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# Multidrug-resistant *Candida auris*: A global challenge

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**ABSTRACT**

*Candida auris* is an emerging fungal pathogen showing resistance to most of the currently available antifungal drugs. The pathogen is spreading rapidly worldwide. It mainly affects immunocompromised individuals such as intensive care unit patients, adults, and newborns who are treated in health care facilities. The isolates can be recovered from a variety of specimens, including mucocutaneous swabs, urine, respiratory specimens, and body fluids; however, bloodstream infections are the most commonly observed invasive infections. The advent of *C. auris* as a human fungal pathogen has been directly linked to the occurrence of new virulence traits and its ability to adhere to various surfaces to form a multidrug-resistant biofilm. With the lack of distinctive traits in *C. auris,* its identification has been problematic. The commercially available biochemical tests often misdiagnose the pathogen to phylogenetically related *Candida haemulonii* species making it difficult for clinicians to initiate proper antifungal treatment in patients. Emergence of resistant isolates has further posed a new challenge to the limited therapeutic options. This review highlights the risk factors involved in infection, virulence traits of *C. auris*, diagnostic methods, and mechanism of drug resistance along with novel antifungal drugs against this fungal pathogen which could provide direction for future work on it.

## 1. INTRODUCTION

The invasive candidemia is predominantly caused by *Candida albicans* and is defined as the most common nosocomial infection in the world. However, the paradigm has changed in the last few years with more incidence of candidiasis due to non-*albicans Candida* species (NACS) [1].

*Candida auris,* an emerging fungal species, has changed the basic insights about candidemia. Unlike other *Candida* species which are abundantly present in the gastrointestinal tract, *C. auris* is a good colonizer of the skin and is also responsible for invasive infections. It belongs to the order Saccharomycetales which are mainly ascomycetous yeasts that reproduce by budding. It was first identified in 2009 in an old Japanese lady suffering from ear infection (Latin: *auris* means "ear") [2]. Fungemia due to *C. auris* is accompanied by a high mortality rate and the key factor behind this is treatment failure due to recalcitrant nature of the pathogen against most of the antifungal drugs [3]. The situation gets critical as scientists are still struggling to quickly and correctly identify this pathogen with the standard laboratory method. There is ample news of its incidence ranging from cases of *C. auris* infections in Venezuela in 2012 [4] to its occurrence in 2013 in the US [5], its emergence in a cardio-thoracic center in London in 2015-2016 [6] and in South Africa in 2016-2017 [7]. In the last 5 years, the pathogen has gained a worldwide presence in India, Pakistan, South Africa, Norway, Japan, Korea, Kuwait, Kenya, Israel, Canada, Venezuela, Spain, Germany, and many other countries [Figure 1] [8-12]. In the US, *C. auris* started spreading around 2015, and in the year 2018, there was about 318% increase in the number of reported cases [13]. As per the Centers for Disease Control and Prevention (CDC), the number of people afflicted by *C. auris* (only clinical case count) till September 22, 2020 in the US alone has risen to 1302 [13]. Candidiasis due to *C. auris* is not confined to any specific age group, affecting preterm infants as well as elderly patients. The report also highlights that majority of *C. auris* infections (more than 90%) are resistant to at least one antifungal and since there are limited antifungal drugs available, this becomes a frightening situation. The propensity with which this pathogen is spreading has indeed alarmed the world and made *C. auris* a worldwide menace.

### 1.1. Characteristics of *C. auris*

*C. auris* produces smooth white cream-colored colonies on Sabouraud's agar and pink to beige colonies on CHROM agar. It forms oval or elongated shaped yeast cells that can be singly present or in pairs or groups and do not have the ability to form pseudohyphae, chlamydospores, and germ tube [14,15]. However, it has been found that under high stress and saline conditions, *C. auris* can form pseudohyphae [3]. It is able to grow at 37°C but exhibits thermotolerance (can grow even at 40°C–42°C) and is also able to grow on high saline conditions. This characteristic helps to differentiate *C. auris* from related species *C. haemulonii* and *C. pseudohaemulonii* that are not able to grow under these conditions.

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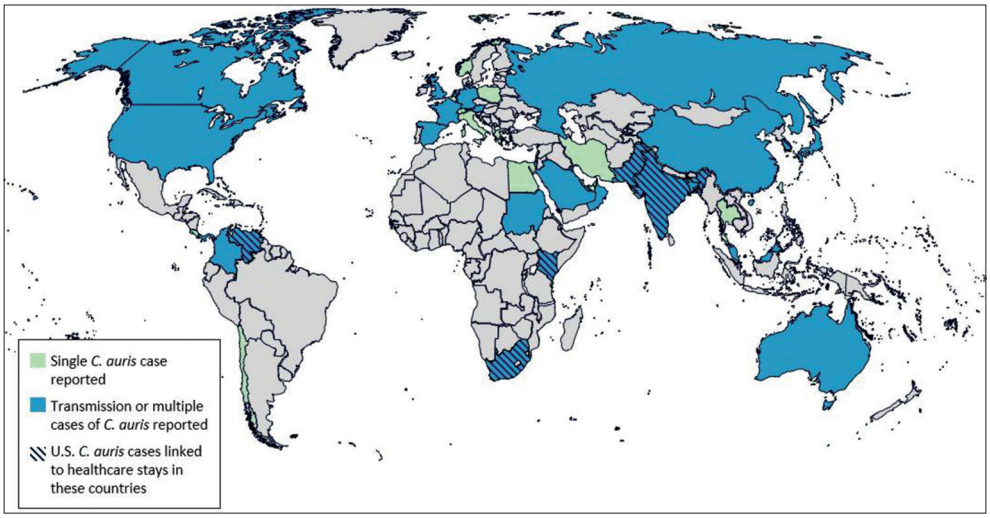


**Figure 1:** Countries from which *C. auris* cases have been reported as of July 31, 2020. Source: https://www.cdc.gov/fungal/candida-auris/tracking-c-auris.html.

*C. auris* can ferment glucose, sucrose, and trehalose but does not have the capacity to ferment galactose, maltose, lactose, and raffinose. It does not have the ability to grow in the presence of 0.01% and 0.1% of cyclohexidine [16]. The haploid genomic size of *C. auris* is about 12.3 Mb with a 45.3% GC content [17]. Its genome analysis has established that there are 6500–8500 protein-coding sequences present; most of these genes encode for the virulence factors in *Candida* species. The sequence comparison of 285bp D1–D2 domain of the large ribosomal subunit of 28S ribosomal DNA gene of *C. auris* has shown that there is a significant variance of *C. auris* from other *Candida* species. In fact, a genetic analysis has further established that *C. auris* is more closely related to *C. haemulonii* and *C. lusitaniae* than to other *Candida* species [18] [Table 1]. Single nucleotide polymorphism (SNP) has been found in different isolates of *C. auris* gathered from different geographical regions, leading to its categorization into four clades [16,19-21].

**Table 1:** Percentage identity of *C. auris* with other *Candida* species using D1-D2 region of rDNA (Source: Jeffery-Smith *et al.* 2017 [18]).

| Organism | Percentage Identity |
|---|---|
| *Candida auris* (South Asian clade) | 100 |
| *Candida lusitaniae* | 82 |
| *Candida haemulonii* | 82 |
| *Candida tropicalis* | 79 |
| *Candida famata* | 75 |
| *Candida parapsilosis* | 70 |
| *Candida albicans* | 43 |
| *Candida krusei* | 43 |
| *Candida glabrata* | 42 |
| *Candida rugosa* | 39 |

### 1.2. Identification of *C. auris*

The genetic variation of *C. auris* from other *Candida* species has led to a major problem of non-identification or misidentification of this pathogen in hospitalized patients using conventional biochemical typing [22]. This has led to inappropriate treatment which has resulted in the arrival of new resistant isolates. Therefore, newer methods of identifying and isolating *C. auris* from human and environmental sites that are rich in diverse microbes have been devised. Culture-based identification of *C. auris* has led to the development of enrichment broth assay that has been designed to screen out *C. auris* from the clinical and environmental samples. The method shows high sensitivity and specificity and has a very low cost. It facilitates easy detection of *C. auris* by exploiting its property to grow under high saline and high-temperature conditions. The broth consists of 10% salt, gentamicin, chloramphenicol, and either dulcitol, mannitol, or dextrose in Sabouraud broth or Yeast Nitrogen Base (YNB) Broth. All four clades of *C. auris* are able to grow under elevated temperature and salt conditions, but the closely related *C. haemulonii, C. duobushaemulonii, C. pseudohaemulonii,* and other *Candida* species (that are not closely related to *C. auris*) are not able to grow under these conditions [23].

The failure of commercially available biochemical identification test such as VITEK2 YST, API 20C AUX, BD Phoenix, and MicroScan in distinctly identifying *C. auris* from other related species is due to a lack of the relevant *C. auris* database in the identification system [Table 2]. However, for phenotypic yeast identification, BioMerieux has now updated the VITEK2 identification to software version 8.01 which is able to identify *C. auris* [24]. However, this updated software is not very competent in identifying *C. auris* isolates from African and East Asian clade but is able to identify isolates from South American clade [25].

Matrix-assisted laser desorption ionisation time-of-flight (MALDI-TOF) mass spectrometry assay is the most reliable method for the identification of *C. auris* [26,27]. This method can provide the correct and consistent method of identification of *C. auris,* provided the spectral library contains the updated and validated reference spectra for all the clades and closely related species of *C. auris*. It is a proteome based low-cost technology. The mass spectrum provides a fingerprint for the particular fungal pathogen. The generated spectrum is very unique to every microorganism, with each peak specific to genera, species, and even strains. The MALDI-TOF MS approach is commercially provided by two manufacturers, Bruker Biotyper (Bruker Daltonics, Berman, Germany) and VITEK MS (BioMerieux). The Bruker Biotyper 3.1 software contains spectra of three *C. auris* strains: Two isolates from Korea and one from Japan. Both Bruker Biotyper and

**Table 2:** Misidentification of *C. auris* by commercial identification methods.

| Method of Identification | *C. auris* misidentified as |
|---|---|
| VITEK 2 YST | *C. haemulonii,*<br>*C. duobushaemulonii* |
| API 20C | *Rhodotorula glutinis*<br>*C. sake* |
| BD Phoenix yeast identification system | *C. haemulonii*<br>*C. catenulata* |
| MicroScan | *C. famata*<br>*C. guilliermondii*<br>*C. lusitaniae*<br>*C. parapsilosis* |
| API ID32C | *C. sake*<br>*Saccharomyces kluyveri* |
| RapID Yeast Plus | *C. parapsilosis* |

Source: Mizusawa *et al*., 2017, Desoubeaux *et al*., 2018, Forsberg *et al*., 2018, Iguchi *et al*., 2019 [91,92,39,35]

VITEK MS include *C. auris* in their research-use-only (RUO) library and FDA approved system databases [22,25,28]. In association with Biotyper, MicrobeNet recently has released the Biotyper Classification Module. The MicrobeNet database contains spectral libraries of all *C. auris* strains and its clades and provides the accurate identification of *C. auris* at species level [29,30].

Accurate identification of *C. auris* can also be done by sequencing of internal transcribed spacer (ITS) regions and D1/D2 region of 28S large ribosomal subunits. The development of PCR specific assay provides the easy identification of *C. auris* and its related species. The culture independent assay includes a TaqMan quantitative PCR (qPCR), a SYBR green qPCR, T2 magnetic resonance assay, and loop-mediated isothermal amplification (LAMP) [31]. These molecular-based methods also help to detect the resistance mutation in *C. auris* [32]. Both Fungiplex *C. auris* RUO real-time PCR assay (Bruker Daltonics) and the GPS™ MONODOSE dtec-qPCR test have also been found to be very useful in the correct identification of this pathogen [33,34]. However, *C. auris* identification is still a big challenge, especially in resource deficit countries and its misidentification often results in a treatment failure in most cases.

### 1.3. *C. auris* Infection and its Associated Risk Factors

Candidiasis due to *C. auris* includes both superficial infections as well as invasive diseases; however, bloodstream infections (BSI) cause significant mortality in intensive care unit (ICU) patients. The primary concerns of healthcare workers associated with *C. auris* are: Misidentification of the pathogen, its resistance to multiple antifungals, and its colonization to human body and environment that can result into outbreak like conditions in health care settings [23,35]. The situation gets aggravated by the fact that *C. auris* also has the ability to survive on biotic and abiotic surfaces for weeks and even for months resulting in further spread. Patient to patient transmission has been found to cause skin colonization and increased risk for candidemia. The hospital environment, therefore, serves as a reservoir for the nosocomial transmission of *C. auris* [36]. The risk factors that are significant for *C. auris* infections are almost same as with any other *Candida* species, as these are opportunistic fungal pathogens. These risk factors are related to severe underlying diseases and immunosuppression (such as bone marrow transplantation and HIV), long stay of patients in ICU, chronic kidney disease, malignancy, neutropenia, recent surgery, corticosteroid therapy, parenteral nutrition, blood transfusions, hemodialysis, diabetes mellitus, use of a broad-spectrum antibiotics or antifungals, prior or concomitant bacterial infections, use of central nervous and urinary catheters, and prolonged hospitalization [37]. Among these, patients suffering from diabetes mellitus and having a long stay in ICU are at major risk to develop *C. auris* fungemia.

### 1.4. Emergence of *C. auris*

The rapid emergence of *C. auris* around the world has led to some extensive research to understand its cause and pattern of transmission. Whole Genome Sequencing (WGS) of *C. auris* isolates demonstrated the independent emergence of four different clades in different geographical locations, thus dispelling all doubts of the spread of one clone from a single source to different regions of the world [17,20]. These geographically specific clades have been described as: South Asian (India, Pakistan), East Asian (Japan), South African, South American (Venezuela), and each is separated by around thousands of single nucleotide polymorphism (SNP) [38]. Isolates belonging to the same clade are highly related to each other or nearly clonal and have very less genetic variation. Further, WGS studies on *C. auris* isolates from four different Indian hospitals found them to be highly related or exhibits less genetic diversity and confirmed the clonal transmission of the isolates [17]. The results were also similar from Pakistan, South Africa, and Venezuela [20]. This further confirmed that isolates within each country or same clade are highly related to each other and differ by less than a hundred SNP as compared to isolates from different regions that differed by thousands of SNP [20,39]. All major clades except for the East Asian clade have been linked to outbreaks causing invasive infections [40]. It has been found that isolates from East Asian clade are involved in causing ear colonization and external otitis. It also shows higher genetic diversity as compared to other clades which often indicates an older natural population and therefore it can be the ancestor of *C. auris* [40]. Recently, another fifth clade has appeared in Iran, where the patient has never travelled abroad and the fungal isolate of this clade was found to be susceptible to the antifungal drugs [41]. The clade is genetically very different from all the other clades with >200,000 SNPs compared with the other four clades.

Many factors are considered to be responsible for the emergence of new *C. auris* strains. Changes in the ecological niche of this fungus and its tolerance to divergent environment conditions such as high temperature and salt conditions might contribute in the development of various virulence traits [40,42]. As the temperature on earth and atmosphere increases, the difference between optimal temperature of the environment and mammalian body temperature will become lesser and lesser; and the emergence of new invasive fungal pathogen can take place [40,43]. This further raises a pertinent question that if this is true, then how will the scientific community ensure that other fungal pathogens do not follow *C. auris* in adapting to non-ambient temperatures in a similar manner.

### 1.5. Antifungal Drug Resistance

The key to the right treatment with an antifungal agent depends on the accurate identification of the type of *C. auris* strain involved in the infection [44]. The pathogen develops resistance very rapidly while the patient is still undergoing treatment, that's why it is very essential to use the antifungals at the right time and in the correct dosage [18]. Unfortunately, the antifungals against *Candida* infections are limited to three basic drugs – azoles, echinocandins, and polyenes (Amphotericin B). *C. auris* shows resistance to antifungal drugs such as fluconazole (FLC) and amphotericin B [29]. Most of the

*C. auris* isolates show susceptibility toward the echinocandin class of antifungals. However, at present, no antifungal can be defined as the absolute drug of choice to combat *C. auris*.

Azole resistance in *C. auris*: The *C. auris* isolates that show resistance to azole class of antifungals are found to have increased expression of *ABC* (ATP-binding cassette) and *MFS* (Major facilitator superfamily) transporters. These transporters help in the efflux of azole compounds from the fungal cell [45] [Figure 2]. Inside the yeast cells, these azole compounds work by inhibiting the enzyme 14α-lanosterol demethylase that mainly functions in the biosynthesis of ergosterol in the cell membrane of the yeast by removing the methyl group from the lanosterol. Ergosterol is an important component of cell membrane which helps in maintaining the integrity of the cell and the inhibition of enzyme leads to the accumulation of toxic precursors in a cell which can inhibit the growth of a fungal cell. Point mutation in *ERG11* gene that encodes 14α-lanosterol demethylase enzyme leads to altered protein structure, reduced binding of azole drugs to the target molecule, decreased susceptibility of the pathogen to azole that will exhibit elevated Minimum Inhibitory Concentration (MIC) to azole [Figure 3]. Whole-genome sequencing (WGS) has identified three different types of amino acid substitution in *ERG11* gene that are associated with azole resistance in *C. auris*. These mutations in *ERG11* gene are found to be very specifically associated with the geographical clade. Isolates from South Africa and South America (Venezuela) share F126L alterations, while Indian isolates harbor Y132F and K143R substitutions [20,31,46,47]. The association between each mutation and geographical clade shows that resistance to fluconazole is acquired independently and is not intrinsic in nature [48]. However, based on antifungal susceptibility testing, it has been reported that isolate from East Asian clade shows less resistance to antifungal drug as compared to isolates from other three clades [49].

Echinocandin resistance in *C. auris*: Most of the *C. auris* isolates exhibits elevated MIC and reduced susceptibility to triazole and amphotericin B class of antifungal agent. This has led to a recommendation for the use of echinocandins in the treatment of invasive candidiasis. Micafungin, a promising echinocandin, proved to be more useful in treating invasive candidemia as compared to fluconazole and amphotericin B. However, due to extensive and indiscriminate use of echinocandins, many of the *C. auris* isolates are increasingly becoming resistant to this drug [50,51]. Draft genome sequencing of *C. auris* has established that it contains single copy of *ERG3*, *ERG11*, *FKS1*, *FKS2*, *FKS3,* and a substantial portion encodes for the ABC and MFS transporters that demonstrate multidrug resistance in this emerging pathogen [17,19,51]. *FKS1* gene encodes β-1,3-D-glucan synthase enzyme and represents the potential target for echinocandin class of antifungal. This enzyme plays a crucial role in the biosynthesis of β-1,3-D glucan, a major component of the *Candida* cell wall. It is composed of two subunits named as FKS1p (encoded by *FKS1*, *FKS2*, *FKS3*) and Rho1p. FKS1p is a catalytic subunit of the enzyme, while Rho1p is a regulatory protein involved in cellular processes, one being the synthesis of β-1,3-D glucan. Inhibition of glucan synthase enzyme by echinocandin results in cell wall lysis and osmotic instability in a cell. Reduced susceptibility to echinocandin mainly occurs through three main mechanisms (a) acquired *FKS* resistance mutation which results in reduced glucan synthase enzymatic activity and elevated MIC to Echinocandins, (b) intrinsic *FKS* mutations, (c) and adaptive stress response that results in increased chitin content in the cell wall of fungi. In most of the *Candida* species, there are mainly two hotspot regions in FKS gene, named as Hotspot-1 (HS1) and Hotspot-2 (HS2) at which amino acid substitution can decrease the echinocandin susceptibility [52-54]. However, in *C. auris,* mutation responsible for resistance occurs as a single amino acid substitution S639Y in FKS1, in Hotspot 1 (HS1) region. This amino acid substitution is equivalent to S645 and S629 in *C. albicans* and *C. glabrata,* respectively.

In general, two different substitutions have been identified in *C. auris*, S639F and S639P [55,56]. In *C. albicans* and *C. glabrata,* the substitution of a phenylalanine (F) results in only a moderate increase in MIC while substitution of proline (P) results in dramatic increase in MIC to echinocandin. For *C. auris*, these both amino acid substitutions result in about 4–8 fold increase in echinocandin MIC values [56]. In response to inhibition of glucan synthase enzyme by echinocandins, there is activation of compensatory pathways, which results in the increased synthesis of chitin in the fungal cell wall. The biosynthesis of chitin occurs through the protein kinase C (PKC), high osmolarity glycerol kinase (HOG Kinase), and by $Ca^{2+}$ calcineurin signaling pathways. Echinocandins are mainly excreted through feces rather than the urine, so very little active drug can be recovered from the urine. The site of infection plays a crucial role in the choice of antifungal agent for the treatment of invasive infections. Echinocandins have high molecular weight; hence, these drugs have inadequate penetration into many sites, including cerebrospinal fluid (CSF). Treatment with this drug in infants and neonates is considered only when the central nervous system (CNS) is not affected. Hence, other medications (amphotericin B with 5-Flourocytosine/ 5-Flucytosine) should be used for CNS and renal tract infections [18,56,57]. Further, CDC

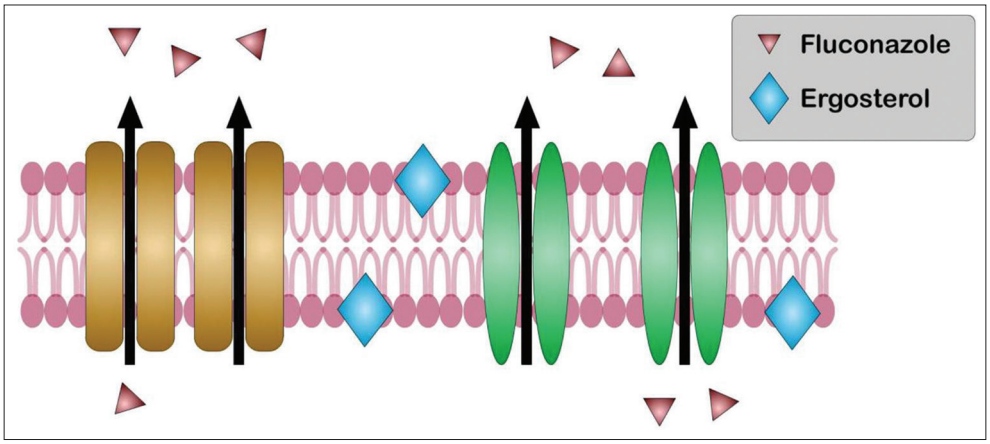


**Figure 2:** Overexpression of (a) ABC efflux pump and (b) MFS efflux pump in azole-resistant *C. auris*. Source: Adapted from Whaley *et al*., 2017 [90].

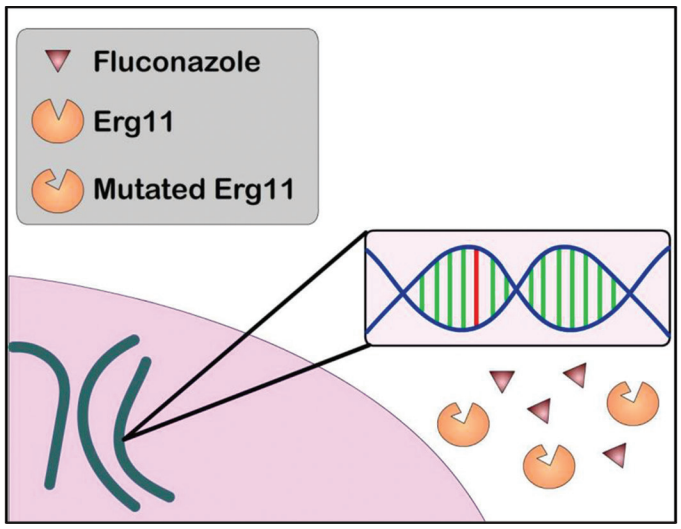


**Figure 3:** Mutation in ERG11 leads to expression of proteins with reduced affinity for fluconazole binding. Source: Adapted from Whaley *et al*., 2017 [90].

recommends amphotericin B deoxycholate (1mg/kg daily) as the first-line treatment in neonates [39].

C) Polyene (Amphotericin-B) resistance in *C. auris*: Several *C. auris* isolates have been found to be resistant to amphotericin B [16]. In almost all cases, it is the modification of the membrane *viz a viz* its sterol composition that seems to be the cause of resistance to this family of antifungal agents.

The role of molecular chaperone Hsp90 in maintaining resistance toward antifungal drugs in various fungal species has also been recently established in *C. auris*. Hsp90 was found to be very important for growth in *C. auris.* It helps clinical isolates to develop tolerance to azoles, thus leading to the development of drug resistance in susceptible strains and this further inhibits biosynthesis of the membrane ergosterol [58]. It was also established that deletion of HSP90 gene leads to morphogenetic transformation of *C. auris* from yeast to filamentous growth.

Another mechanism of drug resistance takes advantage of morphological plasticity of *Candida* that is dependent on changing environmental factors. These morphological changes in *C. albicans* include yeast-filament transition and white-opaque colony transition [59,60]. It is well documented that filamentous *Candida* has high virulence and leads to systemic infections and is mostly associated with drug resistance. Furthermore, the white cells are more virulent than the opaque ones and are more common in systemic infections. It was a common belief that *C. auris* lacks pseudohyphae or hyphal morphology and therefore does not actively form any biofilms. However, contrary to this, it has been found that certain strains of *C. auris* undergo morphological switching under certain temperature fluctuations and this is further aided by passage of *C. auris* through mammalian system [60]. One significant difference that was found in this study was that unlike change of morphogenesis from yeast to hyphal form that ensued at high temperature in *C. albicans* [59], reverse was true for *C. auris* [60]. The characteristic biofilm formation by *C. albicans* with an intricate network of hyphae embedded in the extracellular matrix (ECM) was, however, not well developed in *C. auris* where there is mere adherence or clumping of yeast cells to surfaces. However, despite this very elementary biofilm architecture of *C. auris,* it still is found to be resistant to all major antifungals [61].

### 1.6. Biofilm Formation in *C. auris*

Biofilm can be defined as microbial community sticking to each other and to the surface. The growth of a microorganism in association with the surface is called as a biofilm. In biofilm, organism grows as a community rather than separate surface adherent cells. The cells of a biofilm have a capacity to produce their own extracellular matrix and show specific phenotypes that are different from the phenotypes of a cell growing in suspension called as planktonic cells. The use of devices such as central venous catheters, urinary bladder catheters, and mechanical heart valves are the major risk factors to develop infections that are mainly caused by *Candida* species. These infections arise due to the ability of fungal cells to adhere to devices and their growth occurs in the form of a biofilm [62]. There are mainly three stages involved in the formation and development of biofilm in *C. auris* (i) attachment or adherence of yeast cells to the surface, (ii) proliferation of yeast cells by the process of budding, and (iii) maturation into a structural biofilm [63]. The biofilm consists of yeast cell and hyphae embedded in matrix. ECM is composed of various kinds of polysaccharides, protein, and lipids [64], and it provides a surface for adhesion and helps in maintaining the structure of a biofilm. It also helps in the absorption of nutrients and retention of water. ECM is degraded during the nutrient limiting conditions to provide the carbon and nitrogen source to fungal cells [62]. The polysaccharide, glucan, and mannose component of ECM helps in sequestration of the antifungal drugs. The production of a matrix in biofilm is associated with the stress response regulatory pathways such as calcium/calcineurin signaling pathways. The molecular chaperone Hsp90 is required for the production of a mature biofilm. Many of the transcriptional factors are also involved in the biosynthesis of ECM matrix. Zinc sensing transcription factor negatively regulates the production of matrix, while RLM1 (transcription factor involved in cell wall integrity) acts as a positive regulator for the formation of matrix [64]. The ECM contributes in the pathogenicity by promoting the immune evasion.

Biofilm formation is very important for pathogenicity in *Candida* species. *C. auris* exhibits minimal adherence to silicone elastomer material as compared to *C. albicans;* hence, it plays much less role in catheter-associated candidiasis as compared to *C. albicans* that is generally known to cause such type of infections [65]. Phenotypic observation of biofilm has further revealed that *C. auris* biofilm is intermediate to *C. albicans* and *C. glabrata* [61]. *C. auris* exhibits more propensities to survive on a wide range of surfaces, including dry, moist, and plastic surfaces as compared to *C. albicans* [23,66].

Experiments have been done to determine the pathogenicity and virulence of *C. auris viz a viz* other *Candida* species by using invertebrate *Galleria mellonella* insect model. *C. auris* shows two patterns of cellular morphology, one forming aggregates while the other is non-aggregating type. Non-aggregating form of *C. auris* was found to have more biofilm-forming capacity compared to aggregating strains of *C. auris.* It also exhibited greater pathogenicity as compared to aggregate forming isolates as well as *C. albicans*, and resulted into a significantly higher larval death of *G. mellonella* with much less inoculum concentration [63]. Dissection of larva inoculated with *C. albicans* was found to have more hyphal proliferation in the hemolymph. However, larva infected with *C. auris* strains on dissection did not show any such hyphal or pseudohyphal growth. Larvae that had received non-aggregate strains of *C. auris* exhibited large number of budding yeast cells in hemolymph, while larva infected with aggregate forming strains of *C. auris* exhibited fewer single yeast cells and contained large aggregates of yeast cells. These aggregate isolates are formed due to the inability of *C. auris* to separate out its daughter cell

after the budding and they were resilient to separation even by physical disruption methods [3].

During formation of biofilm in *Candida* species, several genes are upregulated. Transcriptomic analysis shows that adhesion-related glycosylphosphatidylinositol (GPI) anchored cell wall genes (CSA1, PGA26, PGA52) are expressed much earlier when the biofilm formation has just started. As the formation of biofilm enters into intermediate and mature stages, the expression of genes coding for ABC (SNQ2, CDR1) and MFS (YHD3, MDR1) and MFS (YHD3, MDR1) transporters is also increased. These genes control the efflux pump activity of the transporters and are found to be more upregulated in mature biofilm in *C. auris* [44,67]. The upregulation of these genes seems to occur more in sessile cells as compared to planktonic cells and also confirms that formation of biofilm promotes antifungal drug resistance and virulence in the fungi.

### 1.7. Antifungal Drug Resistance in Biofilm

A study has been done to determine the effect of various antifungals on the sessile and planktonic cells of the biofilm. It has been found that both sessile and planktonic cells exhibit enhanced resistance to fluconazole (FLC) and voriconazole (VRC). Both sessile and planktonic cells were found to exhibit increased MIC against the FLC (MIC > 32 mg/L) and VRC [61]. The resistance to FLC and VRC is the result of overexpression of efflux pump transporters in cells. Both sessile and planktonic cells exhibit susceptibility to liposomal amphotericin B, but sessile cells require about 16 mg/L of amphotericin B as compared to planktonic cells which require 4 mg/L. Echinocandins are ineffective to sessile cells, but planktonic cells are susceptible to it. Micafungin is the most effective echinocandin that requires <0.5 mg/L to inhibit planktonic cells, while caspofungin requires 2–32 mg/L to inhibit planktonic cells. To inhibit sessile cells, both micafungin and caspofungin requires >32 mg/L [18,61].

### 1.8. Hog1 Regulates Stress Tolerance and Virulence in *C. auris*

Despite having genetic divergence, *C. auris* has been found to exhibit much higher virulence and pathogenicity as compared to the other pathogenic *Candida* species. However, *C. auris* is incapable to show phenotypic switching from yeast to filamentous growth; hence, it must be using different strategies to infect and colonize the host. An important feature that is essential for the virulence and pathogenicity of an organism is its ability to survive in different kinds of divergent environments. The cellular stress response plays a pivotal role in tolerating various stress conditions imposed by host during the infection. The niches colonized by fungi in the human host are dynamic. These niches show fluctuations in the osmolarity, pH, and the availability of nutrients [68]. To cope up with various stress conditions, *C. auris* has been found to contain stress sensing pathways in which Hog1 related stress-activated protein kinase (SAPK) plays an important role. The Hog1 SAPK is the most conserved fungal protein that helps in stress sensing and signaling. To determine the role of Hog1 SAPK in *C. auris*, the Hog1-deleted strains of *C. auris* were exposed to various kinds of diverse environments and results were examined. Cells deficient in Hog1 were found to be very sensitive to the high concentration of NaCl and KCl. Hog1 was also found to be important for the growth of *C. auris* in highly acidic environments [69].

### 1.9. Novel Antifungal Used against *C. auris*

The rising incidence of resistance in *C. auris* to triazole drugs and amphotericin B has led to use of echinocandins as the first line of treatment [70-72]. Micafungin has also been found to have higher efficacy as compared to fluconazole and amphotericin B in a PK/PD (pharmacokinetics/pharmacodynamic) study of *C. auris* candidemia in mice [73]. However, with the alarming rise of antifungal resistance, there is an urgent need to develop new antifungal therapies for the control of *C. auris* infection. The new antifungal compounds that have been developed show promising results against *C. auris*. These new compounds have various drug targets such as β-glucan synthase inhibitors, enzymes involved in chitin synthesis, and GPI anchored protein [63].

Ibrexafungerp (commonly called as SCY-078) is the new antifungal drug and is currently in a phase III trial for invasive infections caused by *C. auris*. SCY-078 is a triterpene [65], orally available glucan synthase inhibitor that has been shown to exhibit anti-biofilm activity against most *Candida* species. It leads to cellular deformation, pore formation in fungal cells, and inhibits cell division [36]. When *C. auris* strains are treated with the SCY-078, it reduces the thickness of biofilm and also decreases the metabolic activity of the fungal cells in the biofilm [65].

Isavuconazole sulfate is the new second-generation triazoles which demonstrate better results *in vitro* against the fluconazole-resistant *C. auris* strains [65,74]. The new antifungal rezafungin (CD101) is a novel semisynthetic echinocandin with long-acting chemical stability and shows activity against the *C. auris* strains [63,75]. The other new antifungal with a novel mechanism of action is APX001 which has currently completed the second clinical trial. This antifungal targets the glycosylphosphatidylinositol (GPI) synthesis by inhibiting the cell wall transfer protein GWT1 (glycosylphosphatidylinositol-anchored wall transfer protein 1) and can prove effective against *C. auris* [76]. Another new antifungal VT-1598 targets the lanosterol demethylase enzyme and has been found to have *in vitro* activity against *C. auris* [77]. In addition to these new antifungal drugs, research is going on to characterize new antifungal with a drug target mechanism which includes molecular chaperone Hsp90 and calcium calcineurin signaling pathways. Continued research, evaluation, and clinical studies are required to check the potential of existing compounds and new compounds against multi drug-resistant *C. auris* isolates.

### 1.10. Role of Anti-CR3-RP Polyclonal Antibody against *C. auris* Biofilm

*Candida* sp. exhibits virulence-associated surface antigen called as complement receptor-3 related protein (CR3-RP). *C. auris* also possess this cell surface protein that plays an important role in adhesion during the formation of biofilm. It has been found that polyclonal antibody anti-CR3-RP antibody directed against this surface antigen can be used to reduce the adherence and biofilm formation in *C. auris* [78]. It was further seen that these antibodies also demonstrated activity against *C. auris* 24 h pre-formed biofilms almost to the same level as achieved with conventionally used antifungals.

### 1.11. Role of NDA-3V Vaccine against the Multidrug-resistant *C. auris*

*C. auris* has been found to possess an evolutionarily conserved adhesion protein Als3p, which is very essential for the early stages of a biofilm in fungi [79]. Anti-Als3p antibodies have been generated by vaccinating the mice with a NDA-3V vaccine which is formed from N-terminus of the Als3p protein [80]. The vaccine induces the formation of antibody and cell-mediated immune responses in a host cell. These anti-als3p antibodies act as opsonins and increase the sensitivity of *C. auris* to

macrophage killing by the process of phagocytosis [80]. The vaccine has shown high efficacy in a clinical trial that has been done against vulvovaginal candidiasis.

### 1.12. Infection Control and Prevention

The emergence of *C. auris* has grown to the proportion of an outbreak in many countries, with the situation becoming grave due to the persistence of the pathogen in the face of regular antifungals [28,81-84]. An exhaustive study of 350 isolates of *C. auris* from 10 hospitals in India has found about 90% of the strains resistant to azoles [85]. However, the degree of azole resistance has been found to be highly variable with isolates collected from different geographical regions, further suggesting the rate of resistance to be a localized phenomenon and place dependent [85-87]. It has further been seen that the minimum time needed to acquire infection from a patient suffering with *C. auris* infection or from his immediate environment is about 4h or less [6]. Being predominantly a nosocomial infection, there exists a direct correlation of usage of contaminated central venous catheter (CVC), urethral catheters, and long hospital stay with the occurrence of *C. auris* cases, especially in ICUs. In fact method of containment of this fungal infection is largely dependent on understanding its mode of transmission.

The proper implementation of infection control practices is very essential to prevent *C. auris* outbreak like conditions in hospitals. To prevent *C. auris* transmission through patients and medical equipment, its presence in the environment must be recognized and effective control measures should be taken up. Thorough hand cleaning with soap or alcohol-based sanitizer should be done before and after coming in contact with the patient or contaminated environment. Patients suffering from *C. auris* infection should be kept in a separate single room or in isolation and use of personal protective equipment (PPE) should be made mandatory for caregivers to such patients. Disinfectants must be used to completely destroy *C. auris* from the patient room, mobile devices such as temperature probes, glucometers, and ultrasound probes. The quaternary ammonium compounds (QAC) are the most widely used disinfectant in healthcare settings, but they are found to be ineffective against *C. auris* [25]. Disinfectant such as chlorhexidine gluconate, iodinated povidone, and chlorine-based disinfectant should be used. CDC recommends that patients should be screened by taking swab samples from the regions of groin and axilla (these sites are considered to be the most persistently positive sites). *C. auris* has the ability to survive on plastic surfaces where it can survive up to 14 days. For the efficient removal of *C. auris* from these surfaces, sodium hypochlorite (NaOCl) and per-acetic acid should be used. These disinfectants have the ability to kill *C. auris* from all surfaces. Despite all these treatments, some viable cells of *C. auris* are found to remain on non-porous surfaces like stainless steels [88]. Therefore, higher concentration of this disinfectant with a longer period of exposure time helps to reduce the regrowth of *C. auris*. Ultraviolet light also seems to show good result for the surface disinfection, but the density of *C. auris*, time of exposure of UV-C to *C. auris*, and distance to UV source plays an important role in the effective treatment [89]. However, persistence of *C. auris* in a hospital environment despite proper disinfection highlights the tenacity of this pathogen and its strong interaction with surfaces poses a continuous threat, especially in health care facilities.

## 2. CONCLUSION

The emergence of *C. auris* as pathogenic fungi is a major concern among clinical microbiologists. This is the first species in the actinomycetes that can rapidly develop antifungal resistance mechanism and also maintains these mechanisms throughout its generations. The development of novel diagnostic and treatment methods holds a promise for the control of infection by these pathogenic fungi. A close collaboration should be needed between the various clinical laboratories and medical teams to control the nosocomial transmission of *C. auris*.

Accurate identification of this species is very essential to prevent its outbreak. Till date, the scientific community is perplexed with its sudden emergence, the propensity with which it is affecting immunocompromised individuals, its transmission dynamics, its evolving antibiotic resistance, and its eventual impact on mortality of patients. Clearly, it is not a simple ear infection as its name suggests but could lead to invasive fatal infection. There are many unanswered questions regarding *C. auris* and continued research into the matter has the potential to reveal solutions to these puzzling queries.

## 3. AUTHORS' CONTRIBUTIONS STATEMENT

The authors declare that there are no competing interests. The article was conceived by HK; written by HK and KW; and reviewed by KJ and AY.

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## 5. CONFLICTS OF INTEREST

Authors declared that they do not have any conflicts of interest.

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