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Candida auris: Epidemiology, risk factors, virulence, resistance, and therapeutic options

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ABSTRACT

Candida auris emerged as a pathogen resistant to multiple antifungal and has been associated with nosocomial outbreaks with high transmission capacity between hospitalized individuals. *C. auris* was first described in 2009, after being isolated from the external ear canal discharge of a patient in Japan. The difficulty in identification, incorrect use of antifungal drugs, and treatment failure are causes of high mortality. Since then, *C. auris* has been increasingly reported from East Asia to North America, with substantial fatalities and misidentification. This review aims at describing the epidemiology, virulence, risk factors, resistance, and therapeutic options in *C. auris* infections.

1. Introduction

The incidence and prevalence of invasive fungal infections have increased, especially in the population of immunocompromised patients and/or hospitalized with serious underlying diseases, raising the mortality among these patients [1–4]. Among fungal infections, those caused by *Candida* spp. are the most prevalent. In developed countries, candidemia is the most common invasive fungal infection, associated with high costs and 40% of hospital mortality cases. These yeasts are commensal in healthy humans and may cause systemic infection in immunocompromised situations due to their great adaptability to different host niches. The genus is composed of a heterogeneous group of organisms and, therefore, a *Candida* species is often classified into a clade; *C. auris*, for example, belongs to the Metschnikowia/Clavisporaclade. Of the fungi regarded as human pathogens, members of the *Candida* genus are the most frequently recovered from human fungal infections. Containing approximately 500 species [51], this is the largest genus of medically important yeast. At least 30 *Candida* species have been recognized as causes for human infection, and the list continues to expand [52]. Nonetheless, more than 90% of invasive infections are caused by *Candida albicans*, *Candida glabrata*, *Candida parapsilosis*, *Candida dubliniensis*, *Candida tropicalis,* and *Pichia kudriavzevii* (formerly known as *Candida krusei*) [5] However, recently, *Candida auris* has emerged as a serious threat to global health – a multidrug-resistant pathogen, identified for the first time as a human disease from ear swab in 2009, and in blood cultures in 2011. Thus, this review aims a describing the epidemiology, risk factors, virulence, resistance, therapeutic options, diagnostic, and prevention of *C. auris* infection.

2. Epidemiology and risk factors for *C. auris* infection

Candida yeasts have been responsible for many severe systemic infections, especially in critically ill and debilitated patients, resulting in significantly increased hospital stay and healthcare costs [6]. Invasive mycotic diseases associated with nosocomial infections are a public health concern, and candidemia is becoming very prevalent in European and American countries [7,8]. In the USA, candidemia is the fourth most frequent cause of death [4], accounting for more than 85% of all fungemia in the country [5]. In tertiary hospitals, candidemia corresponds to 50% of the documented infections, representing a major challenge to clinicians of different specialties due to the diagnostic and therapeutic difficulties of infections caused by such agents [9]. However, the increased number of immunocompromised individuals, the unjustified use of multiple broad-spectrum antibiotics, and the advent of implanted medical devices paved the way for rare *Candida* species, such as agents of invasive mycoses and nosocomial infections of the bloodstream [10]. Invasive cases of non-albicans candidiasis have been reported in many parts of the world [11]. Although there are differences in the frequencies of yeast isolation in the last 20–30 years, the pathogens involved in 95% of the infections are *C. albicans*, *C.*

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dubliniensis, *C. glabrata*, *C. parapsilosis*, *C. tropicalis,* and *Pichia kudriavzevii,* with the most prevalent being *C. albicans* [12,13]. Usually, *C. albicans* colonizes some regions, including the skin, oropharynx, lower respiratory tract, gastrointestinal tract, and genitourinary system. *C. parapsilosis* causes 30% of candidemia cases among newborns [5]. *C. glabrata* is a most common infectious agent among older adults and neoplastic patients. *C. tropicalis*, on the other hand, is more common in leukemia and neutropenic patients [5]. Since *C. parapsilosis* colonizes the skin, it is a common pathogen in catheter-related infections and may cause outbreaks. *Pichia kudriavzevii,* in turn, is more common among patients with neutropenic leukemia, who receive prophylaxis with fluconazole [5,10].

Although the *C. albicans* species is the main yeast isolated from these infections, a new emerging species, *C. auris*, has been concerning for health professionals and researchers because it can cause invasive infections and is associated with high mortality, being often resistant to multiple antifungal drugs and difficult to diagnose. This yeast was first described in 2009, after being isolated from the external auditory canal of a patient in Japan and 15 Korean patients [14,15]. Since then, reports of *C. auris* infections, including blood infections, have been published in several countries. *C. auris* became an emerging threat to global health, engulfed in a host cell of invasive infections and outbreaks in health facilities. The actual incidence of *C. auris* fungemia and its global prevalence are poorly understood and difficult to diagnose through classical methods; hence, in the current state, this is an underreported and lethal disease [16]. To date, infected patients have been identified in Australia [49] Brazil [23], China [50], Colombia [25], Germany [28], India (the vast majority) [17,18], Israel [29], Kuwait [20], Norway [28], Oman [30], Pakistan [26], Panama [31], South Africa [19], Spain [27], United Kingdom [21], United States [24], and Venezuela [22]. *C. auris* is a yeast, the novel *Candida* species in the *Candida haemulonii* complex, which causes a wide range of infections, especially in hospital settings and intensive care units (ICUs) [32,33]. Of the 15,271 isolates reviewed from 4 continents from 2004 to 2015, only four isolates were identified as *C. auris* [16,26]. However, since 2009 a rapid and global emergence of *C. auris* occurred [16]. An 18-month prospective study in Indian ICUs reported 1400 candidemia cases. *Candida auris* was identified as the 5th most common cause of ICU-onset candidemia, discovered in 19 out of 27 ICUs, with prevalence of 5.3% [34]. A tertiary medical center in South America reported *C. auris* as the 6th most common cause of bloodstream infection in the hospital between March 2012 and July 2013 [22]. The precise mode of transmission within the hospital environment is unknown. Early evidence suggests the pathogen can spread in medical settings through the contact with contaminated surfaces or equipment, or from person to person through contact with contaminated skin. During outbreaks, *C. auris* can contaminate the room of colonized or infected patients. The survival of *C. auris* for weeks, even months, in biotic and abiotic sources within the hospital confirmed the importance of the hospital transmission of this new agent, direct transmission is also a particular risk but this does not prevent the transmission by hands, therefore, hand hygiene needs must be respected as in any other infection. *Candida auris* is a pathogenic agent first diagnosed in hospitalized patients and has been assessed as a hospital pathogen causing infection in certain high-risk populations. Transmission from patient to patient has been documented, leading to skin colonization by *C. auris* and increased risk for candidemia [18]. The hospital environment could represent a reservoir that contributes to the nosocomial transmission of *C. auris* [18,21]. The risk for infection with *C. auris* seems to be related to immunosuppression, to patients hospitalized in intensive care units over long periods, using central venous catheter, and to the early use of antibiotics or antifungal. Recent investigations in Asia, the Middle East, and South Africa have shown that *C. auris* is a nosocomial pathogen of the bloodstream and these strains had elevated azole and caspofungin MICs (Minimum Inhibitory Concentration) [20,23]. The first outbreak of *C. auris* detected in the Americas was reported in Venezuela. Such event occurred between March 2012 and July 2013, in the ICU of a hospital in Maracaibo. The outbreak affected 18 patients, of which 13 were pediatric patients. All isolates were initially identified as *Candida haemulonii*. Further sequencing of the internal transcribed spacer (ITS) region and the Amplified Fragment Length Polymorphism (AFLP) analysis showed that all isolates of the outbreak involved were *C. auris*. Strains of these yeasts resistant to various antifungal agents have already been found in Indian and Korean hospitals, causing fungal infections and deep infections with high mortality rates [23].

The predisposing risk factors for *C. auris* infection are similar to other *Candida* species, as these are opportunistic pathogens. Patients with immunocompromised diseases (diabetes mellitus, malignancy, chronic renal disease, neutropenia, HIV), concomitant bacteremia, broad spectrum antibacterial or antifungal therapy within 90 days, surgery within 90 days, presence of central venous catheters or urinary catheters, ICU stay, and parenteral nutrition (PN) administration have an increased risk of acquiring *C. auris* [16,22]. To date, only a case-control study has been performed to determine specific risk factors predisposing to *C. auris* candidemia [34]. The study was performed in an ICU in India, comparing *C. auris* (n = 74) and non-auris (n = 1087) fungemia cases. The multivariate analysis showed patients with respiratory disease, vascular surgery, and 30-day exposure to antimycotics were more likely to develop ICU-onset *C. auris* fungemia [34].

Available data suggested the risk factors for *C. auris* infections are not different from the risk factors associated with other *Candida* species infections, which include diabetes mellitus, presence of central venous catheter, immunosuppressive state, neutropenia, exposure to broad spectrum antibiotics, parenteral nutrition, blood transfusion, hemodialysis, surgery within 30 days, intensive care, previous antifungal agents within 30 days, bacteremia concomitant with candidemia, permanent urinary catheter, candiduria, chronic renal disease, and chemotherapy. Infections have been reported in patients of all ages, from preterm infants to older adults. Further studies may be required to learn more about the risk factors associated with *C. auris* infection [29,33,35–37]. To describe the epidemiology of *C. auris* infections, the Center for Disease Control (CDC) used genome sequences from 54 isolates collected from Pakistan, India, South Africa, and Venezuela. These data revealed four distinct geographical clades, demonstrating how this multidrug-resistant yeast emerged at the same time on three continents without a clear explanation. It is only known that the increase occurs between patients who have been exposed to antifungal drugs [2,18,26].

Prakash et al. [23] studied the genetic and proteomic diversity of *C. auris* isolates from three different continents – Asia, Africa, and Latin America – using geographic grouping for all three techniques analyzed. Although this study is well restricted by the limited number of isolates tested in different geographic locations, evidences of geographic clustering in Indian and Brazilian isolates were observed. It should be emphasized that the number of *C. auris* reports in countries outside India was limited to a small number of isolates. Molecular studies of *C. auris* strains isolated from Korea and India have shown them to be clones, which evidences the implication in nosocomial transmission.

Most *C. auris* strains (> 60–80%) are resistant to fluconazole, 10–30% exhibit high MIC for amphotericin B, and 10% can be considered resistant to echinocandins [2,18,38].

In London, an outbreak of *C. auris* occurred, involving 22 adult cardiac-thoracic clinic patients with bloodstream, surgical, and urinary wound infections, as well as 28 other colonized patients [21].

Sekyere [35], through a systematic review of *C. auris*, showed that at least 742 isolates were reported in 16 countries, being most in India (≥243), the USA (≥232), and the United Kingdom (≥103) from 2013 to 2017. Most isolates are from men (64.76%) and from blood (67.48%), with a mortality rate of 29.75%. Affected patients also had other comorbidities: diabetes (≥52), sepsis (≥48), lung diseases (≥39), and kidney diseases (≥32). The antifungal agents to which the strains were resistant were fluconazole (44.29%), amphotericin B

(15.46%), voriconazole (12.67%), and caspofungin (3.48%). Overall, the prevalence of *C. auris,* which is predominantly nosocomial, is increasing worldwide [39–42]. As routine detection methods failed to identify *C. auris*, their incidence rates and prevalence are not well known and this infection is more common than imagined.

3. Virulence

Currently, *Candida auris* is the greatest clinical challenge in the control of nosocomial infections. This pathogen can be transmitted from patient to patient and resist to different classes of antifungal agents [28]. The high prevalence of invasive infections and *C. auris* mortality rate are associated with their virulence factors, such as hyphae formation, adherence, formation of biofilms and production of phospholipases and proteinases, as well as their multi resistance to the available antifungal agents. *C. auris* expresses virulence determinants to a lesser degree than *C. albicans* [37]. However, a study performed by Sherry and collaborators (2017) considered *C. auris* highly virulent, even more virulent than *C. albicans* [43].

C. auris may present a peculiar form of *in vitro* growth; this pathogen may not release its daughter cells after budding, resulting in a large aggregation of cells with high physical resistance, which could give them some resistance in tissues and in the environment [33]. In an invertebrate model of *Galleria mellonella*, the non-aggregated form showed greater pathogenicity, similar to *C. albicans* [33]. In addition, the non-aggregated form is able to form stronger biofilms with greater pathogenicity and higher death rates compared with the non-aggregated version [33,44]. Due to this ability to form variant biofilms, *C. auris* is considered a pathogen of difficult eradication and capable of causing hospital epidemics of invasive and persistent infections. Although it was isolated a few years ago, its virulence factors remain poorly understood and further research is required to better explore these features involved in the *C. auris* infection pathogenesis [16].

To answer questions about the virulence of *C. auris*, a draft genome study was carried out. Analyses using *C. albicans* as a reference have demonstrated that *C. auris* shows significant virulence attributes in comparison with other species of *Candida* [45]. Eight oligopeptide transporters were identified, which are related to the versatility in the nutrients acquisition, contributing to the pathogen's adaptation to different environments. Thus, the presence of these transporters is an important feature in the establishment of an infection. A significant presence of families of enzymes involved in the invasion, such as mannosyl transferases, aspartyl-secreted proteases, and lipase has also been shown. However, the families of adhesion genes and integrins were poorly represented. In any case, the presence of these proteins is related to the invasiveness of *C. auris* and its capacity to cause fungemia. In addition, 686 biofilm-related proteins were revealed, including several enzymes, transcription factors, ribosomal proteins, and transporters, which indicates the ability of *C. auris* in forming biofilms. Finally, the analysis also predicted an arsenal of orthologous transporters to *C. albicans*, belonging to the major facilitator superfamily (MFS) and ATP binding cassette (ABC) superfamily. These transporters act as efflux pumps, which may justify the intrinsic resistance of *C. auris* to different antifungal agents, along with 193 possible proteins related to transcription factors [45].

C. auris can adhere differentially to polymeric surfaces, forming biofilms. The development in the biofilm form gives this pathogen the ability to resist to antifungal agents that are active against their planktonic forms [36]. The authors consider that, although the formation of biofilms equivalent to those of *C. albicans* is not possible*, C. auris* demonstrates a remarkable virulence capacity that should be further explored, especially regarding the association of its heterogeneity with its ability to form aggregates. They also emphasize the need for infection prevention measures targeting *C. auris* biofilms in patients, medical devices, and in hospital settings [36].

A study with clinical *C. auris* isolates from the vaginal region demonstrated phospholipase, proteinase, and hemolysin activity, emphasizing their ability to adhere and invade host cells [46]. The presence of these virulence factors, associated with the difficulty in its identification in patients, such as the wrong diagnostic of the *Candida haemulonii* complex using the available biochemical methods [29], turns the infection by this pathogen into a clinical and public health challenge.

4. Resistance and therapeutics options

Regarding its resistance, *C. auris* can present thermotolerance, growing well at 37 °C but maintaining its viability up to 42 °C, as well as salt tolerance. Concerning resistance to available antifungal agents, *C. auris* has demonstrated extensive resistance to azoles, such as fluconazole and amphotericin B [42]. The ABC transporter activity was evaluated and found to be significantly higher in *C. auris* than in *C. glabrata* [29]. This data seems to justify the *C. auris* resistance to azoles, which corroborates the identification of several genes encoding ABC transporters and of the most important families of *C. auris* MFS genes [45].

Most *C. auris* strains present acceptable susceptibility to the class of echinocandins, with some exceptions. *C. auris* isolates unusually resist to the three classes of antifungal agents. However, 41% of clinical isolates from India showed resistance to two classes and 4% to all three classes of antifungal agents [26]. Another study, in a murine model, showed that micafungin was superior among antifungals with greater fungicidal activity [47].

A study evaluated the susceptibility of sixteen clinical isolates of *C. auris* to different classes of widely known antifungal agents and to a more recent drug [37]. *C. auris* responded differently to several antifungals. Among azoles, one clinical isolate showed reduced susceptibility to fluconazole. This clinical isolate with lower resistance to fluconazole was the only strain isolated from a non-blooming source, which supports the hypothesis that virulent strains causing fungemia also appear to be more resistant to various drugs. The strains tested showed high MIC values for fluconazole, amphotericin B, voriconazole, and itraconazole. Among azoles, isavuconazole was the most active. The study also verified that the strains showed a varied susceptibility to the echinocandins class, corroborating the data of other authors [22,33,38]. Furthermore, SCY-078 and VT-1598 were used against *C. auris* [35]. SCY-078 is a triterpene glucan synthase inhibitor (GSI) that has been shown to exhibit both *in vitro* and *in vivo* activity against the most common *Candida* species, including echinocandin-resistant isolates [54]. To identify new drugs that are possibly effective against *C. auris*, the activity of SCY-078, a novel orally bioavailable 1,3-β-D-glucan synthesis inhibitor, was evaluated. It has demonstrated a potent antifungal activity against *C. auris* strains, showing cellular deformation (destruction, wilting, pore formation) and provoking cell division inhibition [35]. This data suggested this drug may have another therapeutic target, in addition to the inhibition of 1,3-β-D-glucan. Thus, SCY-078 is a drug with great potential in the treatment of *C. auris* infections [37]. Lockhart and collaborators [26] showed this specie was resistant to fluconazole and 50% of the isolates were resistant to amphotericin B. The VT-1598 appears to have the broadest spectrum activity. *In vitro* activity has also been reported against *Candida auris* isolates (MIC range 0.03–8 mg/L) [55]. However, it is unknown how effective this agent may be against this emerging pathogen when *in vivo* [56]. Moore et al. [39] studied whether a chlorine-based disinfectant and iodine-based skin antiseptic were effective against *C. auris* and the results suggested that, when applied appropriately, their use could reduce environmental contamination and skin colonization, respectively. Chlorhexidine-based products may also be effective. Other study, conducted by Abdolrasouli and collaborators [40], demonstrated that *C. auris* isolates were inhibited by chlorhexidine gluconate at 0.125–1.5% and for iodinated povidone at 0.07–1.25% concentrations.

Rudramurthy et al. [34] reported the highest number of *C. auris* infections in India. They demonstrated that 16% of the 74 C. *auris*

strains recovered from different patients were multidrug resistant (MDR). The fluconazole resistance rate was 60%, and 13% had a MIC above 1 mg/L for amphotericin B. Echinocandins are considered first-line therapy for *C. auris* infections, but their susceptibility to the pathogen should be performed whenever possible [17].

Molecular mechanisms responsible for this yeast antifungal resistance have not yet been fully elucidated; however, preliminary data suggest the efflux of pumps and mutations in lanosterol 14-alpha-demethylase (*ERG11*) gene may help explain the high rate of resistance to fluconazole [29]. A study performed by Chowdhary and collaborators (2018) [57] demonstrated that 90% of *C. auris* isolated were resistant to fluconazole (MICs 32 to ≥64 mg/L). ERG11 sequences of *C. auris* exhibited substitutions of Y132 and K143 amino-acids in 77% of the fluconazole-resistant strains and no substitutions in these positions were observed in isolates with low fluconazole MICs (1–2 mg/L), suggesting that these substitutions confer a fluconazole resistance phenotype similar to that described for *Candida albicans*.

In summary, the success or failure of treatment with different antifungal agents depends on the virulence of the *C. auris* strain present in the infection. Echinocandin was one of the three antifungal classes with the highest potential against *C. auris*, especially micafungin, being therefore one of the most indicated drugs for the treatment of infections caused by this pathogen. However, the association with other therapeutic approaches should be considered. In addition, further research including clinical trials is required to reveal the therapeutic potential of new drugs such as SCY-078, as well as the discovery of new drugs in different potential sources, like natural products (see Fig. 1).

5. Biochemical and molecular diagnostics

Technologies for identification of *Candida* species have been continuously improved over the past several decades, ranging from conventional biochemical methods (manual and automated) to nucleic acid-based methods [41]. Conventional identification or biochemistry of yeasts through commercial systems such as Vitek 2, BD Phoenix, and API20 are not able to identify or otherwise erroneously identify *C. auris* isolates. Isolation and identification of *C. auris* by traditional methods can be challenging. Most of the time, *C. auris* can be confused with other microorganisms by some phenotypic identification methods (VITEK 2 YST, API 20C), BD Phoenix yeast identification system, and MicroScan. The figure below briefly shows the methods cited and the species that may be erroneously reported in the *C. auris* identification (Fig. 2). In the microscope, the smear shows single or paired ovoid cells. The colonies grow as a smooth and white cream in SDA. The differential diagnosis of *C. auris* and other similar species such as *C. haemulonii, C. duobushaemulonii, C. pseudohaemulonii,* and *C. heveicola* were carried out through several tests, such as germ tube production and chlamydospore formation in corn, in addition to the sugar assimilation and fermentation test and the differential growth in chromogenic medium [41]. *Candida auris* was characterized by the absence of germ tube and formation of chlamydospores in corn root agar, unlike other *Candida* species. *Candida auris* assimilates N-acetylglucosamine, succinate, and gluconate as carbon sources. This assimilation property seems to differ between species of different geographic origins, as it is seen in Indian, Brazilian, and South African isolates but not in Japanese and Korean ones [41,42]. *Candida auris* is inhibited by a medium containing 0.01% cycloheximide, develops pink color in chromogenic medium, and has the capacity to grow at temperatures higher than 42 °C.

In recent years, matrix-assisted laser desorption/ionization - time of flight mass spectrometry (MALDI-TOF MS)-based methods have presented a promising alternative for routine identification of clinically relevant *Candida* species [41,48]. In the USA, the CDC has instructed hospital units to use diagnostic methods such as MALDI-TOF with updated database and DNA sequencing in case of *C. auris* infection suspicion. Laboratories located in the US that have no ability to identify suspected *C. auris* isolates have an option to send samples to the CDC using state public health laboratories for additional characterization [16,28]. This organism can be challenging to identify using standard microbiological techniques and often exhibits multiple drug resistance.

In fact, the correct identification of *C. auris* can be provided only by molecular sequencing of targets in the nuclear ribosome RNA gene (D1/D2 region or the internal transcribed spacer domain) or by using MALDI-TOF MS [16,26]. Similar to other *Candida* infections, *C. auris* are usually diagnosed by culturing blood or other body fluids; however, its identification requires specific laboratory methods since *C. auris* can be easily confused with other yeast species, such as *Candida haemulonii* and *Saccharomyces cerevisiae*.

The proteomic typing detects phenotypic differences within the

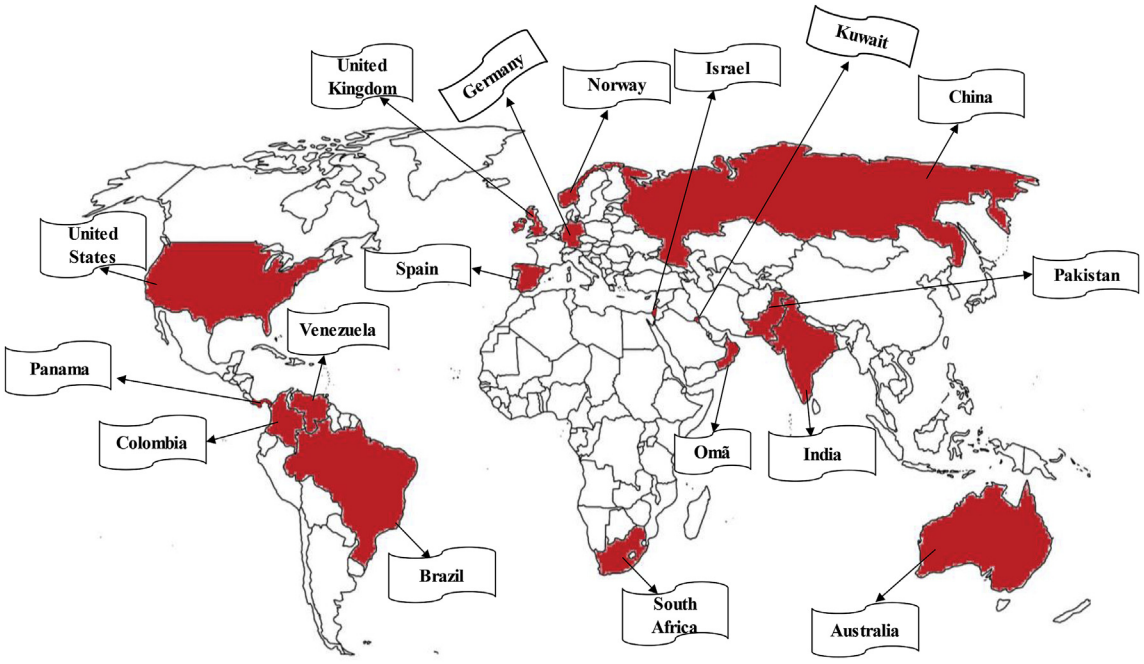

Fig. 1. Representative map of the countries in which *Candida auris* was isolated until now. Adapted from Chowdhary et al., 2017 [58].

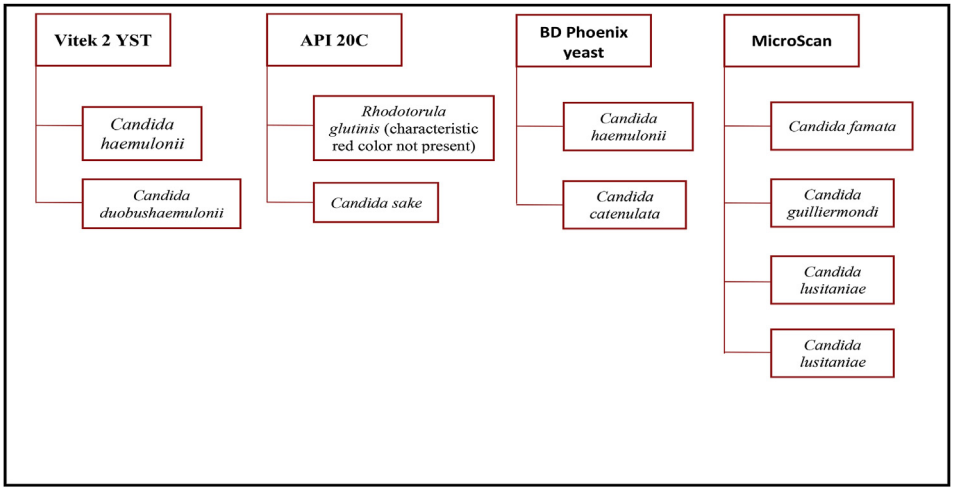

Fig. 2. Summary of common misidentifications, based on the identification method used. Available online: www.cdc.gov/fungal/candida-auris/recommendations.html accessed on August 2018).

species, contrasting with the phylogenetic approach, which detects intrinsic genetic variation. However, this is not the reality of hospitals in developing countries, which leads to misidentification in the treatment and high mortality [16].

6. Conclusion

Considering the increase of this yeast in hospital environments, serious precautions are required for contact among patients and professionals, in addition to a strict control of infection within hospitals through effective and systematic surveillance, as well as molecular tools for the efficient detection and fast and less onerous diagnosis, to prevent *C. auris* infections.

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