-TOF (Keighley et al. 2021). However, the disadvantage of these methods is that they may misidentify *C. auris* or require other, more specific methods (Center of Disease Control and Prevention 2019). A reason why *C. auris* cannot be reliably identified by standard biochemical identification platforms/kits is because there is a lack of this organism in their databases (Mizusawa et al. 2017). Therefore, other more efficient methods are extremely important for a correct and timely identification of this pathogen, such as spectrophotometric, molecular and serological method (Cendejas-Bueno et al. 2012, Keighley et al. 2021). In Fig. 4, it is possible to observe biochemical-based methods commonly used to identify *Candida* species and *C. auris* possible misidentification.

Serological assay

Conventional tests based on fungal culture have limitations in identifying the microorganism, mainly because they do not contain markers or biomarkers for detection and require a longer time for diagnosis. Moreover, culture-based tests can prevent the growth of microorganism species. Non-culture-based tests (NCBT) were developed with the aim of overcoming the limitations of culture tests. Although they are efficient, their low specificity and sensitivity are limitations. As an example, the biomarker, 1, 3-Beta-D-glucan (BDG) can be mentioned. This biomarker has a sensitivity ranging from 75 to 80% for candidemia, which highlights the need to develop a more sensitive test (Chibabhai et al. 2019, Farooqi et al. 2021).

Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALD-TOF)

After obtaining the correct isolate, identification of *C. auris* can be performed using the matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) method (Caceres et al. 2019).

MALD-TOF, promising technique for microbial identification, such *C. auris* using a MALDI Biotyper (Bruker Daltonik; Bremen, Germany and Bruker MALDI Biotyper CA and Research Use Only [RUO] databases) and MALDI-TOF MS BioMerieux 3.2 systems, two important methods available (Schwartz & Hammond 2017, Huang et al. 2021). MALDI-TOF is a proteomic method, based on the spectral comparison generated for each sample type with the reference database (Mahmoudi et al. 2019). This equipment is capable of properly identify several *C. auris* isolates in biological samples (Schelenz et al. 2016, Chowdhary et al. 2017, Chow et al. 2019). It should be emphasized that this method allows faster and more accurate diagnosis of pathogens when compared to conventional tests. However, as disadvantages include the need for a greater investment, which generates low availability of equipment in routine laboratories (Ong et al. 2019).

Molecular assays

As reported, the biggest challenge for the diagnosis of *C. auris* is to avoid identification errors caused by the limitations of conventional and commercial tests available in the routine laboratory. Even assays such as MALDI-TOF have limitations in detecting *C. auris*. In view of this, new methods based on DNA and proteins are being developed and evaluated against the detection of *C. auris* (Mahmoudi et al. 2019, Ong et al. 2019).

Due to the high cost of genomic sequencing, several methods based on independent DNA sequencing have been developed, mainly for the differentiation of *C. auris* from other closely related *Candida* spp that can be easily mis-identified by other tests (Mahmoudi et al. 2019).

A very important technique in microbiological diagnostics is the polymerase chain reaction (PCR) method, such conventional PCR and real-time PCR. The difference between them is that real-time PCR has greater speed, reproducibility, quantitative capacity, sensitivity and reproducibility, and can be substituted for conventional PCR in routine laboratories (Paiva-Cavalcanti et al. 2010).

The sequencing of the internal transcribed spacer (ITS) regions and/or the D1/D2 regions of 28S ribosomal DNA presents the ability to confirm species and phylogenetic information. Studies report the importance of conventional and real-time PCR targeting the ITS2 region as it has the ability to quickly and accurately identify clinical isolates of *C. auris* in a short time (approximately 2 hours). However, test sensitivity was not confirmed for all isolates (Hou et al. 2019, Ong et al. 2019). Other TaqMan real-time PCR test targeting the ITS2 region were able to detect *C. auris* within a period of 4 hours. It is worth mentioning that this test was able to detect *C. auris* DNA even in samples (armpit, groin, nostril, ear, rectal and wound swabs, besides environmental sponges from different hospital sites) with negative results for other assays (Leach et al. 2018). Kordalewska et al. (2017) used 140 fungal isolates and human genomic DNA, and these isolates were evaluated in conventional and real-time PCR. According to the results, the detection accuracy for *C. auris* was 100% for both tests.

C. auris was detected in clinical isolates by Khan et al. (2018) the Specific end-point PCR (Molecular target = ITS1-5.8S-ITS2). All the procedure lasted 4 hours. In this assay, the authors used 12 *Candida* sp. and according to the results, the tested primers did not show identity with the sequences of the corresponding region of these species and *C. auris* was correctly identified. However, it is important that this study did not evaluate species closely related to *C. auris*.

Multiplex Probe Amplification (MPA) technology is another type of PCR that stands out for being an effective method for the simultaneous detection of *C. krusei*, *C. auris* and *C. glabrata*. Containing probes from the variable domains D1/D2 of the LSU rDNA locus, MPA has high specificity and selectivity, and can be used in hospital environment for the control of *C. auris* outbreaks (Jainlabdin et al. 2019).

In order to identify new outbreaks of *C. auris* and avoid the increase of positive cases, genomic sequencing of this microorganism was performed and the amplified fragment length polymorphism (AFLP) was used for molecular typing. Since AFLP is complex and expensive a simpler and less expensive technique was developed based on short tandem repetitions in the *C. auris* genome. The results proved to be accurate for a faster, more reliable and economical technique for genome sequencing analysis, aiding in the investigation of new outbreaks (De Groot et al. 2020).

Other commercially available and high-efficiency methods include PCR-RFLP, T2 magnetic resonance system, loop-mediated isothermal amplification (LAMP) and GPSTM MONODOSE CanAur dtecqPCR (dried single-dose PCR tubes). The latter presents speed in the analysis because it has dehydrated tubes available for use, requiring only the addition of a DNA template. The disadvantages of these experiments are that they are considered high-cost trials and their availability is low, especially in developing countries (Mahmoudi et al. 2019). Results show that GPSTM MONODOSE CanAur dtecqPCR has the ability to detect *C. auris* within 1 hour (Martínez-Murcia et al. 2018).

Other commercial assays can be highlighted, such as the AurisID and the Fungiplex, a test used in surveillance detection or directly for blood samples. Additionally, the T2 magnetic resonance imaging (MRI) assay can be used to detect bloodstream infection or to colonize *C. auris*. It is also worth noting that for positive blood cultures, the Food and Drug Administration (FDA), approved the use of BioFire BCID2 and GenMark Dx Panel ePlex BCID-FP methods (Lockhart et al. 2022). Fig. 5 represents a summary of laboratory tests for the diagnosis of *C. auris*, as described by Lockhart et al. 2022.

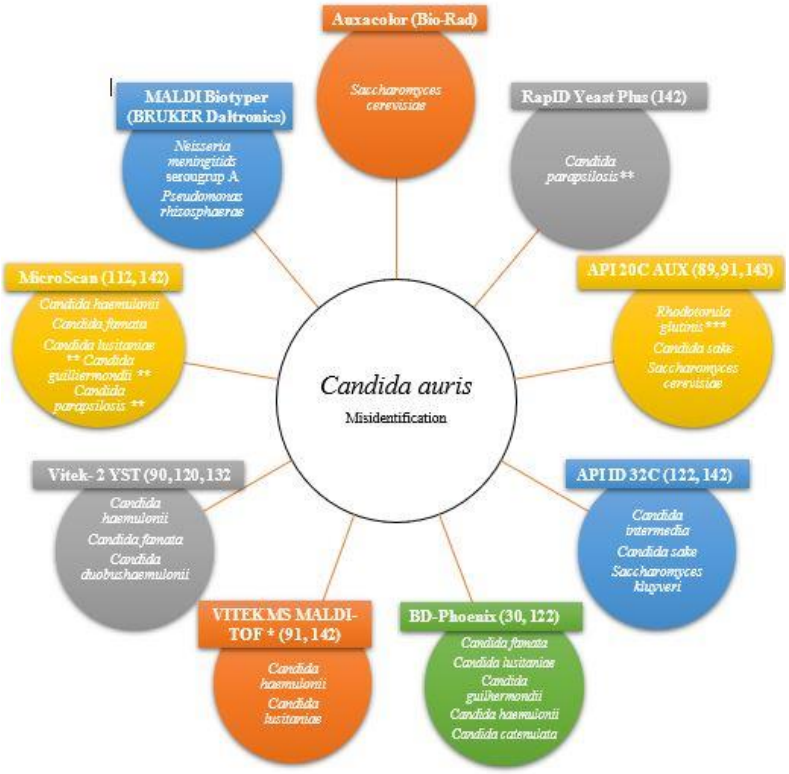

Figure 4 – biochemical-based methods commonly used to identify *Candida* species and associated with *C. auris* misidentification. * Misidentification of *C. auris* with *C. lusitaniae* and *C. famata*. More specific tests need to be performed.** *C. lusitaniae*, *C. guilliermondii* and *C. parapsilosis* can form pseudohyphae on cornmeal agar. In the absence of pseudohyphae, *C. auris* may be suspected, since it does not produce pseudohyphae. However, some species of *C. auris* can form hyphae. It is important to consider the growth of *C. lusitaniae*, *C. guilliermondii* and *C. parapsilosis* identified by the MicroScan test or any *C. parapsilosis* isolates identified in RapID Yeast Plus as possible *C. auris*. Finally, this isolate must be sent for identification tests. *** Characteristic red color not present.

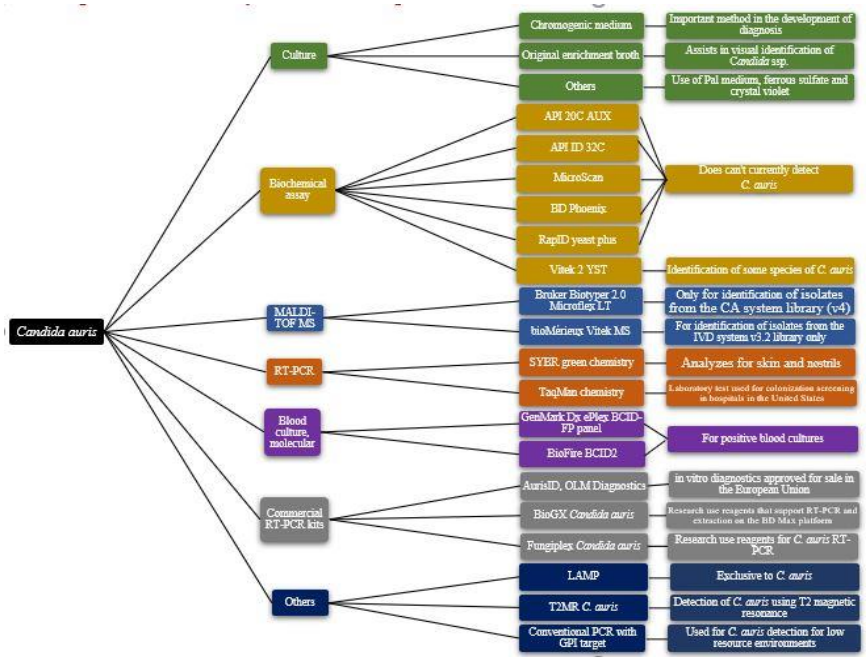

Figure 5 – Methods that may contribute to the diagnosis of *C. auris*.

In conclusion, the correct identification of *C. auris* becomes a serious issue, since a large number of routine laboratories have just biochemical methods for the identification of *Candida* spp., mainly due to the high cost of more sophisticated tests (molecular and MALD TOF tests for example), increasing the chance of misdiagnosis and inappropriate treatment. Table 2 presents the main molecular tests based on *C. auris* detection primers.

Table 2 Primers used to identify *C. auris* using molecular techniques.

Molecular Method	**Target**	**Region**	**Primer name**	**Base Sequences (5'-3')**	**Reference**
Sequence analysis	*C. auris*	ITS1-4	ITS-1 ITS-4	TCCGTAGGTGAACCTTGCGG TCCTCCGCTTATTGATATGC	Kathuria et al. (2015)
AFLP	*C. auris*	ITS	V9G LS266 V9G and ITS1 LS266 and ITS4	TTACGTCCCTGCCCTTTGTA GCATTCCCAAACAACTCGACTC TCCGTAGGTGAACCTGCGG TCCTCCGCTTATTGATATGC	Calvo et al. (2016)
Multiplex PCR	*C. auris* and *C. haemulonii*	ITS2	*C. auris* *C. haemulonii*	CCACCGCGAAGATTGGTG CCGTTGGTGGATTTGTTTCT	Theill et al. (2018)
Real-time PCR	*C. auris*	ITS2	CauF CauR	CGCACATTGCGCCTTGGGGTA GTAGTCCTACCTGATTTGAGGCGAC	Kordalewska et al. (2017)
	C. auris and related species (*C. duobushaemulonii*, *C. haemulonii*, and *C. lusitaniae*)		CauRelF CauRelR	GCGATACGTAGTATGACTTGCAGACG CAGCGGGTAGTCCTACCTGA	
PCR	*C. auris*	GPI-protein genes	03410_F 03410_R	GCCGCTAGATTGATCACCGT TAGGTGTGGGTACCCTTGGT	Ruiz-Gaitán et al. (2018)
			05701_F 05701_R	GCAGCACTCGTGAGAGAACT GGCTGGTTCTCCTGCTCATT	
			05701_F2 05701_R2	TGCAACCACAGTGACCAC CTTGCTACAGTCTGAGAG	
		5.8S rDNA	RDN58_F RDN58_R	GGATCTCTTGGTTCTCGC CGCTCAAACAGGCATGC	
Real-time PCR	*C. auris*	ITS2	CAURF CAURR	CAGACGTGAATCATCGAATCT TTTCGTGCAAGCTGTAATTT	
PCR and Sequence analysis	*C. auris*	ITS1-4	ITS1 ITS4	TCCGTAGGTGAACCTGCGG TCCTCCGCTTATTGATATGC	Kaur et al. (2020)

Table 2 Continued.

Molecular Method	Target	Region	Primer name	Base Sequences (5'-3')	Reference
		D1/D2	NL1 NL4GG	GCATATCAATAAGCGGAGGAAAAG TCCGTGTTTCAAGACGG	
Sequence analysis	*C. auris*	ITS D1/D2	pITS-F pITS-R	GTCGTAACAAGGTTAACCTGCGG TCCTCCGCTTATTGATATGC	Lee et al. (2011)
			NL1 NL4	GCATATCAATAAGCGGAGGAAAAG GGTCCGTGTTTCAAGACGG	
Real-time PCR	*C. auris*	ITS2	V2424 V2426	CAGACGTGAATCATCGAATCT TTTCGTGCAAGCTGTAATTT	Leach et al. (2018)
Loop-Mediated Isothermal Amplification (LAMP)	*C. auris*		AurisFIP AurisBIP AurisLoop-F AurisLoop-B AurisF3 AurisB3	AGGCTACTGAGCTTGCTGGTGTAACCAAACCAACAGGAGAGG ACGGTTTCAGGGTTAGCATGGCTCAACAAAGTCGCTGGTACA CATCTCGAAGGCCTCGGT CACATACTCGAACGGAGTC GGGAAAGGAACCCTGACCT GGACACAGCATTCGAAGTGT	Yamamoto et al. (2018)
Real-time PCR	*C. auris*	ITS1 ITS2	*C. auris*	CGTGATGTCTTCTCACCAATCT TACCTGATTTGAGGCGACAAC	Lima et al. (2019)
Real-time PCR	*C. auris*	ITS2	CA1 4605 CA2 4605	TCAGGTAGGACTACCCGCTG CTGCATTCCCAAACAACTCGACTC	Walchak et al. (2020)
Real-time PCR	*C. auris*	ITS1 ITS2		TCC TCCGCTTATTGATATGC GGAAGTAAAAGTCGTAACAAGG	Teke et al. (2021)
RT-qPCR	*C. auris*	ITS2	V2424F (CAURF) V2426 (CAURR)	CAGACGTGAATCATCGAATCT TTTCGTGCAAGCTGTAATTT	Freitas et al. (2022)

Treatment and prophylaxis of *C. auris* infections

The treatment of infections caused by *C. auris* is a great challenge to be overcome, since many strains are resistant to antifungal agents commonly used in clinical practice, such as azoles, polyenes and echinocandins (Lockhart et al. 2017, Giacobbe et al. 2021). In 2017 the first report of multidrug-resistant *C. auris* occurred in Canada, isolated from a 64-year-old patient with chronic external otitis. In the susceptibility tests, the strain

presented Minimum Inhibitory Concentration (MIC) values of 128.0, 2.0 and 0.5 µg/mL for fluconazole (class of azoles), amphotericin B (class of polyenes) and micafungin (class of echinocandins) respectively. According to the authors, these values were compared with the tentative MIC breakpoints of the CDC, which are ≥ 32, ≥ 2 and ≥ 4µg/mL respectively. Thus, it could be said that the isolated strain was resistant to fluconazole and amphotericin B but susceptible to micafungin (Schwartz & Hammond 2017).

In a study, susceptibility tests were performed on clinical isolates from 54 patients (from South Africa, Pakistan, India and Venezuela) with *C. auris* infection and in the type specimen from Japan. The most common resistance was observed against fluconazole, 93% of the isolates, followed by resistance to amphotericin B and echinocandins, 35% and 7% respectively. It was also observed that 41% of the isolates were resistant to 2 antifungals classes and 4% to 3 classes. It is noteworthy that 63% of the patients were using urinary catheter, 73% using a CVC and 61% had bloodstream infection. For the site of infection, blood, urine and respiratory tract were more prevalent, 61, 7 and 5% respectively. The authors concluded that the treatment of this pathogen is limited due to resistance problems. Additionally, the authors suggested that risk factors and transmission mechanisms need to be better studied to enable efficient control measures (Lockhart et al. 2017).

The CDC recommends three drugs from echinocandin class for *C. auris* infections as initial therapy, are they: anidulafungin, caspofungin and micafungin (Table 3). With tentative MIC breakpoints of ≥ 4 ≥ 2 and ≥ 4 µg/mL respectively. However, if treatment is not sufficient and the infection persists for > 5 days, the CDC recommends switching treatment to liposomal amphotericin B (5 mg/kg per day). It is noteworthy that CDC does not recommends treatment when this fungus is isolated in a non-sterile and noninvasive site (such as urine, external ear, respiratory tract and skin colonization) when the clinical disease is not present (CDC 2021). According to the European Center for Disease Prevention and Control (ECDC) publication, the treatment of this fungus is still a limitation, as it is resistant to both, fluconazole (class of azoles) and echinocandins. However, the resistance to the latter is more variable since almost all *C. auris* isolates are resistant to fluconazole. It is worth noting that these two are the most prescribed options for candidemia treatment once they are less toxic than amphotericin B (ECDC 2018). The Pan American Health Organization, the National Health Surveillance Agency (ANVISA) - Brazil, and the Public Health England - United Kingdom, also brings the class of echinocandins as the first-line treatment (England 2017, ANVISA 2020, Pan American Health Organization 2021).

Echinocandin class is an essential fungicide against most *Candida* spp.They act by inhibiting a cell-wall enzyme complex, causing cell wall damage. Their applications are desirable once they have lower toxicity, less drug interaction (as they are not or poor substrate for tissue or intestinal P-glycoprotein and cytochrome P450 enzymes respectively) and mild adverse effects (like headache, fever, liver toxic effects, local phlebitis (caspofungin), histamine release, hemolysis and rash). The great difficulty in using this class is linked to malabsorption by oral administration, which can lead to low bioavailability, what makes the injectable route a better option (Denning 2003). Despite being considered a first-line treatment, the problem of *C. auris* resistance to this class has been growing more and more. Thus, the study of new drug candidates is increasingly necessary (Mahmoud Ghannoum et al. 2020, Pan American Health Organization 2021).

Among the new therapeutic candidates, ibrexafungerp can be mentioned. Ibrexafungerp is the first antifungal of the enfumafungin-derived triterpenoid class and has a fungicidal action by inhibiting a cell wall component. Its advantage over echinocandin is its good oral bioavailability, which favors administration by this route (Mahmoud Ghannoum et al. 2020). As can be seen in Table 4 several studies have been carried out in order to evaluate the use of this drug in the treatment of *C. auris* strains. In *in vitro* studies, despite the MIC_{90} commonly observed be 1 µg/mL, it was also possible to observe MIC_{90} in the range of 0.06 - 2 mg/L. However, when compared to controls, especially those with a known resistance problem, like fluconazole and amphotericin B, ibrexafungerp proves to be an excellent therapeutic alternative once its MIC values are lower (Berkow et al. 2017, Larkin et al. 2017, Arendrup et al. 2020, Wiederhold et al. 2021).

Table 3. Types of infection and clinical samples of *C. auris* isolation worldwide.

Drug	Adult dosing	Pediatric dosing	Neonatal dosing (2 months of age)	Antifungal class	Mechanism of action	Reference
Anidulafungin	loading dose of 200 mg IV, followed by 100 mg IV daily	Not approved	-	Echinocandin	Inhibits beta-(1,3)-glucan, damaging fungi cell wall	Denning (2003), CDC (2021)
Caspofungin	loading dose of 70 mg IV, followed by 50 mg IV daily	Loading dose of 70mg/m^2/day IV*, followed by 50mg/m^2/day IV	25 mg/m^2/day IV*	Echinocandin		
Micafungin	100 mg IV daily	2mg/kg/day IV, being possible to increase to 4mg/kg/day IV in 40 kg children	10mg/kg/day IV	Echinocandin		

* based on body surface area

Table 4 Main results of articles involving drugs that are already in clinical evaluation stages.

Drug	Mechanism of action	Study type	Strain/	Main test result	Comparative control	Reference
Ibrexafungerp	(1→3)-β-D-glucan synthase (component of the cell wall) inhibition, weakening fungal cell wall	*In vitro*	Clinical isolates (Germany, Japan, India, and South Korea)	MIC_{90}: 1 µg/mL	fluconazole: >64 µg/mL amphotericin B: 4 µg/mL anidulafungin:0.25 µg/mL caspofungin:1 µg/mL micafungin: 1 µg/mL,	Larkin et al. (2017)
			Clinical isolates (From countries all over the world)	$MIC_{90:}$ 1 µg/mL	anidulafungin: 0.125 to >16 µg/mL caspofungin: 0.03 to >16 µg/mL micafungin: 0.03 to >8 µg/mL	Berkow et al. (2017)
			122 clinical isolates collected from individual patients in six tertiary care hospitals in India	$MIC_{90:}$ 0.06–2 mg/L	amphotericin B: 0.5 - 1 mg/L fluconazole: 0.5 – ≥64 mg/L anidulafungin: 0.016 - >32 mg/L	Arendrup et al. (2020)

Table 4 Continued.

Drug	Mechanism of action	Study type	Strain/	Main test result	Comparative control	Reference
					micafungin: 0.03 - >32 mg/L isavuconazole: ≤0.004 - 2 mg/L voriconazole: ≤0.004 - 4 mg/L	
			Reference strains (CBS12372; CBS12373; CBS10913)	MIC_{90}: CBS12372: 0.125 mg/L CBS12373: 0.5 mg/L CBS10913: 0.06 mg/L	-	
			54 isolates	MICs:0.25 – 2 µg/mL MIC_{50} and MIC_{90}: 1 µg/mL	caspofungin and micafungin: 0.06 to >8 µg/mL (mainly 1 to 2 dilutions lower than for ibrexafungerp)	Wiederhold et al. (2021)
		In vivo in Guinea pig model	MRL 35368	Log CFU after the best concentration tested (10 mg / kg) in 7 days of treatment: 2,8 ± 0,7	Non-treated group Log CFU: approximately 4,25 Micafungin Log CFU: 3,6 ± 1,2	Ghannoum et al. (2020)
		In vivo in neutropenic mice	Clinical isolate	Log_{10} after the treatment for 7 days: 1.83 - 3.85 Log_{10} CFU/g (>1.5 Log_{10} CFU/g for 30 mg/kg groups and >2.5 Log_{10} CFU/g for 40 mg/kg groups)	Vehicle control group: 5.36 Log_{10} CFU/g Fluconazole group: 5.79 Log_{10} CFU/g Caspofungin group: 4.50 Log_{10} CFU/g	Wiederhold et al. (2021)

Table 4 Continued.

Drug	Mechanism of action	Study type	Strain/	Main test result	Comparative control	Reference
		Phase 3	30 patients (estimated value) with candidiasis, including candidemia, caused by *Candida Auris*	Recruiting	non-comparator, single arm	National Institutes of Health (2021a)
Fosmanogepix (Manogepix pro-drug)	Enzyme Gwt1 inhibition, compromising cell wall mannoproteins proper localization compromising cell wall integrity, biofilm formation and germ tube formation (defected fungal growth)	*In vitro*	200 isolates (clinical and Surveillance) during an outbreak	MIC_{90}: 0.03 mg/L	anidulafungin: 1.0 mg/L caspofungin: 0.25 mg/L micafungin: 0.25 mg/L fluconazole: 256 mg/L isavuconazole: 1.0 mg/L itraconazole:1.0 mg/L posaconazole:0.5 mg/L voriconazole: 2 mg/L amphotericin B: 2 mg/L flucytosine: 32 mg/L	Zhu et al. (2020)
			11clinical isolates	MIC_{90}: 0.03 mg/L	anidulafungin: 0.25 mg/L micafungin: 0.25 mg/L fluconazole: >128 mg/L posaconazole: 0.5 mg/L voriconazole: 2 mg/L amphotericin B: 1 mg/L	Pfaller et al. (2021)
			10 isolates from CDC FDA Antibiotic Resistance Bank And 3 clinical isolates	MIC_{50}: 0.03 µg/ml MIC_{90}: 0.125 µg/ml	fluconazole: MIC_{50} and MIC_{90} at 64 µg/ml caspofungin: MIC_{50} at 0.25 µg/ml and MIC_{90} values and 0.5 µg/ml.	Wiederhold et al. (2019)
		In vivo in neutropenic mice	UTHSCSA DI17-46	After 8 days of treatment: -kidney fungal burden: Log_{10} CFU/g after the best concentration tested (260	After 8 days of treatment: -kidney fungal burden: vehicle control: 5.61 log_{10} CFU/g caspofungin:3.41 log_{10}	Wiederhold et al. (2019)

Table 4 Continued.

Drug	Mechanism of action	Study type	Strain/	Main test result	Comparative control	Reference
				mg/kg): 3.86 -brain fungal burden: Log_{10} CFU/g after the best concentration tested (260 mg/kg): 2.99 After 21 days of treatment: -kidney fungal burden: Log_{10} CFU/g (range of all doses tested): 4.47 to 4.55 -brain fungal burden: Log_{10} CFU/g (range of all doses tested): 3.10 to 3.27	CFU/g; fluconazole: no fungal reduction (5.88 log_{10} CFU/g) -brain fungal burden: vehicle control: 4.40 log_{10} CFU/g caspofungin: 4.36 log_{10} CFU/g fluconazole: 4,91 log_{10} CFU/g After 21 days of treatment: -kidney fungal burden: vehicle control: 7.90 log_{10} CFU/g caspofungin: - fluconazole: no fungal reduction -brain fungal burden: - vehicle control: - caspofungin: 2.70 log_{10} CFU/g fluconazole: no fungal reduction	
		Phase 2	9 participants with candidemia and/or Invasive candidiasis caused by *Candida Auris*	Not Provided (The trial was closed early due the impact of COVID-19 on trial-related activities - the study were successfully met)	Single Group Assignment	National Institutes of Health (2021b)

The potential of ibrexafungerp in the treatment of *C. auris* was also observed in *in vivo* studies (Table 4), as groups treated with this drug showed a greater reduction in Log_{10} CFU/g than the other groups tested, such as vehicle group, untreated group, micafungin group, fluconazole group and caspofungin group (Mahmoud Ghannoum et al. 2020, Wiederhold et al. 2021). Those promising *in vitro* and *in vivo* results led ibrexafungerp to be considered an excellent therapeutic alternative, so currently this drug is undergoing a phase 3 multicentric study, in recruitment phase. It is an open-label, single-arm and non-comparator study whose objective is to evaluate safety, efficacy, tolerability and pharmacokinetics of ibrexafungerp administered orally, for up to 90 days, in people of both sex, age over 18 with documented *C. auris* infection (National Institutes of Health 2021a).

Another therapeutic option is fosmanogepix, a N-phosphonooxymethylene pro-drug that after systemic phosphatases action gives rise to manogepix, its active moiety (Shaw & Ibrahim 2020). Manogepix is a first-in-class, small-molecule, that targets the fungal enzyme inositol acylase (Gwt1), which catalyzes the initial step in the glycosylphosphatidylinositol (GPI) anchor biosynthesis pathway. The inhibition of this enzyme compromises the proper localization of cell wall mannoproteins, compromising not only the cell wall integrity, but also the germ tube formation (which causes defects in fungal growth) and biofilm (Watanabe et al. 2012, Covel et al. 2019, Zhu et al. 2020). The great advantage about the use of this anti-fungal in the therapy is because its mechanism of action is new, without resistance problems, making it highly effective against strains resistant to echinocandins and azoles, for example (Shaw & Ibrahim 2020).

In vitro and *in vivo* studies have also been carried out in order to assess the potential of this drug in the therapy of *C. auris* infections (Table 4). In *in vitro* assays, more than one study showed MIC_{90} of 0.03 mg/L, a value much lower than the controls used in those articles, such as, anidulafungin, micafungin, fluconazole, posaconazole, voriconazole and amphotericin B. What confirms that fosmanogepix could be an interesting option for the treatment of infections caused by strains resistant to several of those drugs (Zhu et al. 2020, Pfaller et al. 2021). This fact is in agreement with a study carried out in neutropenic rats, where it was observed that the fungal burden in the kidney, in the 8-day treatment, was lower than the one observed in the vehicle and fluconazole groups, and similar to the caspofungin group. As for the fungal burden in the brain, the fosmanogepix group presented fungal burden much lower than the other groups (2.99 Log_{10} CFU/g compared to 4.36 - 4.91 Log_{10} CFU/g in controls). In the 21-day treatment both, fosmanogepix and caspofungin groups, showed significant reductions in fungal burden, both in the kidney and in the brain. Those reductions were not observed in the vehicle and fluconazole groups of both organs. Reinforcing the potential use of this new drug in the therapy of systemic infections caused by *C. auris*, mainly in replacement of drugs with resistance problems, such as fluconazole (Wiederhold et al. 2019). Finally, it is noteworthy that a clinical trial, in phase 2, was conducted. In this trial, the drug was tested in 9 participants with candidemia and/or invasive candidiasis caused by this fungus. Despite not having detailed results available, the clinical trial was successfully met (National Institutes of Health 2021b).

Although only two drugs are in clinical evaluation stages, according to the Clinical Trials website, several other molecules and new strategies have been tested *in vitro* against this pathogen (Wall et al. 2018, Billamboz et al. 2021, National Institutes of Health 2021a, b). Ebselen, for example, has antioxidant, anti-inflammatory, and cytoprotective activity and showed excellent MIC_{50} results (approximately 2.5 µM) against *C. auris* 0390, a strain resistant to azoles and amphotericin B and with decreased susceptibility against echinocandins. Therefore, ebselen is considered a repositionable agent for the treatment of *C. auris* infections refractory to conventional treatments (Wall et al., 2018). Another example that can be cited is miltefosine, a drug currently used to treat leishmaniasis and breast cancer, that has shown activity against several fungal strains, including *C. auris* (Widmer et al. 2006, Spadari et al. 2019, Barreto et al. 2020).

In one study, miltefosine showed MIC values ranging from 1–4 µg/mL, against clinical strains, with a fungicidal effect. When tested against biofilms, this drug showed activity in both situations, during their formation (0.25–4 µg/mL) and on pre-formed biofilms (16–32 µg/mL). The

authors also studied this drug antifungal activity in *Galleria mellonella* larval infection model, but at this time they tried both, the free drug and encapsulated in alginate nanoparticles. This association strategy with alginate nanoparticles was motivated by the inherent toxicity of miltefosine. The possibility of a sustained release that could reduce its toxicity without impairing its anti-*Candida* activity turns out to be extremely desirable. The free drug, in both doses tested (20 or 40 mg/kg), reduced 2 logs of the fungal load of the *C. auris* CBS 10913 strain, and 0.5-1.0 log of *C. auris* CBS 12766 strain (resistant strain considered more virulent and with a faster fungal growth when compared to the other strain tested). The nanosystem (100 mg/kg) was also able to significantly reduce the fungal load of the *C. auris* CBS 10913 strain, but the same was not observed with the *C. auris* CBS 12766 strain. The histopathological analyzes performed corroborated with the fungal load results. Taking into account the results obtained *in vitro* and *in vivo*, and considering the few therapeutic options for *C. auris* infections, the authors consider the free and encapsulated miltefosine as promising alternatives (Barreto et al. 2020).

It is noteworthy that the use of nanotechnology is an excellent alternative when overcoming weaknesses of therapies considered first-line is desirable, such as problems related to toxicity and resistance (Barreto et al. 2020, Carvalho et al. 2020b, Marena et al. 2022a). In a recent study, amphotericin B nanoemulsions were developed, which were evaluated for their potential activity against *C. auris*. This study was motivated not only by the resistance problems that this drug has been showing to *C. auris* strains, but also by its toxicity. In the *in vitro* test (MIC) it was observed that both, the nanoemulsion with amphotericin B and the free drug, had the same MIC value against the *C. auris* strain (CDC B11903), 0.062 μg/mL. However, based on *in vivo* study, also performed in *G. mellonella* larval infection model, it can be said that the nanoemulsion increased the drug's activity. Although amphotericin B initially presented a greater logarithmic reduction of CFU/larva over the days, this reduction was overcome by the nanoemulsion containing the drug, and on days 4 and 5 it was possible to observe more than 1 log difference between them. Finally, in the acute toxicity assay, also carried out in *G. mellonella*, it was observed that free amphotericin B presents greater toxicity than the nanosystems, which did not cause deaths in all concentrations tested. Thereby, in addition to increasing the drug's activity, the nanosystem was also capable to reduce the drug side effects (Marena et al. 2022b).

Although just some of the most recent strategies are mentioned here, it is possible to observed that the concern with the treatment of this emerging fungus is a consensus. Strategies such as the development of new drugs, combinations of drugs already used in therapy with nanotechnology and even drug combinations, such as the association of colistin (an antibacterial drug without antifungal activity) with echinocandins (in order to obtain a synergistic effect), are very current alternatives (Wall et al. 2018, Barreto et al. 2020, Bidaud et al. 2020, Marena et al. 2022b). Despite the need for effective treatments, which is a real necessity, the demand for prevention cannot be forgotten.

In this sense, it is important to highlight the necessity of using infection prevention measures, such as following hand hygiene practices, allocating colonized patients in individual rooms, precautions based on transmission must be followed, cleaning and disinfection (with appropriate products) of the environment in which the patient is being cared. In addition, it is of fundamental importance to screen contacts of cases of newly diagnosed patients and communication between facilities (in the case of transfer) about the infection status. Moreover, an efficient laboratory surveillance of clinical samples is essential for the detection of new cases (Ong et al. 2019, Snyder & Wright 2019, CDC 2021, 2022b).

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