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An Update on the Recent Emergence of *Candida auris*

Monika Jain[1], Anushree Jain[1], Basant Khare[1], Deepak Kumar Jain[2], Rubeena Khan[1], Dolly Jain*[1]

[1] *Adina College of Pharmacy, ADINA Campus Rd, Lahdara, Sagar, MP, 470001*

[2] *Sun Institute of Pharmaceutical Education & Research (SIPER), Bhatpura Road, Lahar, Bhind, MP, 477445*

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*Address for Correspondence:

Dolly Jain, Adina College of Pharmacy, ADINA Campus Rd, Lahdara, Sagar, MP, 470001

Abstract

The incidence of invasive fungal infections (IFI) caused by unusual pathogens is on the rise, partly driven by the increased population of immunocompromised patients. The emerging multidrug-resistant yeast pathogen *Candida auris* (*C. auris*) has been a source of concern as an agent of healthcare-associated infections. *C. auris* is emerging multidrug-resistant yeast that causes serious invasive infections with high mortality. It was first discovered in 2009, and since then, individual cases or outbreaks have been reported from over 20 countries on five continents. Controlling *C. auris* is challenging for several reasons: (1) it is resistant to multiple classes of antifungals, (2) it can be misidentified as other yeasts by commonly available Identification methods, and (3) because of its ability to colonize patients perhaps indefinitely and persist in the healthcare environment, it can spread between patients in healthcare settings. The transmissibility and high levels of antifungal resistance that are characteristic of *C. auris* set it apart from most other *Candida* species. A robust response that involves the laboratory, clinicians, and public health agencies is needed to identify and treat infections and prevent transmission. This review highlights epidemiology, pathogenesis, microbiological characteristics, clinical presentation, diagnostic challenges and treatment options of *C. auris* infections. Infection prevention measures to prevent spread of *C. auris* and special measures during an outbreak situation have also been reviewed. Rapid emergence of hospital onset *C. auris* is worrisome. Early diagnosis of *C. auris* is essential for better outcomes and the implementation of infection prevention measures. Lack of widespread awareness, absence of general availability of diagnostic testing methods, and limited options for treatment of *C. auris* infections make it a difficult-to-treat pathogen. Further studies are needed for better understanding of this emerging pathogen.

Keywords: Fungal infection, Candida, *C. auris*, Candidemia, Bloodstream infection

Email: dollyjain.btpc@gmail.com

Introduction

Candida species commonly colonizes the human mucosal and skin surfaces with potential to cause infections. Disruption in host immunity increases the risk for development of opportunistic infections from *Candida*. Candidemia is recognized as the fourth most common cause of nosocomial bloodstream infections in the United States (US) associated with high morbidity and mortality rates (30%-40%)[1]. *Candida auris* is emerging multidrug-resistant yeast that can cause invasive infections, is associated with high mortality, and can spread in healthcare settings. This yeast was first described in 2009 and has since been reported in over 20 countries on five continents. *C. auris* poses a global health threat for several reasons:

1. Multidrug resistance is common, and a few isolates are resistant to all three of the main classes of antifungal drugs, severely limiting treatment options[2].

2. *C. auris* is commonly misidentified in clinical laboratories. Unless laboratories are aware of possible misidentification and have the ability to perform further evaluation, cases of *C. auris* could go undetected.

3. *C. auris* can be transmitted between patients in healthcare settings and cause healthcare-associated outbreaks. *C. auris* can colonize patients, especially on the skin, perhaps indefinitely, and persist for weeks in the healthcare environment. The lack of decolonization methods and suboptimal efficacy of some commonly used hospital environmental disinfectants compounds the challenge of controlling its spread.

The genus *Candida* comprises an array of phenotypically similar yet genetically highly divergent yeasts. *C. auris* differs markedly from common pathogenic *Candida* species like *Candida albicans* and *Candida glabrata*. In healthcare settings, *C. auris* behaves more like transmissible bacterial multidrug-resistant organisms (MDROs), such as methicillin-resistant *Staphylococcus aureus* (MRSA) and carbapenem-resistant Enterobacteriacea (CRE), than other *Candida* species. Unlike other *Candida* infections, which are generally thought to result from autoinfection from host flora, *C. auris* can be transmitted between patients. Unlike for most other *Candida* species, for which transmission-based precautions are generally not required, *C. auris* requires implementation of specific infection control measures, much like those used for control of MRSA and CRE. With itsmultidrug resistance, transmissibility and severe outcomes, *C. auris* has all the makings of a superbug. Control of *C. auris* requires better understanding of the organism itself, vigilance and accurate identification, appropriate treatment and infection control measures, and a coordinated public health response. We review the emergence of *C. auris*, examining the global advent, biology, challenges of

identification, multidrug resistance, clinical manifestations, treatment, risk factors for infection, transmission, and control of *C. auris.*

Epidemiology

Incidence and prevalence

The incidence of *Candida* infections and causative *Candida* species has varied with time and across geographic locations. Until recently, the most common isolated species during nosocomial fungemia has been *C. albicans*, however with changing epidemiology, non-*C. albicans* has emerged as the predominant species in many countries[1]. *Candida glabrata* is recognized as the most common cause of candidemia in the US while *C. parapsilosis*, *C. tropicalis* and *C. krusei* are common in other parts of the world[1]. The true incidence of *C. auris* fungemia and its global prevalence are poorly understood. This uncertainty is related to failure of conventional diagnostic methods to accurately identify *C. auris* and lack of global availability of diagnostic methods for its rapid identification[3]. Few centers with diagnostic capabilities have estimated incidence and prevalence of *C. auris* fungemia at their healthcare facilities. Prevalence of *C. auris* was rare prior to 2009 according to the investigation conducted on a pool of uncommon *Candida* species included in the international antifungal surveillance program (SENTRY). Of the 15,271 isolates reviewed from 4 continents between2004-2015, only four isolates were identified as *C. auris*[4]. However, since 2009 there has been a rapid and global emergence of *C. auris*. According to a single center study in Sub-Saharan Africa from September 2010-June2013, candidemia attributed to 39% of nosocomial infections. During the study period, *C. haemulonii*, later reidentified as *C. auris*, was the most common cause of hospital-onset fungemia (38%) followed by *C. albicans* (27%)[5]. Another study in multiple hospital systems in South Africa highlighted the prevalence of *C. auris*-related candidemia to be 0.3%[6]. Unfortunately, both these studies did not provide specific data on study period and total number of candidemia cases identified to understand the true impact of *C. auris*. A tertiary medical center in South America reported *C. auris* as the 6th most common cause of bloodstream infection in the hospital between March 2012-July 2013[7]. An 18-month prospective study in Indian ICUs reported 1400 candidemia cases. *Candida auris* was identified as the 5th most common cause of ICU-onset candidemia, discovered in 19 of 27 ICUs, with prevalence of 5.3% (n=74) [8]. A random one-year screening for *C. auris* in patients admitted at a cardiothoracic center in London identified prevalence rateof 0.04% (1/2246 screened patients)[9]. Overall, the prevalence of *C. auris*, predominantly nosocomial-onset, is rising globally.

Isolation of C. auris

Candida auris has been isolated from multiple body sites. First isolation of *C. auris* was from the external ear canal of a 70-year-old woman in Japan[10]. A multicenter surveillance study in Korea (2004-2006) reported 15 specimens isolated from the ears of patients with chronic otitis media as closely related *C. haemulonii* species by sequence analysis, later re-identified as *C. auris*[11]. Vaginal sample from a young woman in India identified *C. auris* as cause of vulvovaginitis[12]. *Candida auris* has been described as the cause of fatal pericarditis in an Indian patient with end stage liver disease[13]. First three cases of bloodstream infection from *C. auris* were reported from South Korea in 2009[14]. A fatal case of donor-derived *C. auris* infection was reported in a 71-year old lung transplant recipient in the US in 2017[15]. Currently, *C. auris* fungemia has been reported nearly from all continents except Australia and Antarctica. As awareness of *C. auris* has grown, novel isolates and previously unidentified *Candida* isolates are increasingly being recognized as *C. auris*. According to the Center for Diseases control and prevention (CDC) in the United States, 86 isolates of *C. auris* have been identified in the US from infectious and non-infectious sources, mostly emerging from the east coast.

Biology and morphology

The closest relatives of *C. auris* are *C. ruelliae, C. pseudohaemulonii, Candida duobushaemulonii, Candida vulturna, C. heveicola, Candida konsanensis, Candida chanthaburiensis, C. haemulonii*, and *Candida haemulonis* var. *vulnera*[16]. *C. auris* is an ovoid to elongate budding yeast, which seldom forms rudimentary pseudohyphae and typically appears as pink, but sometimes white or red, colonies on CHROMagar *Candida* or CAN2 chromogenic medium. This organism has a high tolerance for salinity and heat. Its unique ability to grow at temperatures up to 42 ◦ C[16-20] and to grow in high salt conditions may help to distinguish *C. auris* from other *Candida* species and aid laboratory isolation[19]. However, none of the phenotypic characteristics of *C. auris* are sufficient evidence for definitive identification. Sequencing, mass spectrometry, or a VITEK 2 version 8.01 are needed to accurately distinguish *C. auris* from closely related *Candida* species. Some strains of *C. auris* have been reported to form aggregations in culture, which may allow the organism to resist penetration by detergents, ultraviolet light, or other cleaning methods[21]. *C. auris* also forms biofilms, which provide a mechanism of adherence to surfaces. However, these biofilms are significantly thinner and less complex than those of *C. albicans*, primarily due to the rarity of pseudohyphae. *C. auris* may therefore have reduced ability to attach to surfaces like catheter material as compared to species that can form more robust biofilms[22]. In animal models, *C. auris* exhibits similar or slightly less virulence as *C. albicans* and *Candida tropicalis* and greater virulence than the closely related species *C.* haemulonii[23,24]. Its ability to form biofilms, produce phospholipase and proteinase, and secrete aspartic proteases as well as the presence of oligopeptide transporters and mannosyl transferases may explain some of the virulence seen with *C. auris,* though some of these characteristics have varied by strain[25]. Aggregate-forming strains may be less virulent than strains without cell aggregations. Despite these advances in our understanding of *C. auris*, much remains unknown about its cell biology and virulence characteristics.

Risk factors

Candida auris is a hospital-acquired pathogen causing infection in certain high-risk patient populations. The predisposing risk factors for *C. auris* infection are similar to other candidal species. Patients with immunocompromising diseases (diabetes mellitus, malignancy, chronic kidney disease, neutropenia), concomitant bacteremia, broad-spectrum antibacterial or antifungal therapy in prior 90 days, surgery within 90 days, presence of central venous catheters or urinary catheters, stay in intensive care unit (ICU) and total parenteral nutrition (TPN) administration confer increased risk for acquiring *C. auris*[26-28]. Till date, only one case-control study has been performed to determine specific risk factors predisposing to *C. auris* candidemia[8]. The study was conducted in the ICUs in India comparing *C. auris* (n=74) and non-*auris* (n=1087) fungemia cases. The multivariate analysis showed patients with respiratory illness, vascular surgery, antifungal exposure in prior 30-days and low APACHE II score on admission had higher likelihood to develop ICU-onset *C. auris* fungemia.

Multidrug resistance

C. auris is a highly concerning pathogen because it can be resistant to multiple antifungal drugs, with some isolates resistant to all three major antifungal classes (azoles,

polyenes, and echinocandins). The Clinical and Laboratory Standards Institute (CLSI) and the European Committee for Antimicrobial Susceptibility Testing (EUCAST) have not established clinical susceptibility minimum inhibitory concentration (MIC) breakpoints for *C. auris*. In the interim, CDC has proposed the following tentative breakpoints, conservatively based on those established for other species: ≥32 for fluconazole, ≥2 for amphotericin B (or ≥1.5 if using Etest), ≥4 for anidulafungin and micafungin, and ≥2 for caspofungin[29]. In a collection of 54 isolates from India, Pakistan, South Africa, and Venezuela, 93% of isolates were resistant to fluconazole, 35% were resistant to amphotericin B, and 7% were resistant to echinocandins using the following breakpoints: ≥32 for fluconazole, ≥2 for amphotericin B, and ≥8 for echinocandins. Forty-one percent of isolates were resistant to at least two drug classes and two isolates were pan-resistant.

In the largest study of *C. auris* resistance, on 350 isolates from India, 90% of isolates were resistant to fluconazole by the tentative breakpoints described above, 2% to anidulafungin, 2% to micafungin, and 8% to amphotericin B. In the United States, about 90% of isolates have been resistant to fluconazole, 30% have been resistant to amphotericin B, and 5% have been resistant to echinocandins[29]. Public Health England has reported that all UK isolates have been resistant to fluconazole, approximately 20% have been resistant to amphotericin B, and about 10% have been resistant to echinocandins[30]. Taking data from around the world into account, *C. auris* has been generally resistant to fluconazole, and a substantial portion of isolates has been resistant to amphotericin B and echinocandins Most other species of *Candida* identified in clinical specimens exhibit high *in vitro* susceptibility to antifungal drugs. One of the other drug-resistant *Candida* of high concern has been *C. glabrata*, in which approximately 10% of isolates in the United States exhibit fluconazole resistance and 0–10% exhibit echinocandin resistance[31,32]. In comparison, the level of drug resistance observed in *C. auris* is unprecedented. Molecular mechanisms underlying this resistance are currently under investigation. Twelve *Erg11* mutations, which have been found in fluconazole-resistant but not wild-type *C. albicans,* have been found in *C. auris*[33].Three of these mutations have been directly linked to drug resistance in *C. albicans*, suggesting that they contribute to the resistance observed in *C. auris* as well[34]. Efflux pump activity contributes to azole resistance in other *Candida* species and may contribute to resistance in *C. auris,* though the extent of this contribution is unknown. None of these mechanisms alone can account for the high levels of resistance seen in *C. auris*, so multiple mechanisms are likely involved. Elevated echinocandin MICs are likely the result of *FKS* mutations observed in *C. auris* isolates, such as the S639F mutation observed in isolates from India[33].These mutations correspond to known mutations in other *Candida* species, which have been directly linked to echinocandin resistance[35]. Finally, while resistance to amphotericin B is rare in the most common *Candida* species, it is observed in approximately 30% of US isolates of *C. auris*. Though unconfirmed at this time, it is suspected that this is likely due to a reduction in ergosterol content in the cellular membrane-specifically a mutation in a gene involved in ergosterol biosynthesis[36].

Clinical manifestations

Similar to other *Candida* species, *C. auris* can cause severe invasive infections or colonize patients without infection. *C. auris* has been isolated from normally sterile body sites, including blood, bone, and cerebrospinal fluid, indicating invasive infection. Infections may be severe, and persistently positive blood cultures for >5 days or recurrent candidemia in those with *C. auris* candidemia have been reported. *C. auris* candidemia is associated with mortality rates of about 30–60%, depending on the setting . Other clinical sources found in the course of routine patient care have been bile fluid, the ear, jejuna biopsy, ocular secretion, peritoneal fluid, pleural fluid, the respiratory tract, urine, vaginal fluid, and wounds; some of these represent sites of colonization rather than infection. Patients can also be asymptomatically colonized with *C. auris* on the skin, nares, and other body sites[37-39].

Diagnosis

The under-recognition and delay in accurate diagnosis of *C. auris* species has been attributed to its misidentification by commercial biochemical methods (manual and automated). The conventional commercial diagnostic yeast identification systems such as Vitek 2, BD Phoenix and API20 are not able to identify or frequently misidentify *C. auris* isolates as one of the closely related *Candida* species *C. haemulonii*, *C. famata*, *C. catenulata, C. sake* and *Rhodotorula glutinis*[40].

Molecular testing

Investigators have relied upon molecular methods to facilitate accurate identification of *C. auris* species. One of the most common methods described in multiple research studies and case reports was genomic DNA extraction from the misidentified *Candida* species followed by DNA amplification and sequencing of the internal transcribed spacers (ITS) and D1/D2 regions of the ribosomal DNA. These sequences were re-identified based on 98%-100% homology with *C. auris* isolate using GenBank Basic Local Alignment Search Tool (BLAST) from national center for biotechnology information (NCBI) database[18,41]. The ITS sequencing was also beneficial to define genomic diversity between *C. auris* and closely related *Candida* isolates differentiating them into separate clades with bootstrap value of 99%[18,42]. Rapid, efficient and successful identification of *C. auris* isolates was shown using MSVITEK and Bruker MicroFlex Matrix-assisted laser desorption ionization time of flight mass spectrometry (MALDI-TOF) identification system[43]. However, caution is advised while using MALDI-TOF as not all devices include *C. auris* in the reference database[44]. During laboratory identification and validation of CDC panel containing *C. auris*, incorporation of research-use-only library containing *C. auris* resulted in accurate identification of *C. auris* isolates by both MALDI-TOF systems[45]. Polymerase chain reaction (PCR) and real-time PCR assays have been developed targeting rDNA region nucleotide sequences specific for *C. auris*. The assays showed rapid and accurate identification of *C. auris* similar to DNA sequencing results[46]. The US CDC has provided guidance to healthcare facilities to suspect *C. auris* based on detection of misidentified *Candida* species by standard testing method and for accurate identification of *C. auris* using diagnostic methods such as MALDI-TOF with updated database and DNA sequencing. Laboratories located in the US without capability to identify suspected *Candida* isolates have an option to send samples to the CDC using state public health laboratories for further characterization.

Geographical link

Geographical clustering of *C. auris* isolates has been performed using genomic and proteomic analysis based on mutilocus sequence typing (MLST), MALDI-TOF MS and amplified fragment length polymorphism (AFLP) typing[42]. Among the analytic methods, M13 PCR fingerprinting and AFLP is recognized as most efficient for strain typing and for geographical clustering helpful in epidemiological analysis[42]. The AFLP typing grouped *C. auris* strains mainly into two clusters of Indian and Brazilian origin[42]. Isolates from South African origin were randomly distributed among both clusters. *C. auris* isolates from India, Brazil and South Africa were clonal

for the respective country of origin with 99%-100% nucleotide sequence similarity. A multicenter study in United Kingdom (UK) performed rDNA sequencing of 24 *C. auris* isolates, grouping the *C. auris* strains into three different lineages belonging to India/Malaysia/Kuwait, Japan/Korea and South African origin[47]. Whole genome sequencing (WGS) of *C. auris* isolates showed genome size of 12.5Mb similar to other *Candida* species. The WGS helped establish independent emergence of *C. auris* isolates in different continents as the isolates differed by tens of thousands of single nucleotide polymorphisms (SNPs) between the geographic locations. The isolates from the US seem to be related to those from South Asia (<60 SNPs apart) and South America (<150 SNPs apart), with no proven direct or indirect travel link[48].

Treatment

Only three major classes of antifungal drugs are available to treat invasive fungal infections. *C. auris* poses a real treatment challenge because of high rates of antifungal drug resistance. As reported above, most *C. auris* isolates are resistant to fluconazole, the most widely available antifungal treatment for candidiasis. The alternatives, echinocandins and amphotericin B, are expensive and are not easily available in countries with more limited resources. Amphotericin B is also known for causing severe side effects. Although studies have reported therapeutic outcomes, no systematic study has assessed effectiveness of various antifungals against *C. auris* infections in humans. However, in a mouse model, micafungin wasmore efficacious at killing *C. auris* than fluconazole and amphotericin B. An *in vitro* study examining combinations of treatment with echinocandins and azoles found a synergistic interaction between micafungin and fluconazole and did not find any antagonistic interactions between micafungin or caspofungin and fluconazole or voriconazole. Research is also being conducted on activity of new drugs like SCY- 078, APX001A/APX001and CD101against *C. auris*, but these options are not yet available for clinical use in most settings. Based on the most frequent resistance profiles, echinocandins are the recommended first-line treatment for most *C. auris* infections in adults. Antifungal susceptibility testing is advised to inform treatment and patients should be closely monitored for treatment failure. Acquired resistance while on treatment is a concern. Echinocandin resistance has developed in patients with *C. auris* infection while receiving echinocandin treatment. For neonates and infants under 2 months of age, CDC recommends amphotericin B deoxycholate (1 mg/kg daily) as the first line treatment, with consideration of liposomal amphotericin B (5 mg/kg daily) if unresponsive to amphotericin B deoxycholate. Echinocandin treatment in neonates and infants less than 2 months of age should only be considered in rare circumstances and only after checking that the central nervous system has not been affected. Removal of catheters and lines and surgical debridement has been used alongside antifungal drugs when clinically indicated[49-55].

Conclusion

Within less than a decade of its discovery, *C. auris* surpasses all *Candida* species as the most difficult pathogen to identify and treat. Poor practice of infection prevention measures and stewardship efforts may have led to rapid spread of drug-resistant *C. auris*. Lack of widespread awareness and recognition of this imminent fungal threat is likely to lead to significant consequences. Further research is needed to understand the spread of this emerging pathogen and to develop better management strategies to combat this worrisome infection.

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