https://doi.org/10.31925/farmacia.2023.2.1 **REVIEW**

CANDIDA AURIS: THE UNWELCOME SUPERFUNGUS

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Manuscript received: December 2022

Abstract

The incidence of nosocomial fungal infections has increased in recent years. The most common infection of this type is candidiasis. Some yeasts of the genus *Candida* are commensal in healthy humans, but can cause systemic infections in immunocompromised situations due to their great adaptability to different physiological states of the host. Although only discovered in 2009, *Candida auris* is one of the species that has rapidly become a serious threat to global health. The severity of infections with this species is characterized by multidrug resistance to antifungal treatment, a short transmission time and an aggressive epidemiological profile. It is difficult to identify and can be easily confused with other fungal species. The emergence of outbreaks in some parts of the world is still difficult to explain, but the emergence of infection prevention and management protocols may minimise the risks. *C. auris* has also attracted the attention of researchers from a genetic point of view, its ability to resist treatment being characterised by the presence of specific resistance genes. Understanding the traits of *C. auris* species is particularly important for developing appropriate therapies and implementing effective prevention strategies. We can say that this species represents one of the current challenges for public health systems worldwide.

Rezumat

Incidența infecțiilor fungice nosocomiale a crescut în ultimii ani, cea mai frecventă infecție de acest tip fiind candidoza. Unele drojdii din genul *Candida* sunt comensale la omul sănătos, dar pot provoca infecții sistemice la pacienții imunocompromiși, datorită marii lor adaptabilități la diferite stări fiziologice ale gazdei. Deși a fost descoperită abia în 2009, *Candida auris* a devenit rapid o amenințare serioasă pentru sănătatea globală. Gravitatea infecțiilor cu această specie se caracterizează prin multirezistență la tratamentul antifungic obișnuit, un timp de transmitere scurt și un profil epidemiologic agresiv. Este dificil de identificat și poate fi ușor de confundat cu alte specii fungice. Apariția unor focare în unele părți ale lumii este încă greu de explicat. *C. auris* a atras atenția cercetătorilor și din punct de vedere genetic, capacitatea sa de adaptare la tratament fiind caracterizată de prezența unor gene de rezistență specifice. Înțelegerea caracterelor speciei *C. auris* este deosebit de importantă pentru dezvoltarea unor terapii corespunzătoare și implementarea unor strategii de prevenție eficiente. În concluzie, putem spune ca această specie reprezintă una dintre provocările actuale ale sistemelor de sănătate publică la nivel mondial.

Keywords: *Candida auris*, multidrug-resistance, therapy, biofilm, mutations, prevention

Introduction

The incidence of nosocomial fungal infections has been increasing in recent years. The most common infection of this type is candidiasis [1]. Some yeasts of the genus *Candida* are commensal in healthy humans and can cause systemic infections in immunocompromised situations, due to their great adaptability to different physiological states of the host. The most common species isolated from intensive care units (ICU) patients is *C. albicans* being an opportunistic infectious agent [2]. Also, in recent decades, non-albicans species with increased virulence have been identified as *C. glabatra, C. krusei, C. tropicalis*, which represent real public health problems. Recent years have seen the discovery of a new species, *Candida auris*, which has been classified as one of the multi-drug-resistant fungi capable of causing nosocomial infections. [3].

The source of *Candida auris* has yet to be determined, and some have suggested that global warming may have enabled its selection. Evidence suggests that animals with higher body temperatures, such as birds, may have transmitted the fungus to urban areas, leading to its infection of humans. Furthermore, the mechanism by which *C. auris* invades the epithelial layer without forming hyphae is yet to be elucidated. Recent studies have indicated that *C. auris* isolates with a non-aggregating phenotype are able to evade the immune system and spread to other hosts more easily. Studies have demonstrated that *C. auris* transmission in health-care institutions can occur through contact with contaminated surfaces or equipment, as well as from

person-to-person. Additionally, the presence of the fungus on the skin of individuals with *Candida* infections has been reported. To minimize the spread of *C. auris*, measures such as proper hygiene, sanitation, and cleaning should be taken. Further research is needed to gain a better understanding of the transmission dynamics of this pathogen.

Candida auris has been shown to have a preference for colonizing the skin rather than other mucosal surfaces such as the gastrointestinal tract, potentially leading to person-to-person transmission. Moreover, the pathogen can also spread through systemic bloodstream infection known as candidemia, often associated with a crude mortality rate ranging from 30% to 70%. The virulence of *Candida* species is attributed to several factors, such as secreted proteases and lipases, mannosyl transferases, oligopeptides, siderophore-based iron transporters and biofilm formation. The involvement of these elements is known to be involved in the invasion, colonization, and nutrient acquisition of the pathogen [4].

Global prevalence of *C. auris* infection

In 2009, *Candida auris* was first isolated from the external ear canal of a patient in Japan, with subsequent reports of its involvement in otitis media in 15 individuals from 5 hospitals in Korea [5].

The global emergence of *C. auris*, has been reported in more than 30 countries, including the United States, United Kingdom, Canada, India, South Africa and Colombia. It is known to cause blood, wound, and ear infections and is difficult to diagnose and treat due to its resistance to antifungal drugs. Transmission of *C. auris* is thought to occur through contact with infected patients, contaminated environmental surfaces, or medical equipment. Therefore, proper infection prevention and control measures are essential to limit the spread of *C. auris* in healthcare settings [6].

The Pan American Health Organization (PAHO) first reported the emergence of *Candida auris* in the Americas region in March 2012, when Venezuela experienced the first outbreak of the fungus. Since then, isolated cases and outbreaks of *C. auris* have been reported in Colombia (2015), the United States (2016), Panama and Canada (2017), and Chile and Costa Rica (2019) [7].

An investigation conducted in skilled nursing facilities in the Chicago, Illinois, USA, areas revealed a high incidence of colonization by *Candida auris* among patients receiving mechanical ventilation, those with gastrostomy tubes and those with urinary catheters. Outcomes related to invasive *C. auris* infection showed mortality rates of between 22% and 57% in the United States. Isolates of Candida auris often demonstrate decreased susceptibility to the antifungal agent fluconazole, as well as variable susceptibility to other antifungal agents. The CDC recommends echinocandins as empirical treatment for suspected or confirmed *C. auris* infections. Nevertheless, recent studies have demonstrated reduced susceptibility to echinocandins, and there is a suggestion that resistance may be induced through antifungal pressure [8].

In the United States, the occurrence of *Candida auris* infection remains relatively uncommon; however, the Centers for Disease Control and Prevention (CDC) have provided several best practices for both patients and healthcare personnel to help mitigate the risk of contracting this infection [9]. Also, after the yeast was identified in 2022 in a Wisconsin resident, the responsible authorities started a prevention campaign for this infection [10].

The COVID-19 pandemic has led to an increased susceptibility to co-infection with the opportunistic pathogenic yeast *Candida auris* in 2020. This is evidenced by *C. auris* infections in mechanically ventilated patients in ICUs in countries such as Brazil, Guatemala, Mexico, Peru and Colombia [7]. A case report from Brazil showed that *C. auris* superinfections in critically ill COVID-19 patients were linked to high 30-day mortality rates, typically over 50% [11].

In Guatemala, in December 2020, *C. auris* was isolated in soft tissue and bone biopsies from a patient diagnosed with acute osteomyelitis of the right tibia. In addition, a second case, from the same general surgery service, was recovered from a leg tissue biopsy of a multiple trauma patient with a surgical site infection [12].

A recent study published in 2019 found that more than 10% of candidiasis cases in Southern Africa are attributable to *Candida auris*, the third most common species of *Candida*. The incidence of *Candida auris* candidemia was found to be highest in hospitals located in Gauteng Province, South Africa, during the surveillance period. This is thought to be due to a combination of factors, including a highly concentrated and mobile patient population, a high volume of referrals and admissions of patients with complex cases, indiscriminate utilization of antimicrobial agents, including azoles and echinocandins, and inadequate infection control practices. Additionally, international travel to and from Gauteng Province may have contributed to the observed epidemic, as evidenced by reported cases and outbreaks caused by the *C. auris* clade in other countries [13, 14].

In 2016, at the La Fe Polytechnic University Hospital in Valencia, Spain, a 66-year-old man who underwent a liver resection for hepatocellular carcinoma was admitted to the Intensive Care Unit after surgery, with surgical site infections, liver abscesses, and viscera. After 84 days of treatment with multiple antifungal agents, the patient was successfully saved. This was the first reported case of its kind in the Continental Europe [15].

A total of 786 cases of *C. auris* colonization/infection were reported in Spain from the first Spanish case in

2016 until 2019, with a decline in cases observed from 2017 to 2019. Nevertheless, *C. auris* cases have resurged since the onset of the COVID-19 pandemic, with 591 new cases reported between 2020 and 2021 [16, 17].

In Liguria, Italy, an outbreak of *Candida auris* has been reported, with 277 cases identified to date. The initial case was detected in July 2019 in one hospital, with sporadic occurrences continuing to emerge. In February 2020, a rapid increase in cases was observed when *C. auris* was detected in an intensive care unit for patients with severe COVID-19 in the same hospital. Subsequent to this outbreak, 277 cases have been documented in at least eight different healthcare facilities in the Liguria region and 11 cases have been reported in facilities in nearby Emilia-Romagna [18].

In 2013, the first instance of *Candida auris* infection was reported in the United Kingdom. It spread immediately, with three major UK hospitals becoming hotbeds for infection. Since then, the number of cases has been on the rise, which is why the British authorities have issued a guide on the prevention, diagnosis and treatment of *C. auris* infection, which is updated whenever necessary [19, 20].

Sporadic cases have been reported in the rest of Europe [19].

Identification Methods

Biochemical identification

Bacteria and fungi are frequently identified using biochemical techniques. The assimilation and fermentation patterns are identical to those of other closely related yeast species, which makes the *C.auris* identification a difficult problem. However, rather than requiring a perfect match, some identification algorithms identify a species based on the assimilation and fermentation pattern that matches it the closest by percent. They will make a mistaken identification rather than say "no identification". Several early *C. auris* isolates have been misidentified as *Rhodotorula glutinis*, *Saccharomyces cerevisiae*, or *Candida* sake when using the API 20C AUX or API ID 32C systems, or as *Candida haemulonii* while using the Vitek 2 system, as a result of this restriction [20]. Research into the incorporation of *C. auris* into databases has about gained in some improvements. The CDC has developed algorithms to detect when further analysis is necessary for certain biochemistry-based identification systems [21].

Identification based on mass spectrometry

Due to the emergence of *C. auris* as a novel species, MALDI-TOF MS techniques were initially unable to identify it. As the organism has spread to numerous countries, the addition of *C. auris* to research-exclusive and subsequently FDA-approved databases has been carried out by commercial MALDI-TOF MS manufacturers [22, 23].

Identified based on colony colour

The morphology and pigmentation of colonies of *C. auris* recovered from culture can be utilised to identify the species; however, this method is not always reliable. Distinguishing *C. auris* from other *Candida* species requires the use of additional techniques due to the absence of pseudohyphae and germinative tubules in *C. auris* cells. While some strains do not, other stains are able to form cellular aggregates. A feature that sets *C. auris* apart from most other *Candida* species is its ability to grow well at temperatures ranging from 40 - 42°C. The traditional cromogenic media used to identify *C. auris* colonies typically display a white or rosy colouration, although some colonies may be red or purplish in hue. Novel cromogenic media have been developed to simplify the process of identifying *C. auris* [23]. Using CHROMagar™ *Candida* Plus agar, the colonies of *Candida auris* exhibited a distinct blue halo that bled into the surrounding media. From the over 50 distinct *Candida* species and allied genera cultured concurrently, only the uncommon *Candida diddensiae* species had a similar appearance. Furthermore, compared to the Sabouraud dextrose agar, the conventional mycological isolation medium, swabs containing pure and mixed *Candida* species showed a significantly increased growth rate and quantity of *C. auris* colonies on CHROMagar™ Candida Plus agar [24].

Molecular identification

The initial discovery of *Candida auris* as a new species was enabled by DNA sequencing, and further identification and delineation of it from closely related species in the *C. haemulonii* species complex was achieved by PCR amplification of either the D1/D2 region of the 28S sequence or the complete internal transcribed spacer of the ribosomal cistron.

A team of Spanish researchers has developed a PCR assay method that is both rapid and easy to apply for reliable identification of *Candida auris*. The primers used to identify *C. auris* have been designed from single genes encoding GPI (glycosylphosphatidyl-inositol) protein, and the specificity of these primers has been evaluated using a panel of 19 different *Candida* species, including the most clinically relevant and phylogenetically related ones. The efficacy of the PCR approach was further validated by correctly identifying 112 *C. auris* isolates from an outbreak in a Spanish hospital, of which 20% were not reliably identified by MALDI-TOF MS, and 27 genotypically diverse *C. auris* isolates from hospitals in different countries in a test that included negative (blind) controls. The utilization of two primer pairs for the GPI protein in a single PCR provides an enhanced robustness to the PCR assay, and helps to avoid potential false negatives due to recent evolutionary events, as observed in two isolates. The PCR approach, which depends on the singularity of chosen genes encoding the GPI protein, is a viable and cost-

effective means of accurately identifying *C. auris* infections in clinical settings [25].

Pathogenesis of *C. auris*

Investigations related to the ability of *Candida auris* to adapt to host-imposed stresses have been conducted in order to gain insight into its pathogenicity. By employing animal models of disseminated infection, it has been demonstrated that *C. auris* is as virulent as *C. albicans*, the most pathogenic species of *Candida* [26]. Because of its recent emergence, the biology and virulence attributes of *Candida auris* remain largely unknown. Two phenotypes, aggregating and non-aggregating, have recently been described, the latter exhibiting higher virulence *in vivo*. While some characteristics are strain-dependent, *C. auris* expresses several key virulence factors, such as phospholipases, proteinases, secreted aspartic proteins, adhesins and the ability to form biofilms. The resistance of *Candida auris* to physiologically relevant stresses was evaluated and compared to that of *Candida albicans. C. auris* was observed to be more resistant to hydrogen peroxide, cationic stress, and cell wall damaging agents, while highly sensitive to organic oxidative stress inducing agents. In contrast to other C*andida* species, *C. auris* was unable to grow in an anaerobic environment. These outcomes demonstrate the unique stress resistance profile of *C. auris* and support the role of the stress-activated Hog1 protein kinase (SAPK) in promoting stress resistance and virulence in this species. In addition, *C. auris* was shown to be thermotolerant, with an optimal growth temperature of 37ºC and viability up to 42ºC. In contrast to other *Candida* species, *C. auris* has been shown to tolerate both temperature and hyper-saline environments, which can induce pseudohyphae-like morphologies in other *Candida* species [27].

Candida auris infections have been reported in a variety of clinical sites, including the bloodstream, wounds, and urinary tract. This species is also capable of colonising the skin, nose, wounds, and urine, which makes it a potential indicator of disease risk. Patients with invasive *C. auris* infections often present with fever or sepsis, similar to those with candidiasis caused by other species. Those hospitalized in long-term care facilities and those with prolonged hospital stays in intensive care units are particularly at risk of *C. auris* infections. Other associated risk factors for acquiring *C. auris* infection, as opposed to non-auris candidemia, include prior antimicrobial therapy, placement of a central vascular catheter, administration of total parental nutrition (TPN), and the presence of underlying co-morbidities, such as respiratory, neurological, or renal disease. Individuals diagnosed with *Candida auris* infection have often had multiple medical interventions, such as the insertion of vascular catheters, urinary catheters, and percutaneous enteral feeding tubes [28].

Mechanisms of antibiotic resistance

Several studies have been conducted to characterize the virulence determinants of *Candida auris*. Results suggest that germination, adherence, biofilm formation, phospholipase and proteinase production may all contribute to the pathogenicity of *C. auris.* Despite its inability to form germ tubes, pseudohyphae or chlamydospores *in vitro, C. auris* may still produce phospholipase and proteinase in a strain-dependent manner [29].

Biofilm formation in C. auris

Adherent communities of *Candida spp*. embedded in an extracellular matrix, commonly referred to as biofilms, are frequently observed on medical surfaces and have been linked to numerous medical device infections, including urinary catheters, central venous catheters, implanted cardiac devices, prostheses, and others. Clinical studies of *C. auris* have reported a high frequency of catheter-associated bloodstream infections, suggesting that biofilm formation may play a role in the pathogenesis of this organism [23]. An investigation into the adherence and proliferation of *Candida auris* to catheter surfaces in a mice model of catheter-associated bloodstream infection revealed that isolates of this species formed biofilms composed of both yeast cells and hyphae [30].

The extracellular matrix of *Candida* species is responsible for biofilm formation and sequestration of drugs, which may account for the antifungal tolerance displayed by these species. *Candida auris* has been found to form biofilms which facilitate adhesion to surfaces; however, due to the lack of true hyphae, these biofilms are not as robust or intricate as those formed by *C. albicans*. Analysis of the composition of the *C. auris* biofilm matrix revealed an abundance of mannan-glucan polysaccharides, thereby indicating a similarity with the biofilm matrices of other *Candida* species.

A study comparing the antifungal susceptibility of *C. auris* isolates grown in planktonic and biofilm states revealed that planktonic cells were resistant to fluconazole, but displayed susceptibility to echinocandins and polyenes, whereas biofilms exhibited resistance to all antifungal agents [31]. Transcriptomic analysis of *C. auris* biofilm formation over time has revealed that efflux-mediated resistance may explain the species' wide-ranging tolerance to antimicrobial agents. These findings underscore the critical role of biofilms, including those on intravascular catheters and other medical devices, in the antifungal resistance of *C. auris* [28]. Biofilms of *Candida auris* demonstrate augmented resistance to antifungal agents from the full range of pharmacological classes. Moreover, *C. auris* biofilm formation has been associated with an increased resistance to antifungal drug classes, such as azoles,

echinocandins, and polyenes. The presence of biofilms has been demonstrated to produce additional resistance to treatments, thus complicating therapies. This has been illustrated by the use of echinocandin drugs to manage invasive *Candida auris* infection, as this class of drugs has been found to have decreased rates of drug resistance. The concentrations of echinocandin medications necessary to suppress *C. auris* biofilms are higher than those that can be given to patients without harm, as is the case with the other types of antifungal medications [32]. To develop novel treatment plans, it is important to comprehend how C. auris biofilm production affects drug resistance [28].

Mutations in the genome of C. auris have been associated with increased resistance to drugs

C. auris has been documented in 47 countries throughout the world, however it is likely to be more common due to the difficulty of identifying *C. auris* from other species. Five primary clades of *C. auris* isolates have been identified using genomic research, with Clades I, III and IV being the most prevalent. The fast spread of *C. auris* has been made possible by high rates of patient-to-patient transmission, longer survival on animal sites, and rapidly acquired anti-fungal treatment resistance. Triazoles, polyenes, and echinocandin antifungal acquired resistance are becoming more and more prevalent, which has led to the creation of pan-resistant isolates that have been spread from patient to patient during epidemics in the United States.

Mutations in the sterol-demethylase-encoding gene, ERG11, and the concurrent activation of drug export routes are commonly observed in drug-resistant clinical isolates, indicating the efficacy of triazoles as a target [32].

Fluconazole resistance in *C. auris* isolates has been linked to three amino acid changes in ERG11: V125A/F126L, Y132F, and K143R.

The extremely high levels of fluconazole resistance (MIC > 256 g/mL) observed in numerous *Candida auris* isolates cannot be attributed to mutations in the ERG11 gene alone. Activating mutations in the transcriptional regulator of drug efflux pumps, TAC1B (11), have also been implicated in conferring high levels of fluconazole resistance, and deletion of TAC1B was demonstrated to eliminate this resistance [33].

A representative West African study conducted in Nigeria compared the genomes of four individuals infected with *Candida auris*, who all presented with comorbidities and were admitted to intensive care. Of these, two received antifungal medication. Ultimately, all four individuals succumbed to sepsis.

Antifungal resistance testing was performed, revealing non-susceptibility. Subsequent genome characterization and assembly enabled the investigation of specific mutations that may be responsible for this antifungal resistance. Mutations were identified in the ERG11 gene in all of the isolates, with an additional non-synonymous mutation in the FKS1 gene present in one case and an additional E39D mutation in the ERG2 gene in one case [34].

An *in vitro* evolutionary approach was used to generate a collection of isogenic *Candida auris* strains with elevated fluconazole resistance, with MICs up to 64-fold higher than the parental strain. Whole genome sequencing of over 300 *C. auris* isolates revealed the TAC1B gene, a close homolog of the *C. albicans* transcriptional regulator CaTAC1, as a novel genetic determinant of fluconazole resistance. Subsequent introduction of the most common TAC1B mutation found among fluconazole-susceptible clinical isolates was associated with a significant increase in fluconazole MIC, demonstrating its prevalence and significance as a genetic determinant of fluconazole resistance among *C. auris* clinical isolates [35].

A research effectuated on a total of 314 *C. auris* isolates from 126 patients conducted in Kuwait identified mutations in the FKS1 gene that conferred resistance to micafungin [31].

The molecular chaperone Hsp90, which stabilizes key regulators of cellular responses to drug-induced stress, has been implicated in the development of drug resistance in a variety of fungi. Additionally, Hsp90 modulates *Candida albicans* temperature-dependent morphogenesis, an integral factor in its pathogenicity. However, the role of Hsp90 in the pathobiology of *C. auris* remains unknown. To investigate the regulatory roles of Hsp90 in *C. auris*, its transcription was suppressed *via* a doxycycline repressible promoter. It was demonstrated that Hsp90 is essential for the development of *C. auris* and that it enables clinical isolates to tolerate azole compounds, which block the formation of the membrane sterol ergosterol. Unexpectedly, the high azole resistance was not dependent on Hsp90 but rather on the ABC transporter CDR1, which when removed caused the resistance to dissipate. Additionally, it was observed that *C. auris* underwent a morphogenetic switch from a yeast form to filamentous growth in response to HSP90 depletion or cell cycle arrest, yet not in response to other stimuli that induce filament formation in *C. albicans*. Further investigation revealed that this shift in growth form was accompanied by the induction of genes associated with cell walls and broad transcriptional alterations [37].

A study conducted from 2012 to 2015 in Pakistan reported cases of *Candida auris* infection, adding to previous findings from Japan, South Korea, India, South Africa, Venezuela, and Kuwait. Whole genome sequencing (WGS) analysis of 47 isolates from four locations (South Asia, East Asia, South America, and South Africa) revealed a high number of single nucleotide polymorphisms (SNPs) with minimal genetic diversity within the region, which suggests a quasi-simultaneous occurrence of *C. auris* in these locations as opposed to recent spread from a single source. The

exact cause of its emergence remains unknown, though potential contributing factors may include new or intensified antifungal selection pressures in humans, animals, or the environment. The fact that this infection has only recently been discovered may be an explanation for its seeming recent emergence.

In South Africa, *C. auris* appears to have spread more rapidly in private sector hospitals, where the utilization of echinocandin is notably higher than in public sector hospitals [38].

Table I and Figure 1 show the prevalence of resistance to antifungal treatment in different parts of the world.

Table I

Prevalence of resistance to antifungal treatment in different parts of the world of *C. auris* strains

Country; years of observation	India (2009 - 2017)	USA (2013 - 2017)	Columbia (2015 - 2016)	UK (2015 - 2017)	Multi-national survey (2008 - 2015)	USA (2016 - 2017)
The group size	350	99	85	79	54	51
Prevalence of resistance to selected antifungal drugs in the study group						
Fluconazole (%)	90.3	88.9	12.9	100	92.6	98.0
Voriconazole (%)	14.9	-	0	97.5	53.7	-
Echinocandin (%)	2.0	6.1	0	0	7.4	0
Amphotericin B (%)	7.8	33.2	30.6	17.7	35.2	29.4
Flucytosine (%)	16.0	-	-	0	5.6	-
≥ 2 drug classes	25.1	39.4	0	17.7	40.7	25.5
≥ 3 drug classes	2.0	-	0	0	3.7	0
Reference	[39]	[40]	[41]	[6]	[42]	[43]

"-" No data were reported

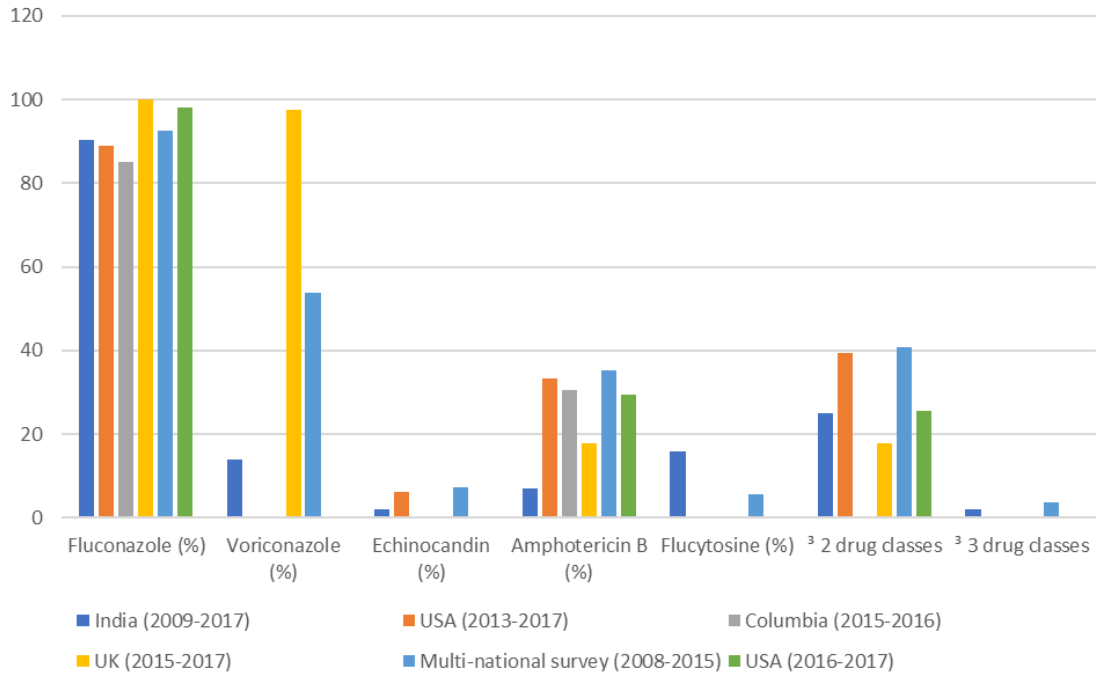

Figure 1.

Prevalence of resistance to antifungal treatment in different parts of the world of *C. auris* strains

Treatment of *C. auris* infections

C. auris is a mondial emerging pathogen of great concern, due to its ability to readily spread in the environment and easily transit among hospitalization patients, as well as its high levels of antifungal resistance and difficulty to diagnose with common microbiological methods. This multidrug-resistant species is associated with high morbidity and mortality rates in immuno-compromised individuals, causing challenges to infection control policies worldwide.

Since *C. auris* has developed resistance to azoles and amphotericin B, echinocandins are the first-choice treatment for this infection. However, echinocandin resistance has also been documented, demanding meticulous patient monitoring and regular re-evaluation by microbiological culture to spot therapy failure and potential resistance formation. When echinocandins are ineffective, liposomal amphotericin B should be provided (either alone or in conjunction with an echinocandin) and consulting an infectious disease specialist is advised. Additionally, MICs of azoles like itraconazole, posaconazole, and isavuconazole are low, and these medications show good *in vitro* activity. This is perhaps because yeast isolates hadn't

previously been exposed to these substances, or it could be because the azole-target protein combination (CYP51A/Erg11) has a different structure. The successful use of drug combinations suggests that synergistic interactions may play a role in the treatment of *C. auris*. This was demonstrated by the combination of micafungin and voriconazole. In the light of the increasing prevalence and spread of multi-drug resistant *C. auris* isolates, there is a need to broaden the range of antifungal treatments available [44, 45].

Ibrexafungerp is a first-class triterpenoid antifungal agent that has been shown to inhibit (1-3)-D-glucan synthase, a crucial component of the fungal cell wall, similarly to echinocandins. Its wide-ranging *in vitro* activity against several *Candida spp.*, including *C. auris* and *C. auris* isolates with fks mutations, is demonstrated by MIC50 and MIC90 values of 0.5 g/mL and 1.0 g/mL, respectively. Furthermore, two cases of successful ibrexafungerp treatment of invasive candidiasis and candidemia in the CARES (Candidiasis Caused by *Candida auris*) study have been reported, which suggests that ibrexafungerp may be an effective novel antifungal medication for the treatment of *C. auris* infections [46].

The *in vitro* activity of 122 Indian isolates of *Candida auris* was determined in a single-centre study in order to establish wild-type upper limits (WT-UL) for the new echinocandin, *rezafungin*, currently in clinical development. Identification of the 19 *Candida spp*. isolates was achieved through use of Chromagar and matrix-assisted laser desorption ionization (MALDI-TOF) and their susceptibility to rezafungin, anidulafungin, micafungin, amphotericin B and fluconazole was assessed. EUCAST epidemiological cut-off values for rezafungin have yet to be established. WT-ULs were established in accordance with EUCAST principles for the visual and statistical evaluation of ECOFF. Sequence analysis of the fks target genes was performed for non-rezafungin isolates. Rezafungin exhibited comparable activity to that of anidulafungin and micafungin. On a milligram per litre basis, rezafungin was generally found to be less active than anidulafungin and micafungin, although it was as active or more active than fluconazole and amphotericin B against the most common species of *Candida*, excluding *C. parapsilosis*. Rezafungin displayed broad *in vitro* activity against *Candida spp.*, including *C. auris*. The fks1 mutations caused a much smaller increase in the MICs of rezafungin compared to the MICs of anidulafungin and micafungin in *C. auris* [47].

A fungus-sensing chemical called *farnesol* inhibits the yeast-to-hyphal transition and encourages reverse morphogenesis in the *Candida albicans* fungus. To further understand the origins of the previously noted antifungal action, the effects of farnesol exposure on *C. auris* growth, biofilm development, production of oxidative stress-related enzymes, sensitivity to triazoles, and virulence were investigated. The *in vivo* studies conducted have indicated that farnesol has a promising therapeutic efficacy against *C. auris*; furthermore, it has been demonstrated to reverse the noted resistance of *C. auris* to newer triazoles [48].

Sertraline, a repurposed drug with a long history of use in humans for the treatment of depression, was evaluated for its antifungal activity against three different isolates of *C. auris*, resulting in efficient inhibition. Analysis of the killing kinetics and post-antifungal impact of sertraline supported its antifungal action. Sertraline prevented *C. auris* yeast from developing into hyphae, and additional treatment resulted in a 71% reduction in the production of biofilms. After sertraline therapy, *C. auris*-caused cell damage was discovered using SEM, and cell membrane damage was determined using flow cytometry. Sertraline did not appear to have any impact on the cell wall and did not appear to work by binding to membrane ergosterol, according to the results of the sorbitol protection experiment and the ergosterol effect assay. Using *in silico* docking studies, it was possible to understand the mechanism of action of sertraline against *C. auris*. These studies showed that sertraline binds to sterol 14 alpha demethylase, a key enzyme in the formation of ergosterol [49].

The medication *miltefosine* is used to treat breast cancer and leishmaniasis. Studies have demonstrated that miltefosine has substantial antifungal activity, which is associated with the induction of cell death. Additionally, it has been shown to interfere with the production of fungal biofilms and to effectively eradicate *Candida auris* biofilms that have already developed. Nevertheless, it may cause adverse side effects, such as gastrointestinal distress, haemolysis and hepatotoxicity [50].

Synthetic compounds and antimicrobial peptides (AMPs) provide antibacterial action against a variety of diseases. AMPs, also known as host defence peptides, are frequently documented in a variety of microbes as well as humans. They are essential for the innate immune response. The efficacy of cathelicidin LL-37 against clinical isolates of *C. auris* was assessed both alone and in combination with three other antifungal treatments. Also, the effect of cathelicidin LL-37 on cell cycle progression and cell membrane integrity in *C. auris* was examined. According to the findings, cathelicidin LL-37 exhibits potent antifungal activity both on its own and when combined with other anti-fungal medications. Also, it was shown by insight processes that cathelicidin LL-37 alters the integrity of cell membranes, causes oxidative stress, and halts the cell cycle in the S phase. To better comprehend additional mechanisms and the cytotoxicity of this antimicrobial peptide on mammalian cells, *in vivo* research is necessary. All things considered, our results imply that cathelicidin LL-37 would be a potential option for the creation of an antifungal therapy [51].

Considered to be effective anti-C*andida* therapeutics are *nanoparticles.* Trimetallic Ag-Cu-Co nanoparticles that are biologically active were created in a single step by a straightforward biosynthetic process employing an aqueous extract of the polyphenol- and flavonoid-rich *Salvia officinalis* plant. These crucial phytochemicals for medicine serve as a reducing agent and stabilize/ regulate the production of nanoparticles. The produced nanoparticles were characterized by Fourier transform infrared measurements, scanning and transmission electron microscopy, energy dispersive X-ray, X-ray powder diffraction and thermogravimetric analysis (TGA). Also, the antifungal efficacy of the produced nanoparticles against several *C. auris* clinical isolates was assessed. Trimetallic Ag-Cu-Co nanoparticles might cause apoptosis and cell cycle arrest in G2/M phase in *C. auris*, according to a thorough investigation. Due to the synergistic interaction of the three metals present, these nanoparticles also showed superior antibacterial capabilities in comparison to their mono-metallic counterparts [52].

The function of *Lactobacilli spp.* has been extensive studied on maintaining a healthy vaginal microbiota, with a focus on the use of probiotics in particular. In this regard, it has been established that the bacteria *Lactobacillus casei* Shirota, which is obtained from fermented milk, has the capacity to prevent the development of *Candida auris*, probably by producing lactic acid [53].

The effects of *antimicrobial photodynamic therapy (APDT)* on *C. auris*, a multidrug-resistant organism, were explored *in vitro* and *in vivo* using four phenothiazinium photosensitizers: methylene blue (MB), toluidine blue (TBO) and two MB derivatives, novel methylene blue (NMBN) and the pentacyclic derivative S137. To evaluate each photosensitizer's *in vitro* effectiveness, the minimum inhibitory concentrations and survival fraction were evaluated. The *Galleria mellonella* insect was utilized as an *in vivo* model to evaluate the effectiveness of APDT against infection and therapy. The findings suggested that *C. auris* had clinical antifungal resistance, but not to APDT using any of the four photosensitizers. However, G was only able to survive when APDT was carried out with S137. *Mellonella*-infected larvae in the *in vivo* model, indicating that the structural and chemical characteristics of the photosensitizers have a significant impact on the outcomes of APDT *in vivo* and emphasizing the necessity of synthesizing and developing new photosensitizer molecules to combat multidrug-resistant microorganisms [54].

Prevention and control strategies of *Candida auris* infection

The Mycotic Diseases Branch of the Centers for Disease Control and Prevention (CDC) is actively tracking cases of *Candida auris*, a newly-emerged fungal pathogen that poses a serious threat to global health. Through careful monitoring of *C. auris* cases over time, the Mycotic Diseases Branch is able to gauge the efficacy of preventive measures and shape public health policies accordingly. The majority of *C. auris* infections in the United States are linked to local transmission within and between healthcare facilities in the same geographic region. Healthcare staff should be particularly alert to potential introductions of *C. auris* from patients who have received medical care abroad or in other areas of the country where *C. auris* is widely spread. The CDC encourages medical staff and patients to take measures to prevent and control the infection, having clear instructions regarding the mode of transmission, hygiene and isolation of the infectious outbreak [55].

Hospitalized patients who were extremely ill have been documented to have *C. auris* outbreaks, with disturbingly high death rates ranging from 30% to 72%. Patients with bloodstream infections (BSIs) caused by *C. auris* often exhibit common risk factors similar to those of BSIs caused by other *Candida* species, such as recent major surgery, diabetes, usage of broad-spectrum antibiotics, prolonged hospitalizations and presence of medical devices, such as feeding tubes, breathing tubes, and central venous catheters. However, patients at risk of *C. auris*-induced candidemia demonstrate different risk factors. For instance, individuals with neurologic illnesses in long-term care who are using multiple medical devices may be particularly vulnerable to invasive *C. auris* infections in the United States [56].

The European Centre for Disease Prevention and Control (ECDC) has highlighted the importance of pursuing a range of strategies to reduce the risk of transmission of *Candida auris* in healthcare settings across the European Union (EU) and the South-East Europe (SEE) region. These include enhanced laboratory detection, implementation of universal infection control measures, prevention of interhospital and cross-border transmission, and increased preparedness of EU/SEE countries to detect, investigate and respond to *C. auris* infections [57].

The United Kingdom has developed a preventative guide containing comprehensive guidelines in response to the substantial *C. auris* outbreaks experienced in the country [58].

The emergence of *C. auris* has posed a new challenge to global healthcare. While numerous outbreaks have occurred, and investigations have been conducted to elucidate its origin and the optimal management strategies, evidence-based therapeutics for this novel pathogen remains largely absent. This paper provides a synthesis of real-world experience in the management of a transmission case of *C. auris*, with the aim of offering guidance to clinicians for future cases.

Conclusions

Candida auris has rapidly become a pathogen of public health concern worldwide, particularly due to resistance to therapy. Clinically approved libraries for several commonly used identification systems have only recently been released, and the characterization of strains in this species is becoming more difficult. At the same time, access to effective therapy is an impediment. Aspects regarding the origin of the species, the transmission of the infection and the mutagenesis capacity remain unclear. Public health authorities worldwide encourage the use of primary prevention methods and the isolation of outbreaks of infection.

Acknowledgement

This paper was financially supported by "Carol Davila" University of Medicine and Pharmacy Bucharest, Romania through Project CNFIS-FDI-2023-F-0708.

Conflict of interest

The authors declare no conflict of interest.

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