Candida auris: An Overview of the Emerging Drug-Resistant Fungal Infection

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ABSTRACT

Candida auris is an invasive fungal pathogen that has been recognized globally as a serious health threat due to its extensive innate and acquired resistance to antifungal drugs. A growing number of emerging cases of C. auris have been reported with resistance to the standard antifungal treatments including azoles, echinocandins, and polyenes, making it difficult to treat. Unlike other Candida species, C. auris is challenging to diagnose using the standard laboratory methods and are typically prone to misidentification, resulting in inappropriate management. Consequently, C. auris infections have spread globally. The Centers for Disease Control and Prevention data showed that clinical cases of C. auris increased from 329 in 2018 to 1,012 in 2021. The incidence and prevalence of this invasive fungal infection are high in immunocompromised and hospitalized patients. Patients who had an organ transplant, are on immunosuppressive agents, are diabetic, recent antibiotic use, catheter use, and prolonged hospital or nursing homestays are vulnerable to C. auris infections. C. auris is rapidly spreading across healthcare settings globally and monitoring of its virulence as well as devising appropriate treatment approaches are thus highly required.

Keywords: Candida auris; Minimum inhibitory concentration; Candidemia; Invasive fungal infection; Multidrug-Resistant, Fungal

INTRODUCTION

First reported in 2009 at a hospital in Japan, an isolate from the external ear emerged as a multidrug-resistant (MDR) fungus, Candida auris [1, 2]. Initially, C. auris isolates were grouped into four geographically restricted clades: clade I (South Asia), clade II (East Asia), clade III (South Africa), and clade IV (South America) [3-5], a possible fifth clade from Iran has also been reported [3]. Following this classification, approximately thirty-nine countries, which include but not limited to North America, South America, Europe, Africa, the Middle East,
and East Asia have reported cases of \textit{C. auris} infection [1, 4]. The incidence and prevalence of this infection have increased and are observed in immunocompromised patients or those who have been hospitalized for a long time [4, 6].

Currently, the origin of \textit{C. auris} is yet to be elucidated, with some speculating that global warming played a role in the selection of this species [7-9]. It is thus suggested that transmission was facilitated by animals with high body temperatures, such as birds, which could be responsible for spreading the fungus into urban areas, eventually infecting humans [8]. Furthermore, understanding how \textit{C. auris} invades the epithelial layer without forming hyphae remains unclear. According to recent findings, \textit{C. auris} isolates with a non-aggregative phenotype may be evading the immune system [7, 10-12].

Known as the largest genus of medically important yeast, the genus \textit{Candida} includes approximately 200 species [13]. They are commensal colonizers of all host mucosal surfaces [14]. However, \textit{C. auris} prefers to colonize the skin than other mucosal surfaces such as the gastrointestinal tract, leading to potential person-to-person transmission [1, 3, 15]. In addition, \textit{C. auris} can spread to internal organs through systemic bloodstream infection known as candidemia and is associated with 30 – 70\% crude mortality rate [3, 16, 17]. The pathogenicity of \textit{Candida} species is due to virulence factors, which include but not limited to secreted proteases and lipases, mannosyl transferases, oligopeptide, siderophore-based iron transporters, and biofilm formation [3, 4, 18]. The participation of these factors is observed in aspects of pathogen invasion, colonization, and acquisition of nutrition [3].

Appropriately identifying and diagnosing \textit{C. auris} is often challenging as it is commonly misidentified with other species (\textit{i.e., Candida parapsilosis}, \textit{Candida guilliermondii}, \textit{Candida haemulonii}, \textit{Candida lusitaniae}, and \textit{Candida famata}) using the current tests and methods [17-19]. Due to this misidentification, infection prevention may be delayed resulting in increased transmission [17]. Furthermore, \textit{C. auris} has the attribute to transform into a persistent yeast capable of surviving under harsh physical and chemical conditions, and thus becoming resistant to antifungal drugs such as fluconazole, amphotericin B, and echinocandins [3, 4, 17, 19-21]. The mechanism of drug resistance in \textit{C. auris} cannot be fully explained, although \textit{ERG11} [17, 22], ergosterol biosynthesis, are more predominant in resistant \textit{C. auris} [3], and the relationship between minimal inhibitory concentration (MIC) and clinical outcomes is a topic that needs further investigation [17].

This review aims to present the increasing trend of \textit{C. auris} focusing on epidemiology, drug resistance and therapeutic options, diagnostic, associated risk factors, and infection control.

\section*{METHODS}

An electronic literature search was performed on databases including PubMed, Google Scholar, EBSCOhost, Mendeley, and MedLine Plus. The search was limited to applicable journals and articles published on \textit{C. auris} through February 2022. A manuscript was selected if it was relevant to \textit{C. auris}, candidemia, fungal infection, multidrug-resistant pathogen, and invasive fungus. Articles were then reviewed and included based on the applicability of the topic, to provide information on the overview of \textit{C. auris} and its emerging resistance to various drugs.
Epidemiology of C. auris

Invasive strains of C. auris became prevalent in hospitalized patients worldwide. It was observed that the C. auris cases recorded in Japan appeared to be primarily ear infections; the fungus was discovered because of an ear infection, thus the name "auris." In Japan, the fungus does not appear to produce invasive illness since it does not enter the circulation. However, in Korea, the same strain of C. auris does [23-26]. In the United States, the earliest case was recorded in 2013 from a patient that was transferred from the United Arab Emirates [23]. As of February 2018, over 250 cases of C. auris have been identified across New Jersey, New York metropolitan area, and Illinois [23]. The worldwide distribution of C. auris depicting the clades is described in Figure 1. Epidemiologic research suggests that C. auris cases were found mostly in hospitalized patients receiving antifungal drugs, suggesting that changes in drug pressure resulted in emergence of resistant organisms within the healthcare setting [23]. Anthropogenic climate change has also been implicated in the emergence of C. auris strains associated with thermal tolerance [27]. In early 2019, the Centers for Disease Control and Prevention (CDC) recorded 685 confirmed cases of MDR C. auris in the United States [19, 20]. As of June 30, 2019, the CDC has reported 195, 126, and 355 confirmed cases of drug-resistant C. auris in Illinois, New Jersey, and New York, respectively [19, 20]. The clinical cases recorded by the CDC across the United States between 2018 and 2021 are shown in Table 1. The CDC reported that clinical cases of C. auris increased from 329 cases in 2018 to over a thousand in 2021 based on emerging data [19, 20]. In addition, 2,386 patients in the United States were diagnosed to be infected with C. auris in 2021 [19, 20].

In Europe, the first case of C. auris infection was imported from India in 2009 [25]. Cortegiani and colleagues outlined worldwide reports of C. auris in chronological order from 2013 to 2018 [28]. Spontaneous and rapid outbreaks throughout continental Europe began at a cardio-thoracic center in London with 50 cases from April 2013 to 2017 [28]. Meanwhile, the first reported outbreak of C. auris infection in India was in 2013 when 12 patients with positive microbiological clinical samples collected between 2009 and 2012 were identified; genetically related strain also spread to Pakistan [28]. In South America, the first outbreak was reported in Venezuela between March 2012 and July 2013, whereas sporadic cases have been reported
since 2012 in Colombia [28]. In the African continent, the first sporadic cases and outbreaks occurred in South Africa and Kenya, with the first four South African cases isolated between 2012 – 2013 [28]. In the Gulf region, the initial cases were reported in Saudi Arabia, Kuwait, and Oman; subsequently, the United Arab Emirates also reported infection [28].

Along with many Candida infections that invade the bloodstream, C. auris has also been isolated from numerous sites including but not limited to the respiratory tract, muscles, and even penetrating the central nervous system (CNS) [24, 29]. Apart from heat tolerance (37 – 42°C), C. auris can also tolerate high salinity and resist other environmental stressors, enabling it to thrive in a variety of environments [30]. C. auris can survive outside of the human host for longer periods, indicating that nosocomial C. auris infections can arise from environmental sources such as contaminated medical devices or the hands of health care workers, without prior colonization of the diseased host [30]. This promotes the likelihood of transmission and explains reports of C. auris infections in hospital settings [30]. C. auris has also been isolated from sterile, non-biological environments such as urine, providing evidence why it can survive in traditionally sterilized healthcare settings [24]. No age-specific infection is observed in C. auris candidemia [23].

**C. auris drug resistance and therapeutic options**

Classified as Saccharomycetes belonging to phylum Ascomycota, C. auris is included in a single clade of MDR human-pathogenic fungi/yeast that consists of Candida dubiuschaemulonii, Candida pseudohaemulonii, and Candida haemulonii [3]. The environmental reservoir for C. auris is unknown; however, climate change and agriculture contribute to the MDR of the fungi [3, 23]. In addition,
genetic diversity due to polyploidy, aneuploidy, and chromosome rearrangements [3], as well as biofilm formation, mutation of the drug target, overexpression of the drug target, and limiting drug intake/efflux are implicated to its multi fungal drug-resistance [3, 4].

The three main classes of antifungal drugs used in both the clinical and therapeutic management setting are azoles, echinocandins, and polyenes [17, 22]. MDR of at least two antifungal classes is observed in ≥40.0% of C. auris and approximately 4.0% displayed resistance to all three classes of drugs [17]. Similarly, Chow and colleagues corroborate the findings after analyzing three hundred C. auris isolates and found that 24.0% were resistant to at least two antifungal classes, 1.0% were resistant to all three classes, and 7.0% to micafungin, 23.0% to amphotericin B, and 80.0% to fluconazole [3, 9, 24].

The mechanism of action for fluconazole is to prevent cell growth by inhibiting the synthesis of ergosterol specifically lanosterol 14-α-demethylase, which is encoded by the ERG11 gene [3]. It can be concluded that mutations of ERG11, TAC1b, Y132F, K143R, and F126L genes as well as the ATB-binding cassette (ABC) and major facilitator superfamily transporters conferred resistant to azole [3, 25]. Furthermore, substitution mutations of certain strains of C. auris that are restricted to geographical clades are proven resistant to azole [3]. Approximately 90.0% MICs of fluconazole greater than 16 µ/ML, were observed in India and South Africa based on a study of 350 C. auris isolates [17].

Efflux pumps are also an important mechanism of antifungal resistance, especially during the initial stages of biofilm development. As the biofilm matures, its antifungal resistance is increased by the biofilm matrix itself, as it can inhibit drug diffusion [24]. Biofilm formation is, therefore, a crucial factor in the pathogenesis of Candida species and its resistance to antifungals [31]. C. auris has 686 biofilm-related proteins (ribosomal proteins, transporters, several enzymes, and transcription factors) and expresses a greater ability to form biofilms [25]. In a study that compared two clinical isolates of C. auris and Candida albicans, it was suggested that while both strains are comparable, the two C. auris strains displayed a profile that supports MDR [24]. There were six notable drug efflux transporters produced by both C. auris and C. albicans organisms, with fluconazole-resistant C. auris identified as having two or more efflux transporters, a higher abundance of superoxide dismutase, as well as several more proteins in the biofilm matrix [24]. When comparing transcription factors and proteins involved in biofilm formation and the biofilm matrix, 8 of the 24 reported proteins were detected at higher expression levels in C. auris isolates than in C. albicans [24].

The MIC is the lowest measured amount of a drug needed to inhibit the growth of an organism. According to the data [21], C. auris strains display an increase in the MIC for three major classes of antifungal drugs (Table 2). C. auris has been documented resistant to

| Drugs                          | Tentative MIC breakpoints (mcg/ml) |
|-------------------------------|-----------------------------------|
| Fluconazole                   | ≥32                               |
| Voriconazole (and other second-generation azoles) | N/A |
| Amphotericin B                | ≥2                                |
| Anidulafungin (Echinocandins) | ≥4                                |
| Caspofungin (Echinocandins)   | ≥2                                |
| Micafungin (Echinocandins)    | ≥4                                |

Data sourced from Centers for Disease Control and Prevention - Antifungal Susceptibility Testing and Interpretation [21].

MIC, minimum inhibitory concentration; N/A, not available.
fluconazole, with recent reports indicating higher MIC to amphotericin B, voriconazole, and caspofungin [28]. The resistance to fluconazole has been identified as a point mutation in the \textit{ERG11} gene and has been detected in a global collection of fifty-four \textit{C. auris} isolates [28].

With the increasing resistance to azoles and amphotericin B, echinocandins are becoming the first-line therapy for \textit{C. auris} infection. However, \textit{C. auris} are also developing resistance as mutations are observed in the \textit{FKSI} gene that encodes a subunit of the \(\beta\)-D glucan synthase, which is targeted by echinocandins [28].

Although geographical differences can play a role in the resistance of \textit{C. auris} to amphotericin B as detected in 30.0\% of the cases in the United States, \textit{C. auris} is susceptible to this antifungal drug potentially due to the reduction in ergosterol content in the cellular membrane [17]. Changes to the cell membrane sterol and/or a given point mutation are a potential source of amphotericin resistance [3]. Similarly, susceptibility or resistance of \textit{C. auris} against echinocandins can be observed depending on geographic locations [17]. Impairment of the structural integrity of the fungal cell wall, via inhibition of \(\beta\)-D glucan synthase, mimics osmotic stress that can cause resistance with echinocandins [3]. The management of \textit{C. auris} is listed in Table 3 [32, 33].

**Diagnosis of \textit{C. auris}**

The diagnosis of \textit{C. auris} remains problematic, suggesting that the spread of the pathogen is underestimated, and the molecular mechanisms of virulence and antifungal resistance of this species are yet to be explored [24]. Diagnosis of \textit{C. auris} infections include culture of fungus in blood, body fluids, and pus from infected sites and use biochemical-based tests, such as analytical profile index strips and VITEK 2 (bioMérieux, Marcy-l’Étoile, France), for identification of yeasts [6, 34]. Nevertheless, these tests sometimes are unable to identify the yeasts due to the lack of a comprehensive database for species identification [6]. The \textit{Candida} isolates are proven to be difficult to identify using the standard laboratory methods; therefore, Matrix-Assisted Laser Desorption Ionization Time of Flight (MALDI-TOF) or molecular identification by sequencing the D1–D2 region of the 28S ribosomal DNA are now being used [6, 34]. Conventional laboratory methods are prone to misidentification resulting in inadequate management and therapeutic approaches, consequently causing the rapid spread of \textit{C. auris} in the healthcare setting [19, 20].

### Table 3. Management of \textit{Candida auris}

| Patient age  | Antifungal first-line agent | Alternative treatment               |
|--------------|-----------------------------|-------------------------------------|
| ≥18 years of age (Adults) | - Anidulafungin<br>- Caspofungin<br>- Micafungin | - Liposomal amphotericin B          |
| ≤2 months of age (Children) | - Caspofungin<br>- Micafungin | - Liposomal amphotericin B          |
| ≤2 months of age (Neonates) | - Amphotericin B deoxycholate<br>- Liposomal amphotericin B<br>- Caspofungin<br>- Micafungin | |

The guideline contains the first line and alternative treatment options for patients with \textit{C. auris} infections with reference to Infectious Diseases Society of America and Centers for Disease Control and Prevention. Alternative therapy may be used in patients with \textit{C. auris} who are unresponsive to the first-line treatment approach or in those with persistent candidemia (greater than 5 days) [32, 33].
C. auris can be cultured in blood culture bottles where it can be detected after 33.9 hours of incubation. It can be sub-cultured on Sabouraud dextrose agar or CHROMagar supplemented with Pal's agar, where it forms white-cream-colored smooth colonies at 37–42°C in 24–48 hours of incubation [25]. Traditional methods used for identifying the yeast, C. auris, with VITEK 2 YST (bioMérieux), API 20C (bioMérieux, Hazelwood, MO, USA), API ID 32 C (bioMérieux, Marcy-l’Étoile, France), BD Phoenix (BD Diagnostic Systems, Sparks, MD, USA) yeast identification system, and MicroScan have reported errors in the classification of strains from certain mycology clades [17, 35]. Table 4 summarizes several misidentifications using various testing methods. Various Candida species may be misidentified as C. auris using the conventional biochemical testing methods because of the overlapping biochemical profiles [17, 35]. For example, while VITEK 2 (bioMérieux) can detect C. auris with high reliability, studies showed it has greater precision in identifying the South American clade that was otherwise identified as the East Asian and African clades of C. auris [17]. It is therefore recommended to use, in conjunction with the commercially available identification tests, a practical algorithm available from the CDC [17, 19, 20]. In addition, the slow turnaround time to identify the culture appropriately phenotypically may serve as a substantial limiting factor in the identification and therefore, affect treatment and disease prevention [4, 17].

Risk factor and infection control
Understanding the innate and adaptive mechanism of host defense against Candida species plays a role in C. auris infections across diverse healthcare and community settings [1, 36]. The skin and mucosa serve as the initial physical barrier, while neutrophils, monocytes, and macrophages are a part of the innate immunity [1, 37]. Furthermore, fungal pathogen-associated molecular pattern recognition and the release of proinflammatory cytokines are crucial in shaping the adaptive immunity and induce long-term barrier against C. auris [1]. Reduced activity in these protective barriers may allow colonization of nosocomial C. auris at multiple body sites (i.e., nares, external ear canals, oropharynx, wound sites, and catheter exit sites) [1, 17]. Healthy individuals can be a carrier of C. auris, and can transmit infection to

Table 4. Misidentification of Candida auris by diagnostic biochemical tests

| Candida auris misidentified as | Commercially available identification test |
|--------------------------------|--------------------------------------------|
| Candida haemulonii            | VITEK 2 YST® (bioMérieux, Marcy-l’Étoile, France) |
| Candida duobushaemulonii      |                                            |
| Other Candida spp.            |                                            |
| Rhodotorula glutinis          | API 20C (bioMérieux, Hazelwood, MO, USA)   |
| Candida sake                  | API ID 32 C (bioMérieux, Marcy-l’Étoile, France) |
| Candida intermedia            |                                            |
| Candida sake                  |                                            |
| Saccharomyces klyveri         |                                            |
| Candida haemulonii            | BD Phoenix (BD Diagnostic Systems, Sparks, MD, USA) yeast identification system |
| Candida catenulata            |                                            |
| Candida famata                | MicroScan (YIP; Baxter-MicroScan, W. Sacramento, CA, USA) |
| Candida guillermondii         |                                            |
| Candida lusitaniae            |                                            |
| Candida parapsilosis          |                                            |
| Other Candida spp.            |                                            |

Data reproduced from the Centers for Disease Control and Prevention and Fasciana et al., reporting on various misidentifications of C. auris among other species of Candida and/or different organisms.

*C. auris has also been misidentified as Candida famata and Candida lusitaniae on VITEK 2.

*Candida guillermondii, Candida lusitaniae, and Candida parapsilosis typically make pseudohyphae on cornmeal agar; whereas C. auris does not make pseudohyphae or hyphae; however, it is not to be ruled out as some C. auris isolates have formed pseudo/hyphae [17, 35].

BD, Becton, Dickinson, and Company.

https://doi.org/10.3947/ic.2022.0008
another person [5, 20]. Hospitalized or nursing home patients are susceptible in developing severe complications from \textit{C. auris} [4, 19]. In addition, patients who have undergone recent surgery, with chronic disease, and/or with recent use of a broad-spectrum antibiotic or antifungal are at a heightened risk of mortality [19, 20]. Specifically, patients who recently had an organ transplant, on immunosuppressant medication, have diabetes, have a history of receiving antibiotics, had indwelling devices such as catheters, and prolonged hospital or nursing home stays have the highest risk for acquiring \textit{C. auris} infection due to its ability to enter the bloodstream and cause invasive infection [4, 14, 19, 20].

Understanding the spread of \textit{C. auris} in healthcare settings is essential for infection control and transmission [15]. Healthcare personnel and use of hospital equipment may play a role in transmitting this infection; therefore, adequate hand hygiene should be performed with soap and water, alcohol-based hand cleansers, or chlorhexidine hand rub use [23]. To contain the spread of \textit{C. auris}, patients should be quarantined in separate rooms, the contact of origin should be traced to identify other potential patients who may have been exposed to the fungi, and screening those for asymptomatic colonization should be performed [23]. Commercial cleaning products and white distilled vinegar are proven ineffective against this fungus, but sodium hypochlorite and topical hydrogen peroxide-based products are most effective in cleaning rooms and equipment of infected individuals [23]. New methods such as the efficacy of pulsed-xenon ultraviolet light technology on \textit{C. auris} are being tested in laboratory settings. Findings suggest a 99.6% reduction on \textit{C. auris} after a 10-minute cycle at a 2-m distance vs. a 99.4% reduction after a 5-minute cycle at a 1-m distance [38]. However, further studies are required in hospitals to fully assess the impact of repeated sessions with this machine [38]. \textbf{Figure 2} shows the infection control practices recommended for \textit{C. auris} [39].

\section*{CONCLUSION}

\textit{C. auris} is a drug-resistant, widespread fungal infection associated with high mortality. Due to the recent emergence, discussions regarding the pathogen’s increased drug resistance, difficult diagnostic criteria, limited therapeutic options, and associated risk factors require further attention. Morphological diversity is a key virulence factor of \textit{Candida} spp., and thus \textit{C. auris} differs from other \textit{Candida} species. Aside from its resistance to treatment, there is difficulty in identifying and distinguishing this pathogen from other \textit{Candida} spp. because of molecular, cellular, and genetic features.

The emergence of the fungus poses a global health threat and should be met with a global call for action. \textit{C. auris} is resistant to various antifungal medications (azoles, polyenes, and echinocandins), and current optimal treatment regimens are unknown; thus, other methods of treatment must be discovered. Multidisciplinary research to investigate potential methods of treatment should be commissioned along with increased methods of detection, reporting, and utilization of effective environmental cleaning methods. Additional extensive research is needed on this topic to provide insight into the global epidemiology of multidrug-resistant \textit{C. auris} infection. Moreover, risk factors and methods of transmission need to be exhaustively identified to guide measures for prevention and to control the spread of the pathogen.
**Candida auris: An emerging global health concern**

**Identification of cases**
- Identify the species of *Candida* isolated from sterile sites
- Identify the species of *Candida* isolated from non-sterile sites

**Consider screening patients who**
- Are close healthcare contacts to new cases
- Have had an overnight healthcare stay abroad in the past year
- If transmission is suspected, expand screening to all individuals on the ward cases have been identified

**Hand hygiene**
- Healthcare personnel (HCP) should practice proper and frequent hand hygiene
- Monitor HCP adherence to hand hygiene practices and provide feedback

**Transmission-based precautions**
- Place all patients infected or colonized with *C. auris* in acute care hospitals or long-term acute care hospitals on contact precautions

**HCP adherence to transmission-based precautions should be frequently monitored**
- Use signage to indicate patient are on transmission-based precautions
- Signage should be placed in a visible area and clearly indicate what precautions and personal protective equipment are required

**Environmental cleaning**
- Use registered hospital-grade disinfectant
- Thorough daily and terminal cleaning and disinfection are needed in *C. auris* patient care areas
- Shared medical equipment should be cleaned and disinfected thoroughly
- Monitor environmental cleaning and disinfection adherence

**Patient decolonization**
- There is currently no established protocol for the decolonization of patients with *C. auris*

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**Figure 2. Candida auris infection control guidelines.**

Summarized infection-control practices and recommendations [39]. [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6958335/](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6958335/)

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