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Review

Genetic Variation and Antifungal Susceptibility Profile of *Candida auris*

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ABSTRACT

Candida auris is an invasive yeast that has spread worldwide since it was first identified in Japan in 2009. *C.auris* has spread through four genetic clades that emerged between 2008 and 2013 and caused nosocomial outbreaks. The mortality rates of *C.auris* infections vary significantly between regions, ranging from 30 to 60%. *C.auris* infections can cause fungemia, invasive candidiasis, and spread to various organs. *C.auris* has a defense mechanism against the innate immune response and virulence factors that are not fully understood. High thermal and salinity tolerance, excretion of protease enzymes, and the ability to form biofilms are the main virulence factors that influence the pathogenicity of *C.auris*. Due to limited facilities, the diagnosis of *C.auris* infections is still hampered in some countries. Accurate strain identification methods are essential to prevent the rapid spread of this pathogen. Molecular techniques, including PCR and sequencing of the D1/D2 region of 28s rDNA or internal transcribed spacer using specific primers, are recommended for faster and more accurate identification. Genetic analysis revealed single-nucleotide polymorphisms (SNPs) that differed between clades, especially in the nuclear and mitochondrial genomes. *C.auris* exhibits high resistance to fluconazole, amphotericin B, and echinocandins, with some strains being resistant to all three. Resistance mechanisms include ERG11 gene mutations, Erg11p overexpression, and efflux pump activity. The rise of multidrug-resistant strains and high genetic variation complicates infection management, requiring heightened attention to prevent further spread.

Keywords: *Candida auris*, multidrug-resistant, SNPs, virulence

INTRODUCTION

Fungal infections are increasingly acknowledged as a significant health threat, impacting approximately 1.7 billion people globally.[1] Invasive fungal infections primarily affect patients with compromised immune systems and/or comorbidities.[2] In these conditions, infections can worsen rapidly, leading to high morbidity and mortality.[3] Candidemia and invasive candidiasis of internal organs are the most common nosocomial invasive fungal infections and cause primary bloodstream infections (BSIs) with significant mortality rates.[2,4] Approximately 400,000 BSI infections are caused by *Candida* species worldwide each year, with a mortality rate of more than 40%.[1] *Candida auris* is a new etiological agent causing candidemia and invasive candidiasis.[4]

The rise of multidrug-resistant *Candida auris* infections has worsened its status as a global public health threat.[4] First identified in 2009 in a patient's ear canal in Japan[5], *C. auris* has since become a significant concern, earning a place on the World Health Organization's (WHO) Fungal Priority Pathogen List (FPPL) as a critical pathogen. Despite its recognition, there are many uncertainties regarding its origin, transmission, and persistence. A key mystery is the sudden, simultaneous, and independent emergence of five major *C. auris* populations (clades) across distinct geographic regions worldwide, raising questions about the factors driving its rapid global spread.[6]

Candida auris, an Ascomycetes fungus, has recently emerged as a major concern due to its high pathogenicity, multidrug resistance, and ability to cause hospital-associated outbreaks.[7] The Centers for Disease Control and Prevention

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(CDC) categorizes *C. auris* as an urgent threat, the highest level of concern, because of its frequent resistance to multiple antifungal drugs, rapid spread in healthcare environments, and association with severe invasive infections that have high mortality rates.[8] Additionally, this microorganism also spreads rapidly between patients, persistently colonizing the skin and surfaces of medical devices in hospitals, and is often difficult to identify accurately.[9]

The process of identifying and diagnosing *C. auris* accurately is often challenging, as current diagnostic techniques frequently misidentify it as other species, such as *Candida parapsilosis*, *Candida guilliermondii*, *Candida haemulonii*, *Candida lusitaniae*, and *Candida famata*. This misidentification can delay infection control measures and increase the transmission risk. Additionally, *C. auris* can transform into a persistent yeast form, allowing it to survive under extreme physical and chemical conditions. This resilience contributes to its resistance to multiple antifungal drugs, including fluconazole, amphotericin B, and echinocandins. While the exact mechanisms of drug resistance in *C. auris* are not fully understood, the most commonly identified mechanism involves mutations in the *ERG11* gene, which plays a key role in ergosterol synthesis, particularly in the function of lanosterol 14-α-demethylase.[10]

In addition, it is important to investigate further the relationship between minimal inhibitory concentration (MIC) and patient clinical outcomes to establish a consensus on classification cutoff values for determining sensitive and resistant *C. auris* isolates (MIC breakpoints).[11] Accurate detection and identification of the pathogen, along with assessing its antifungal susceptibility, monitoring of appropriate treatment, and implementing effective infection prevention and control measures, are essential to limit the spread of *C. auris*.[12]

DISCUSSION

Epidemiology of *Candida auris*

In October 2022, WHO classified *Candida auris* as one of four critical human fungal pathogens. Although initially reported in Japan in 2009, its earliest known clinical occurrence dates back to 1996 in South Korea, where it was initially misidentified as *Candida haemulonii*.[1,7] Before 2009, *C. auris* infections were rarely reported in hospitals, making its sudden emergence a topic of significant debate. Some researchers have speculated that global climate change may have played a role in its rise, as the fungus has recently been isolated from tropical wetlands. This suggests that increasing global temperatures may have enabled *C. auris* to adapt to higher temperatures and environmental stresses, mirroring conditions in the human body and potentially contributing to its ability to infect humans.[7]

Invasive strains of *C. auris* are now frequently found in hospitalized patients worldwide.[10] To track its emergence and spread, prospective surveillance and retrospective analysis of yeast culture collections are continuously conducted at both national and international levels. These efforts aim to gather crucial data on the timeline of *C. auris* infections and their global distribution.[13] The first identification of *C. auris* was made in 2009, and it was found in the earwax of a 70-year-old Japanese patient.[5] *Candida auris*, recorded in Japan, is a primary ear infection found in the ear, hence the name "Auris." In Japan, *C. auris* infections do not lead to invasive diseases, as the fungus does not enter systemic circulation. However, in South Korea, the same strain of *C. auris* has been reported to cause invasive infections.[10]

The first *Candida auris* isolate was identified in South Korea in 1996 but was initially misclassified as *Candida haemulonii*.[1] Similarly, misidentified isolates were later discovered in Japan in 1997 and Pakistan in 2008. In 2009, *C. auris* was officially recognized as a new species, and reports of invasive infections and hospital outbreaks soon followed. The disease emerged simultaneously in South Africa and India in 2009, and then spread to Kenya in 2010 and China in 2011. By 2012, *C. auris* had been detected in Venezuela, followed by its emergence in Colombia in 2013.[13]

Around 2012–2013, four genetically distinct groups of *Candida auris* emerged independently in different regions of Asia, South Africa, and South America, marking the turning point for the emergence of the first four clades. Following their emergence, these clades rapidly spread to other countries, primarily due to human migration. In 2013, *C. auris* reached Europe, with initial sporadic

cases reported in the UK, followed by a prolonged outbreak from 2015 to 2017. It then spread across Europe, appearing in Germany (2015), Belgium (2016), Norway (2016), Spain (2016), France (2017), Switzerland (2017), Austria (2018), Greece (2018), the Netherlands (2018), Poland (2018), and Italy (2019). In the same period, cases were reported in Australia (2015). Around the same time as its emergence in the UK, *C. auris* entered the United States in 2013, leading to large, prolonged outbreaks in New York, New Jersey, and Chicago from 2013 to 2017. In 2017, the number of cases surfaced in Canada. In the meantime, outbreaks began in intensive care units in Venezuela and Colombia between 2015 and 2017. *C. auris* has also begun spreading to the Middle East, North Africa, and South Asia, first appearing in Kuwait in 2014. In East and Southeast Asia, it expanded to Singapore in 2012, Taiwan in 2017, and both Malaysia and Thailand in 2018.[13] In 2018, a genetically distinct isolate was identified in Iran that is likely representing a new clade of *C. auris* (Figure 1).[14] There are several interesting things about the global distribution map of *C. auris*. Rapid and simultaneous emergence of genetically distinct clades of *C. auris* occurred between 2008-2013, with only rare isolates detected before 2008. This pattern suggests a relatively recent emergence of this fungus.[13]

Although *C. auris* was first isolated and identified in 2009, a retrospective study revealed that the earliest known isolate dates back to 1996. Researchers have classified *C. auris* into four distinct clades based on cultures collected between 2009 and 2015: the South Asian clade (I), East Asian clade (II), South African clade (III), and South American clade (IV). By 2021, at least 47 countries have reported one or more cases or outbreaks of *C. auris* infections. According to the US Centers for Disease Control and Prevention (CDC), this pathogen has spread across most of the United States by 2022, with 2,377 clinical cases reported (https://www.cdc.gov/fungal/Candida-auris/tracking-c-auris.html).

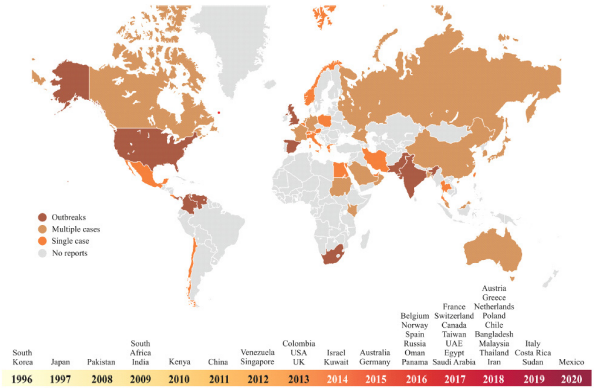

Figure 1. Timeline of the global distribution of *C. auris* [13]

The epidemiology of *C. auris* infections has evolved over time. Initially associated with sporadic invasive infections, it became a major cause of hospital outbreaks. The rising number of reported cases indicates that *C. auris* is increasingly affecting vulnerable patients in healthcare settings.[15] Mortality or case fatality rates of *C. auris* infection vary significantly across geographic regions.[4]

In 2019-2020, 12 patients were reported to be infected with *C. auris* in the Americas, with mortality rates of 67% in Mexico and 40% in the United States. Between 2018 and 2019, Asian countries such as Kuwait, Oman, Russia, and Saudi Arabia experienced a surge in cases. Kuwait reported 71 cases with a 51% mortality rate, Oman had 32 cases with a 53.1% mortality rate, Russia reported 38 cases with a 55.3% mortality rate, and Saudi Arabia reported 35 cases with a 20% mortality rate. In 2017-2020, *C. auris* cases were also documented in Europe, including 47 in Spain, where the mortality rate was 23.4%. These statistics highlight the widespread and deadly nature of *C. auris* infections across diverse geographic regions.[15]

Pathogenesis of *Candida auris*

Candida auris infection can lead to fungemia and invasive candidiasis.[16] It has also been found in the respiratory tract, muscles, and even the central nervous system (CNS). *C. auris* is not only thermotolerant (37-42°C), but also resistant to high salinity and various other environmental stresses, allowing it to grow and live well in various environments. It can persist outside the human body

for extended periods, making it a persistent threat in healthcare environments. Nosocomial infections occur through contact with contaminated medical equipment or the hands of healthcare workers, contributing to their rapid spread in hospitals. Notably, *C. auris* has also been isolated from sterile non-biological environments, such as urine, highlighting its ability to survive in sterile healthcare settings. This bloodstream infection, known as *C. auris* candidemia, can affect individuals of all ages, further emphasizing its widespread and dangerous nature.[10]

Candida cells must enter the bloodstream before spreading throughout the human body. The fungi faces various challenges, including limited nutrition and the human immune system. The innate immune system, which includes the complement system, monocytes, and neutrophils, serves as the primary defense against *Candida* infection in the bloodstream. To deal with innate immune cells, several *Candida* species such as *C. albicans, C. glabrata, C. tropicalis*, and *C. parapsilosis* develop survival strategies to avoid these immune responses, especially from neutrophils, monocytes (dendritic cells), and the complement system. *C. auris*, in particular, resists neutrophil attacks by inhibiting the release and formation of Neutrophil Extracellular Traps (NETs), allowing it to evade the innate immune system and spread throughout the body, leading to invasive infections.[17] This makes it resistant to neutrophil activity, especially NETs, and ultimately can evade the human innate immune response so that it can spread throughout the body and cause invasive infections. In addition to candidemia, *C. auris* is also responsible for urinary tract infections (UTIs), otitis, wound infections, skin abscesses, myocarditis, meningitis, and osteomyelitis.[18]

Virulence Factors of *Candida auris*

The virulence factors of *Candida auris* are poorly understood and have not yet been well studied. However, many genes linked to *Candida albicans* virulence have orthologs in the *C. auris* genome. For instance, the Hsp90 protein, which is known for its role in *C. albicans* morphogenesis and virulence, has an ortholog in *C. auris* that is linked to growth, morphology, and tolerance to antifungal drugs. Various factors that influence the pathogenicity of *C. auris* are shown in Figure 2.[19]

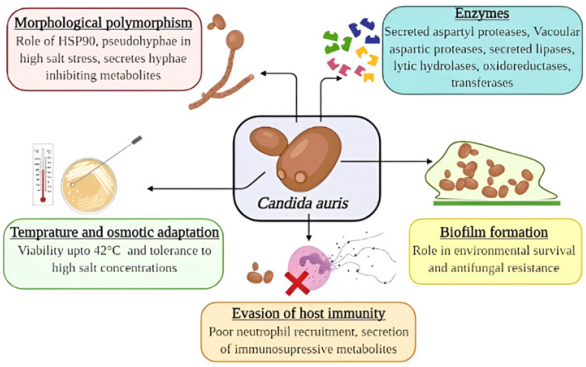

Figure 2. Virulence factors associated with *C. auris* pathogenesis[20]

Due to the high genetic diversity of *C. auris*, several reports regarding its virulence vary. Genes associated with *C. auris* virulence mostly encode hydrolases, mannosyl transferase, hemolysin, oxidoreductase, oligopeptide transporters, aspartyl-secreted proteases (Saps), lipase, and phospholipase. The level of Saps produced by *C. auris* is similar to *C. albicans*, and is expressed even at 42°C, thus its pathogenicity remains even at high temperatures.[20,21] Mannosyl transferase plays a role in maintaining the shape of the cell wall in *C. albicans* and also as a marker for fungal recognition by the immune system, as well as to facilitate adhesion to host cells. This fungus also has a transporter protein that acts as an efflux pump, and plays an important role in resistance to various antifungal drugs.[21] *C. auris* has a higher thermal tolerance, namely optimal growth at 37°C and remains alive at 42°C compared to *C. haemulonii*. This fungus also has higher ATP-dependent drug efflux activity, which means it has higher virulence.[20,21] *C. auris* also can tolerate high salt concentrations and has the ability to aggregate into large clusters, making it difficult to eliminate and allowing it to persist in hospital environments.[22] Previous studies have found elongated cells with pseudo hypha-like shapes in high salinity environments (10%). This suggests that imperfect cell division can occur at high salt concentrations.[23] However, the molecular mechanisms behind this phenomenon and its role in infection remain unclear.[21]

Environmental stressors such as salinity, oxidative stress, pH variations, and temperature

fluctuations play a critical role in shaping the in vivo pathogenicity of *C. auris*. Among these, salinity is especially crucial as *C. auris* commonly inhabits environments with fluctuating osmolarity, including the bloodstream, urine, and sweat-rich skin folds. Its ability to tolerate high salt concentrations allows it to persist in hyperosmotic environments, contributing to bloodstream infections (candidemia) and urinary tract colonization. This resistance is regulated by the high-osmolarity glycerol (Hog1) pathway, which helps *C. auris* to maintain cell integrity under osmotic stress. Additionally, exposure to salinity has been linked to enhanced biofilm formation, a major virulence factor that increases antifungal resistance and persistence in medical devices such as catheters and ventilators. These biofilms act as a protective barrier, making infections harder to treat and increasing the risk of hospital-acquired infections.[24]

In addition salinity, *C. auris* must also survive in diverse pH environments within the human body. Unlike *C. albicans*, which thrives under both acidic and alkaline conditions, *C. auris* is highly resistant to alkaline stress (pH 13), but is more sensitive to extreme acidity (pH 2). This suggests that while *C. auris* can survive in alkaline environments such as hospital surfaces and disinfectant-treated areas, it may struggle to establish infections in highly acidic stomach. However, its pH adaptability allows it to persist on the human skin and mucosal surfaces, facilitating transmission between patients. This adaptability is an important factor in its ability to spread within healthcare settings, particularly in intensive care units where immunocompromised patients are highly vulnerable.[24]

Temperature stress also plays a crucial role in the pathogenicity of *C. auris*. Unlike many fungal pathogens that struggle to survive at high temperatures, *C. auris* displays exceptional thermotolerance with the ability to grow at 47°C. This trait enhances survival in febrile patients fever is a natural immune response aimed at limiting microbial growth. While fever effectively restricts the growth of many pathogens, the resistance of *C. auris* to high temperatures allows it to thrive in infected patients, making it particularly difficult to eliminate. Furthermore, this thermotolerance allows *C. auris* to survive in warm hospital environments, persisting on medical equipment, bed linens, and other surfaces, contributing to nosocomial outbreaks.[24]

Infections typically do not occur under a single environmental stressor but rather as a result of multiple stressors. *C. auris* demonstrates resistance to individual stressors, but certain combinations of stressors can weaken it. For example, *C. auris* was found to be sensitive to a combination of salt stress (1M NaCl), extreme pH (pH 2 or 13), and heat stress (47°C). These findings suggest that targeting multiple stress pathways simultaneously could be a promising antifungal strategy, as *C. auris* may lose its resilience under specific stressor combinations.[24]

The resistance of *C. auris* to environmental stressors has significant clinical implications, particularly for hospital infection control. Many standard disinfectants rely on quaternary ammonium compounds, but *C. auris* can survive these treatments and persist on surfaces for extended periods. However, it remains susceptible to sodium hypochlorite (bleach, pH >12) and high heat (>80°C), suggesting that appropriate hospital sterilization protocols, such as thorough laundering of contaminated linens and heat-based decontamination, can help curb its spread. Additionally, its ability to withstand oxidative stress makes it more difficult to eliminate with standard antifungal treatments, requiring alternative therapeutic strategies targeting its stress response pathways.[24]

Due to its high salinity and temperature tolerance, the emergence of *C. auris* is thought to be related to global warming.[21] Rising global temperatures may have driven the adaptation and selection of thermotolerant *C. auris*, allowing it to overcome the thermal barriers in mammals and cause invasive infections.[20] In terms of biofilm formation, *C. auris* has 686 biofilm-related proteins, including ribosomal proteins, transporters, several enzymes, and transcription factors. Biofilms are mostly composed of yeast cells enveloped in an extracellular matrix.[21] Some isolates fail to release daughter cells, leading to the formation of large aggregates that are difficult to break apart. This biofilm formation likely contributes to the fungus's ability to survive in the environment for extended periods.[20] Disinfecting surfaces and medical equipment contaminated with *C. auris* is challenging because its biofilms show resistance to common disinfectants like hydrogen peroxide and chlorhexidine. Due to its

high infectivity and resistance to standard cleaning methods, *C. auris* has caused outbreaks in healthcare settings, particularly in intensive care units.[25]

Laboratory Diagnosis of *Candida auris*

Diagnosing *C. auris* remains a significant challenge, which has led to its underestimation as a threat to public health. However, the molecular mechanisms driving virulence and antifungal resistance are not well understood. Currently, *C. auris* infections are primarily diagnosed using fungal cultures from blood, body fluids, or pus samples, along with biochemical-based yeast identification methods such as analytical profile index (API) strips and the VITEK 2 system. However, these methods can be unreliable due to incomplete species databases.[10] Blood culture tests have shown that *C. auris* is usually detected after about 33.9 hours of incubation. When there was growth in the culture bottle, subculturing was performed on Sabouraud dextrose agar (SDA) media. Colonies formed on SDA medium were creamy white. The growth pattern was similar to that of *C. albicans*, with the stationary phase reaching approximately 20 hours. A rapid differentiation test between *C. auris* and *C. haemulonii* can be performed using CHROMagar with Pal's agar. *C. auris* forms smooth, creamy white colonies at 37–42°C within 24–48 hours, whereas *C. haemulonii* develops smooth, light pink colonies and does not grow at 42°C. However, an automated identification system is still necessary to distinguish *C. auris* from other *Candida* species that may also form pink colonies on CHROMagar Candida medium, highlighting the need for more precise diagnostic tools.[21]

Conventional methods for identifying *Candida auris*, such as VITEK 2 YST, API 20C, API ID 32 C, BD Phoenix, and MicroScan, have been widely reported to cause errors in strain classification (Table 1). This is because some *Candida* species share overlapping biochemical profiles, which leads to misidentification. To improve accuracy, the CDC recommends using practical identification algorithms along with commercially available tests. However, phenotypic identification methods can be slow, delaying proper diagnosis and potentially impacting treatment and infection control measures.[10]

Table 1. Errors in Identification of *Candida auris* using Biochemical Tests[10]

Misidentification *C. auris* as:	**Commercial Identification Test**
Candida haemulonii *Candida duobushaemulonii* Other *Candida* species	VITEK 2 YSTa (bioMérieux, Marcy-I'Étoile, France)
Rhodotorula glutinis *Candida sake* *Candida intermedia* *Candida sake* *Saccharomyces kluyveri*	API 20C (bioMérieux, Hazelwood, MO, USA) API ID 32 C (bioMérieux, Marcy-I'Étoile, France)
Candida haemulonii *Candida catenulata* *Candida famata* *Candida guilliermondii* *Candida lusitaniae* *Candida parapsilosis* Other *Candida* species	BD Phoenix yeast identification system (BD Diagnostic Systems, Sparks, MD, USA) MicroScan (YIP; Baxter-MicroScan, W. Sacramento, CA, USA)

Due to the high risk of misdiagnosis with conventional methods, experts recommend using Matrix-Assisted Laser Desorption Ionization Time of Flight (MALDI-TOF) or PCR-based molecular identification, particularly sequencing the D1-D2 region of 28S ribosomal DNA. These techniques are now widely adopted for accurate detection of *C. auris*. Conventional laboratory methods often lead to misidentification, which can result in inadequate management and treatment of infections, leading

to rapid spread of *C. auris* in healthcare settings.[10] Molecular approaches, such as PCR amplification and sequencing of ribosomal DNA (rDNA), offer greater accuracy. Specifically, sequencing the D1-D2 region of 28s rDNA and the internal transcribed spacer (ITS) region can reliably identify *C. auris*. Additional methods, including 18S rRNA sequencing and phylogenetic analysis, also aid in detection. By sequencing genetic loci and PCR/qPCR examination, it has been successfully applied to identify *C. auris*. PCR and qPCR are particularly advantageous because of their speed and high specificity when using species-specific primers. These methods can efficiently identify *C. auris* in clinical samples such as blood and serum.[26]

The currently available diagnostic tools primarily rely on PCR or mass spectrometry, making them expensive and inaccessible in resource-limited settings. While culture-based methods are more affordable, they lack specificity and cannot reliably differentiate *C. auris* from other *Candida* species. Loop-mediated isothermal amplification (LAMP) has emerged as an alternative. LAMP is an emerging technology that is widely used for the rapid detection of nucleic acids and is highly effective in identifying human pathogens, including viruses, fungi, bacteria, and malaria. However, it fails to differentiate between live and dead cells, leading to potential false positives. In contrast, the reverse transcription LAMP (RT-LAMP) assay, uses RNA as a template, allowing the detection of live and metabolically active cells. The method was designed to target a specific 869-bp DNA sequence (encoding a pyruvate: ferredoxin oxidoreductase domain) unique to *C. auris*. This study evaluated the limit of detection (LOD), sensitivity, and specificity of this approach using RNA extracted from cultures and tested it on 10 clinical isolates. The findings revealed that RT-LAMP could detect as little as 1 attogram (ag) of RNA, whereas conventional DNA-based LAMP had an LOD of 10 femtograms (fg), demonstrating the superior sensitivity of the RNA-based approach. Moreover, the assay showed 100% specificity, successfully distinguishing *C. auris* from other *Candida* species and bacterial strains such as *Escherichia coli*. When tested on 10 clinical isolates, the RT-LAMP method produced results that were 100% concordance with culture-based identification, confirming its accuracy.[27]

To effectively combat disease, particularly in resource-limited areas, there is a need for simple, affordable, and rapid diagnostic methods for clinical use. In the current era of isothermal-based amplification techniques for disease detection, this study—although still in its early stages—provides strong proof of concept for RT-LAMP-based methods for the rapid identification of *C. auris* infections. However, further research is necessary to refine and develop these methods to bridge the diagnostic gap in developing countries.[27]

Genomic Variation of *Candida auris*

C. auris has four main clades characterized based on genetic and genomic information and geographic origin: South Asian Clade I, East Asian Clade II, South African Clade III, and South American Clade IV. Analysis of rDNA sequences from the 28S D1/D2 region and the 18S ITS region, as well as 50 detected protein sequences, place *C. auris* in the Metschnikowiaceae family within the Candida/Clavispora clade (Figure 3). Like other species in this group, such as *C. albicans, C. tropicalis, C. haemulonii,* and *C. lusitaniae*, *C. auris* is part of the CTG clade—a unique group that translates the CTG codon as serine instead of leucine.[1,28]

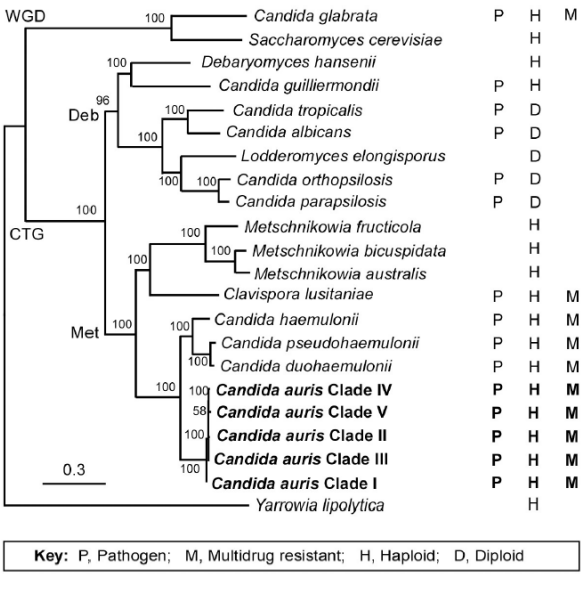

Figure 3. Phylogenetic tree of CTG and Whole Genomic Duplication (WGD) clade species (based on maximum-likelihood estimation)
[1]

Whole genome sequencing has revealed significant genetic differences among *C. auris* species, leading to the identification of four primary geographic clades (Clades I–IV). These clades are separated by thousands of single nucleotide polymorphisms (SNPs), indicating deep evolutionary divergence (Clades I–IV).[28] Each clade has minimal genetic variation within itself (fewer than 70 SNPs) but is separated from others by thousands of SNPs. Recently, a potential fifth clade was identified in Iran, distinguished by more than 200,000 SNPs from the other clades (Figure 4).[1] Table 2 describes the main characteristics of each clade.[6]

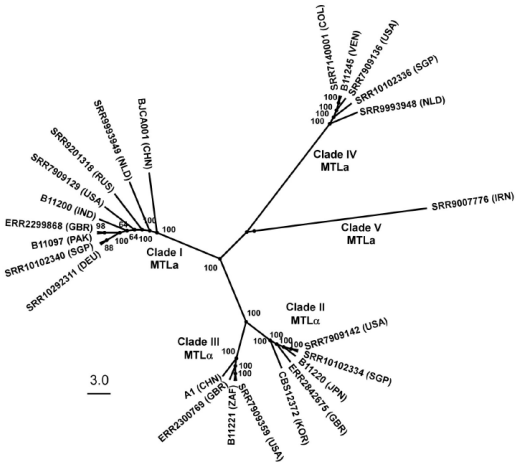

Figure 4. Phylogenetic tree of five clades of *C. auris* based on SNPs distance[1]

Table 2. Main characteristics of *Candida auris* clades[6]

Characteristics	Clade				
	South Asian (I)	**East Asian (II)**	**African (III)**	**South America (IV)**	**Iranian (V)**
Antifungal susceptibility profile	Resistant to FLU, cross-resistant to echinocandins and AMB, some are pan-resistant	Lower resistance to antifungal agents	Resistant to FLU, cross-resistant to echinocandins and AMB, some are pan-resistant	Resistant to FLU, cross-resistant to echinocandins and AMB, some are pan-resistant	Resistant to FLU, cross-resistant to echinocandins and AMB, some are pan-resistant
Clinical isolation site	Ear, blood, or other invasive sites	Mainly ear	Ear, urine, blood, or other invasive sites	Blood, or other invasive sites	Nail, skin, ear
Mating type	MTLa	MTLα	MTLα	MTLa	Not known
***ERG11* mutations**	Y132F or K143F	K143R, L43H, Q357K	F126L	Y123F, K143R, K177R, N335S, E343D	Y132F, I466L
***TAC1B* mutations**	R495G, A640V, A657V, A15T, S195C, P595L	F214S	None	F214S, F862_N866del, K247E, M653V, A651T, P595H	Not known
Outbreaks	Invasive infections	Ear infections	Invasive infections	Invasive infections	Invasive infections
Geography	Dominates in the United States, Europe, South Asia	Dominates in Korea, Japan	Dominates in Europe, Africa	Dominates in the United States	Dominates in Iran
Phenotypes					
Growth on actidione	No	Yes	Yes	Not known	Not known
Pseudohyphae	Yes	No	No	Not known	Not known
Large cellular aggregates	No	Yes	Yes	Not known	Not known
Assimilation of L-rhamnose	No	No	Yes	No	Yes
Utilization of N-acetyl glucosamine	Yes	No	Yes	Yes	Yes

AMB, amphotericin B; del, deletion; FLU, fluconazole.

Resistance Mechanisms and Antifungal Therapy Choices

The three primary classes of antifungal drugs—azoles, echinocandins, and polyenes—are commonly used to treat *C. auris* infections, but resistance poses a significant challenge. Over 40% of *C. auris* strains exhibit multidrug resistance (MDR) to at least two antifungal classes, with approximately 4% resistant to all three. A study by Chow et al. analyzing 300 isolates revealed that 24% were resistant to at least two drug classes, 1% were resistant to all three, 7% showed resistance to micafungin, 23% to amphotericin B, and 80% to fluconazole. This growing resistance emphasizes the urgent need for improved antifungal strategies and enhanced surveillance to curb the spread of *C. auris* infections.[10]

Currently, there are no definitive minimum inhibitory concentration (MIC) breakpoints for assessing the antifungal susceptibility of *C. auris*. However, tentative breakpoints proposed by the CDC (2019) and supported by studies using neutropenic mouse models. These guidelines provide a framework for evaluating resistance levels to fluconazole, amphotericin B, and echinocandins, including caspofungin, anidulafungin, and micafungin. A heatmap (Figure 5) visually represents these resistance patterns, revealing that *C. auris* is often highly resistant to fluconazole, with some studies reporting resistance in over 90% of isolates. However, lower fluconazole resistance rates (11%) have been observed in regions like Colombia and South Korea. While amphotericin B resistance is not as prevalent as fluconazole resistance, it remains a significant concern, particularly because amphotericin B resistance is uncommon in other fungal pathogens.[29]

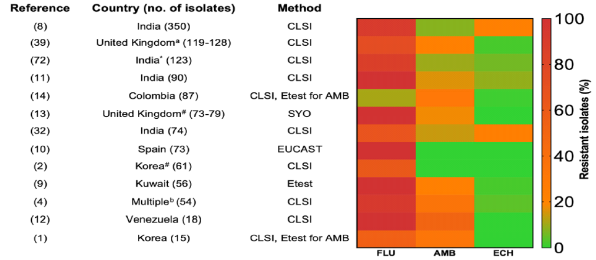

Figure 5. Geographical distribution of antifungal resistance to fluconazole (FLU), amphotericin B (AMB), and echinocandin (ECH) against *Candida auris* [29]

C. auris has evolved various molecular strategies to resist drugs (Figure 6), such as (1) mutations in drug targets, (2) overexpression of these targets, (3) changes in drug absorption and expulsion, (4) activation of stress response pathways, and (5) the formation of biofilms. When *Candida* species form aggregated colonies and biofilms, their resistance to antifungal medications can increase by as much as 1000 times. A critical player in this process is the Hsp90 chaperone protein family, which regulates biofilm dispersal, tolerance to antimicrobial agents, and remodeling of the cell wall. In *C. auris*, these proteins strengthen cell wall integrity and enhance stress responses, especially when exposed to azole treatments, further driving the pathogen's increasing resistance to drugs.[30]

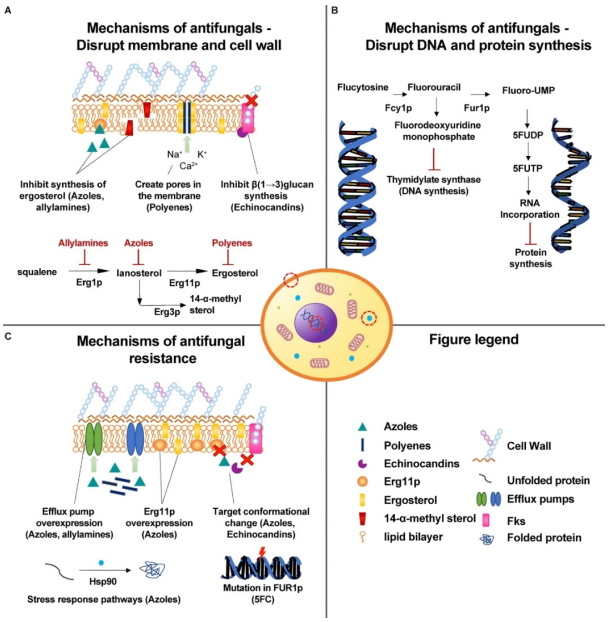

Figure 6. Mechanism of action and drug resistance in *C. auris*. (A) The primary mechanism of most antifungal drugs involves disrupting the integrity of the fungal cell membrane or cell wall. (B) 5-flucytosine blocks the production of fungal DNA and RNA within the nucleus. (C) Mechanism of antifungal resistance to drugs that target the cell membrane or cell wall [30]

Specific mutations in the *ERG11* gene, which encodes the target of azole antifungal drugs, significantly contribute to azole resistance in various *C. auris* isolates. These mutations vary by clade: the South African clade exhibits an *F126L*

mutation, the South American clade has a *Y132F* mutation, and the South Asian clade shows either *Y132F* or *K143R* mutations. Notably, the *Y132F* and *K143R* mutations have recently been linked to increased fluconazole resistance in *C. auris*. Fluconazole resistance, driven by point mutations in the *ERG11* gene, has been identified in a global collection of 54 *C. auris* isolates, highlighting the role of these genetic changes in the pathogen's growing resistance to antifungal treatments.[10]

The mechanism of action of fluconazole involves inhibiting the synthesis of ergosterol, a crucial component of the fungal cell membrane, by targeting lanosterol 14-α-demethylase, an enzyme encoded by the *ERG11* gene in *Candida*. This inhibition prevents cell growth and replication. However, resistance to azoles, including fluconazole, arises through various genetic and molecular mechanisms. Mutations in genes such as *ERG11*, *TAC1b*, *Y132F*, *K143R*, and *F126L*, as well as the activity of ATP-binding cassette (ABC) transporters and other superfamily transporters, contribute to this resistance.[10] Additionally, overexpression of Erg11p, the enzyme encoded by *ERG11*, can occur due to increased transcription factors like Upc2p or gene duplication (Figure 6). This overexpression leads to higher ergosterol production, reducing the effectiveness of azole drugs.[30] Studies have shown high fluconazole resistance in regions like India and South Africa, where approximately 90% of 350 *C. auris* isolates exhibited fluconazole minimum inhibitory concentrations (MICs) greater than 16 µg/ml, underscoring the widespread challenge of azole resistance in this pathogen.[10]

Azole activity can be diminished by reducing the intracellular concentration of the antifungal through efflux pumps. Recent research has identified up to 20 ATP-binding cassette (ABC) transporters in the *C. auris* genome that are believed to function as efflux pumps. Among these, two well-studied drug transporters in *C. albicans*, *CDR1* and *MDR1*, have orthologs in *C. auris* that are overexpressed in azole-resistant strains. *CDR1*, an ABC transporter, contributes to resistance against azole derivatives, while *MDR1*, a member of the Major Facilitator Superfamily (MFS), is associated with fluconazole resistance.[30] Efflux pumps are a critical mechanism of antifungal resistance, particularly during the early stages of biofilm formation. As biofilms mature, their resistance to antifungals increases due to the biofilm matrix's ability to hinder drug diffusion. This highlights the importance of biofilm formation in *Candida* pathogenesis and its role in antifungal resistance. *C. auris* possesses 686 biofilm-associated proteins, including ribosomal proteins, transporters, enzymes, and transcription factors, which enable it to form robust biofilms, further enhancing its resistance to antifungal treatments.[10]

In a study comparing clinical isolates of *C. auris* and *C. albicans*, both strains demonstrated similar pathogenicity, but *C. auris* exhibited a multidrug-resistant (MDR) profile. The study identified six drug efflux pump transporters shared by both species, with fluconazole-resistant *C. auris* strains expressing two or more efflux transporters, higher levels of superoxide dismutase, and a greater number of proteins in their biofilm matrix. When analyzing transcription factors and proteins involved in biofilm formation and the biofilm matrix, 8 out of 24 reported proteins were found to be expressed at higher levels in *C. auris* compared to *C. albicans*.[10] These findings highlight the enhanced resistance mechanisms of *C. auris*, which is concerning given its emerging resistance to nearly all antifungal drugs. Notably, *C. auris* isolates demonstrated high resistance to fluconazole, a first-line treatment for candidemia, with minimum inhibitory concentration (MIC) values exceeding 64 mg/mL, underscoring the urgent need for alternative therapeutic strategies.[30]

Additionally, other azoles, such as voriconazole, exhibited variable antifungal activity against *C. auris*. Over 95% of isolates from India were resistant to the topical allylamine terbinafine, while nearly one-third of the isolates studied so far showed resistance to amphotericin B, a polyene drug often used as a last-resort treatment. Nucleoside analogs like 5-flucytosine have demonstrated success in treating more than 95% of *C. auris* infections in vitro. However, their clinical use is limited due to the rapid emergence of resistance, which can develop during treatment, and the risk of severe side effects, such as bone marrow toxicity, which can be life-threatening, particularly in immunosuppressed patients.[30]

Approximately 2–7% of *C. auris* isolates have developed resistance to echinocandins, a newer class

of antifungal drugs. Despite this, echinocandins remain the most effective treatment for most *C. auris* infections, as reported side effects are generally mild, including nausea and dose-dependent increases in liver aminotransferase levels. However, the emergence of multidrug resistance is a growing concern. During an outbreak in North America from 2012 to 2015, 4% of *C. auris* samples exhibited resistance to all three major classes of antifungal drugs—azoles, polyenes, and echinocandins—highlighting the urgent need for alternative therapies and improved strategies to manage and prevent the spread of resistant *C. auris* strains.[30]

Outbreak Management Strategies

Patients at risk for invasive *Candida auris* infections often have the same risk factors as those with other *Candida* species. Around 10% of *C. auris*-colonized patients develop invasive infections, especially those in ICUs who require mechanical ventilation or invasive medical devices. Reported mortality rates for *C. auris* infections vary widely, ranging from 0% to 72%. Because of these risks, the CDC and other international health organizations have established specific guidelines to prevent and control *C. auris* outbreaks in healthcare settings.[31]

Preventing the transmission of *Candida auris* in healthcare settings requires a comprehensive strategy that include early identification, strict infection control measures, and effective environmental decontamination. Rapid detection through molecular-based diagnostics, such as real-time PCR, is crucial for identifying infected or colonized patients, especially those recently admitted from high-risk facilities. Once detected, patients should be immediately isolated in single rooms with connected toilets, or cohorted when single rooms are unavailable, with dedicated healthcare workers assigned to their care. Healthcare workers must follow strict hand hygiene protocols, using alcohol-based hand rubs (ABHR) and washing visibly soiled hands with soap and water before applying ABHR. Personal protective equipment (PPE), including gloves, gowns, and face masks, should be used consistently, and visitor access should be limited to minimize exposure. Environmental cleaning and disinfection play a vital role in controlling the spread, as *C. auris* can persist on surfaces for weeks and is resistant to many standard disinfectants. Hospital-grade chlorine-based disinfectants (≥1000 ppm sodium hypochlorite), hydrogen peroxide vapor, and ultraviolet (UV-C) light are among the most effective decontamination methods, with rooms and high-touch surfaces requiring cleaning at least two to three times daily. Reusable medical equipment, such as thermometers and blood pressure cuffs, should be disinfected after each use, while disposable alternatives should be used whenever possible. Additionally, ongoing surveillance, including routine screening of high-risk patients and periodic environmental sampling, is essential for monitoring *C. auris* persistence and ensuring the effectiveness of infection control measures. Although there are no standardized decolonization protocols, strategies such as chlorhexidine gluconate washes, mouth rinses for ventilated patients, and disinfectant-soaked pads for catheter sites may help reduce colonization. However, recolonization remains a challenge due to the organism's persistence on personal items like bedding and pillows. To further control the spread, patient transfers should be minimized, and those with *C. auris* should be scheduled last for medical procedures to allow thorough disinfection afterward. Healthcare facilities can effectively control *C. auris* outbreaks and prevent transmission to vulnerable patients by integrating these strategies: rapid identification, patient isolation, stringent hygiene practices, rigorous environmental cleaning, and continuous monitoring.[31]

CONCLUSION

The epidemiology of *Candida auris* highlights its rapid global spread and significant impact on healthcare settings, particularly in immunocompromised patients. From its earliest identification in Japan in 2009 to its classification by the WHO as a critical pathogen in 2022, *C. auris* has evolved into a formidable challenge due to its high virulence, biofilm formation, and resistance to multiple antifungal agents. The pathogen's ability to thrive in high-temperature and high-salinity environments, possibly linked to climate change, along with its genetic diversity across distinct clades, underscores the need for advanced diagnostic methods and stringent infection control measures. The development of antifungal

resistance mechanisms, particularly against azoles and echinocandins, further complicates treatment, necessitating ongoing research and tailored therapeutic strategies to manage this emergent threat effectively. Preventing and controlling *Candida auris* infections in healthcare settings requires a multifaceted approach such as early identification, strict infection control measures, and thorough environmental decontamination are essential to minimizing transmission. By implementing these comprehensive strategies, healthcare facilities can significantly reduce the risk of *C. auris* transmission and protect vulnerable patients.

Conflict of Interest

The author(s) declare no conflict of interest regarding the publication of this literature review. All sources and data used in this review were obtained from publicly available scientific literature and reports.

Author Contribution

Conceptualization, M.S.A., F.S., A.R; methodology, M.S.A, A.A.H, and F.S.; data curation, M.S.A, F.S., R.A.; writing—original draft preparation, M.S.A., F.S., A.R.; writing—review and editing, M.S.A., F.S., A.R, A.A.H., R.A. All authors have read and agreed to the published version of the manuscript.

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