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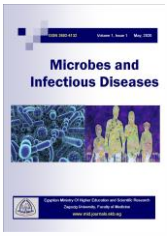

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Review article

Emergence of *Candida auris* infection: A review

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ABSTRACT

Background: *Candida auris (C. auris)*, first described in 2009, is an emerging pathogenic fungus that has been documented globally with large outbreaks and high mortality rates associated with therapeutic failure. This is an important, multidrug-resistant, nosocomial pathogen causing invasive infections. The common therapeutic failures of *C. auris* infections are caused by laboratory misidentification and multi-drug resistance profiles. Widespread resistance to fluconazole, as well as variable susceptibilities to amphotericin B, echinocandins, and other azoles contributes to its infection. Because of multi drug resistance, improper antifungal medication use, persistence in hospital environments and treatment failure, the emergence of *C. auris* is alarming. Accurate identification, effective treatment strategies and implementation of infection control measures are crucial for the prevention and control of outbreaks. The aim of this review is to provide updated information and summarize the introduction, epidemiology, clinical characteristics, drug resistance, identification, therapeutic options, infection prevention and control, conclusive remarks and future prospective of *C. auris*.

Introduction

The most common fungal infection around the world is candidiasis [1]. The frequently encountered and isolated *Candida* species in the clinical setting is *Candida albicans*. Due to the long-term use and limited options of antifungal drugs the incidence and prevalence of non-albicans *Candida* species has increased over recent years [2]. *Candida auris (C. auris*) is a novel *Candida* species which is an emerging, multidrug resistant pathogen that has been associated with worldwide outbreaks [3,4]. *Candida auris* was first identified in 2009 after being isolated from a patient's external auditory canal in Japan [3], there after it has been reported and isolated from many countries.

Candida auris isolate exhibits a close relationship with *Candida haemulonii*, *Candida pseudohaemulonii*, *Candida ruelliae*, and *Candida heveicola*. Which is differentiated based on sequence analysis of the D1/D2 domain of the large ribosomal subunit (LSU) of 26S rRNA gene and the internal transcribed spacer (ITS) regions of the nuclear rRNA gene operon [1,3]. The unique ability of this organism is to grow at 42°C and carbon assimilation patterns further confirmed this distinction [5]. Infections caused by *C. auris* have become a global threat due to its properties of multidrug resistance and rapid worldwide emergence [2]. Healthcare-associated outbreaks of *C. auris* is associated with its ability to be transmitted person-to-person by direct contact, biofilm formation, persist in the surfaces of the hospital environment and on shared equipment and resist chemical disinfection by certain products [6].

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Risk factors for *C.auris* infection may differ by the population of which infection reported. Infections can occur in all age groups, but most infections have been reported from adults [7]. The commonest habitat of *C. auris* in human is the skin, however, several studies have reported their isolation from the gut, oral and esophageal mucosae of infected individuals [8]. The three important characteristics of *C. auris* includes: antifungal resistance, colonization of the skin, gut, anterior nares, and other body sites of asymptomatic carriers and ease of transmition between patients in health care settings. Due to which *C. auris* is generating health issues and attracting attention. Asymptomatically colonized patients with *C. auris* for long periods of time contributes to the contamination of environment and transmission within health care settings [9].

The present review provides information regarding introduction, epidemiology, clinical characteristics, drug resistance, identification, therapeutic options, infection prevention and control, conclusive remarks and future prospective of *C. auris*. This review also helps to characterize the emergence of *C. auris* infection, pathogen, status of outbreak, drug resistance and interventions for prevention and control of transmission in health care settings.

Epidemiology

Candida auris was isolated and reported in South Korea from ear specimens of 15 patients with chronic otitis media. Some of these isolates showed resistance to fluconazole, and pulsed-field gel electrophoresis (PFGE) analysis revealed that 15 isolates of *C. auris* from three South Korean hospitals shared seven PFGE patterns, which suggests that these isolates are responsible for clonal transmission [10,11]. *Candida auris* readily spread and cause outbreaks in health care settings. Its ability to colonize skin and other body sites as well as its ability to persist for weeks on surfaces and equipment facilitates the transmission of this yeast, which is documented with healthcare associated infection and person to person spread [1,12]. Single case or multiple cases of *Candida auris* are reported from different countries since its first description in 2009. Phenotypic, chemotaxonomic and phylogenetic analysis indicates an affiliation to *Candida* genus, with a close relation to other species of candida such as *C. haemulonii* and *C. pseudohaemulonii* which are unusual [3]. Based on published literature and data from the Center for Disease Control and Prevention (CDC), *C. auris* has been isolated in over 45 countries across 6 continents. **Table 1** summarizes the first reported case/cases of *C. auris* in different countries. *C. auris,* a particularly problematic pathogen due to its multidrug resistance, rapid global emergence and high mortality rates and gained a considerable attention from the public, medical professionals and researchers.

Table 1. First reported cases of *Candida auris* in different countries

Country	First reported year
Japan [3]	2009
South Korea [10]	2011
Venezuela [13]	2012
India [14]	2013
United Kingdom [15]	2013
Colombia [13]	2013
South Africa [6]	2014
Kuwait [16]	2014
Israel [17]	2014
Germany [18]	2016
Pakistan [19]	2016
United States [20]	2016
Oman [21]	2016
Switzerland [22]	2017
Russia [23]	2017
United Arab Emirates [24]	2017
Saudi Arabia [25]	2018
Iran [26]	2018
China [27]	2018
Australia [28]	2018

Clinical characteristics

Candida species are the fourth leading cause of all hospital-acquired infections and predominant cause of nosocomial fungal infections. The incidence of *C. auris* infection is significantly higher in immunocompromised patients, secondary to therapeutic management of hematologic malignancies, bone marrow transplantation and other conditions requiring immunosuppressive

therapy [29]. Virulence determinants of *C. auris* are adherence, biofilm formation, phospholipase, and proteinase production which contribute to *Candida* pathogenesis [30].

Risk factors of *C. auris* infection are similar to that of infections caused due to other species of *Candida*, which includes immunocompromised condition, diabetes mellitus, neutropenia, hemodialysis, presence of central venous catheters, urinary catheters, recent surgery, exposure to broad spectrum antimicrobials, intensive care unit admission, chronic kidney disease and other comorbidities and residence of long term health care facility. Other factors which also provoke the *C. auris* infections are previous antifungal agents within 30 days, concomitant bacteremia, concomitant candidemia, candiduria, and chemotherapy [13,31]. The persistence of pathogen on environmental surfaces may colonize or infect hospitalized patients and healthcare workers. Colonized patients also acts as a source of transmission to other patients. Isolation of this organism from nonsterile body sites may be more likely associated with colonization rather than infection. The presence of signs and symptoms of infections can help to differentiate whether colonization or infection [13,20,29,19,32].

Candida auris has been reported clinically as a causative agent in fungemia, osteomyelitis, malignant otitis, complicated intra-abdominal infections, pericarditis, complicated pleural effusions, and vulvovaginitis. Bloodstream infections (fungemia), myocarditis, urinary tract infection, surgical wound infections, skin abscesses (related to catheter insertion), otitis and burn infections are the reported clinical conditions [10,33–37]. This fungi have recently emerged as a major cause of human diseases, especially among hospitalized patients or in immunocompromised. The increasing incidence of nosocomial bloodstream infection and affecting persons of all age groups, establishes that this new species is capable of causing invasive infections. The mucocutaneous over growth of this pathogen is responsible for bloodstream infections [13,16,19].

Drug resistance in *Candida auris*

Candida auris frequently demonstrates resistance to fluconazole and variable susceptibility to other azoles, amphotericin B, and echinocandins, and has caused outbreaks of hospital-acquired infections associated with high levels of mortality [32,38–40]. Resistance to fluconazole with this species has attracted attention because of its reduced susceptibility to azoles and amphotericin B and its misidentification as *C. haemulonii* or *Rhodotorula glutinis* by commercial yeast identification systems. The phenotypic methods in routine use are not reliable for the rapid identification of *C. auris* infection, molecular based detection methods are not yet widely available. The misidentification and reporting is reasonable to more frequent cause of candidemia treatment failure than previously recognized [4,10,14]. The genome encoding ATP-binding cassette and major facilitator superfamily transporter families along with drug transporters explain the multidrug-resistant nature of *C. auris* [41]. There are separate clonal strains displaying the distinct mechanisms of antifungal resistance. The almost half of *C. auris* isolates are found multidrug-resistant, showing resistance to two or more classes of drugs, but the resistance to all classes of antifungals are found in low numbers. Infections caused by *C.auris* are commonly treated with echinocandins [1,42]. **Table 2** summarizes the antifungal drugs and their resistance mechanism developed in *C.auris.*

Some yeast strains are found intrinsically resistant to flucytosine because of impaired cellular uptake mechanism secondary to a mutation in cytosine permease. Mutations in uracil phosphoribosyl transferase or cytosine deaminase cause flucytosine metabolism abnormalities, which lead to acquired resistance [42].

The resistance to azoles has been linked to three single nucleotide polymorphisms (SNPs) and an increased copy number of ERG11(the gene encoding the fluconazole target lanosterol 14-α-demethylase). The efflux pump of azoles in *C. auris* acts as an ATP binding cassette (ABC) transporter Cdr1 [51–53].

The amphotericin B resistance is due to the defects in ERG3 gene, which is involved in erogosterol biosynthesis and lead to accumulation of other sterols in the fungal membrance [42]. While other studies show that *C. auris* ERG6 mutations serve as a mechanism for the clinical tolerance of *C. auris* to amphotericin B [54].

Table 2. Antifungal drugs used in *Candida auris* with their resistance mechanism.

Antifungal drugs	Mechanism of resistance
Azoles	Mutations in ERG11 gene [43–45]
Echinocandins	Mutations in FKS1 and FKS2 genes [46–48]
Flucytosine	Mutations in FCY1 and FCY2 genes [43,44]
Polyenes	Mutations in ERG2, ERG3, and ERG6 genes [17,44,49,50]

ERG: ergosterol; FKS: caspofungin; FCY: 5-fluorocytosine

Identification

There are many challenges in the identification of *C. auris*. *Candida auris* has been recovered from blood, catheter tips, cerebrospinal fluid, bone, ear discharge, pancreatic fluid, pericardial fluid, pleural fluid, peritoneal fluid, sputum, respiratory secretions, swab, skin and soft tissue samples, urine, and vaginal secretions. As for other *Candida* infections, usually fungal culture of blood, urine, body fluids, sputum, swab and pus from the affected site are taken for the diagnosis of *C. auris* infections. However, *C. auris* is more difficult to identify from routine fungal cultures compared with other *Candida* spp. [32,55].

The misidentification of *C. auris* can often be encountered in conventional diagnostic laboratories using biochemical testing. In several investigations, the accuracy of phenotypic diagnostics and molecular methods for the identification of *Candida* species were compared. Most commonly, *C. auris* isolates have been misidentified as *C. haemulonii*, a rare cause of infection in humans, but also a range of other *Candida* species, *C. famata, C. sake*, and *Rhodotorula glutinis, Rhodotorula mucilaginosa*, and *Saccharomyces* species are also reported. Rarely, *C. auris* has been identified as *C. catenulate, C. lusitaniae, C. guilliermondii* [10,39,56,57]. Therefore, accurate identification is important for the treatment strategies, which is directed by species identification of *Candida*.

The identification of the reported isolates of *Candida auris* infections in several countries, is routinely carried out by matrix-assisted laser desorption ionization time of flight mass spectrometry (MALDI-TOF MS). However if commercial yeast identification databases are used, this technique can misidentify the *C. auris* as other *Candida* species. The clonality within *C. auris* isolates has previously been identified from India, Brazil, South Africa, and South Korea using amplified fragment length polymorphism (AFLP) and multilocus sequence typing (MLST). However, the low discriminatory power and reproducibility given by these techniques, genetic relatedness between isolates cannot be investigated in routine investigation of fungal outbreak. The whole-genome sequencing (WGS) is prominent to assess the relatedness of isolates to analyze the patterns of nosocomial infections and global spread [58].

Many clinical labs frequently misidentify this pathogen using biochemical-based identification platforms; examples include VITEK 2 and API 20C AUX, which have allegedly misidentified *C. auris* isolates as *C. haemulonii*. The matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS), helps in accurate identification of this pathogen which is typically not readily available in most clinical laboratories, especially in resource-limited settings. The use of molecular technologies improves the diagnostic sensitivity. The most accurate identification is made with devices using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) with appropriate reference databases, which helps in the differentiation of *Candida auris* from other *Candida* species [33,59].

Identification of C. auris by MALDI-TOF MS

The rapid and accurate identification of *Candida* can be done by matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS). The characteristic mass spectra generated by MALDI-TOF MS are unique for each microorganism, that can be used as their fingerprints. This technology generates characteristic mass spectral fingerprints, that are unique signatures for each microorganism for an accurate identification and strain typing of microbial at the genus and species levels [56,60].

Routine culture and identification

Candida auris can be a challenge to identify and treat, if molecular identification may not be immediately available, especially in resourcelimited settings, where isolates were

initially identified and reported as *C. haemulonii*, but later sequencing confirmed that as *C. auris*. Colony color on CHROMagar *Candida* medium and morphology on rice Tween 80 agar are two phenotypic characteristics of isolates recognized by conventional mycological methods. It shows growth patterns at different temperatures, 37°C, 42°C, and 45°C. The assimilation tests for yeast helps in identification [57]. On culture, *C. auris* appears pale purple to pink on CHROM agar and grows at 37°C–42°C. This characteristic can help differentiate *C. auris* isolates from *C. haemulonii*, which does not grow at 42°C [57,61]. *Candida auris* appears as butyrous to viscous, white to gray, smooth and glistening, with an entire margin on malt extract agar at 25°C. Pseudohyphae are not produced on slide culture at 25°C even after incubation for 59 days [3].

Nucleic acid-based identification method

Various molecular-based assays, conventional and real-time PCR, T2 magnetic resonance or Loop-mediated Isothermal Amplification (LAMP), have been developed, and can be used for the identification of species. The amplified product with standard primers, provides an accurate identification of *C. auris* and differentiation from other yeast by using sequencing of rDNA genetic loci, namely internal transcribed spacer and D1/D2 region of large subunit (LSU) [62].

Five different clades of *C. auris* have been previously identified by using whole-genome sequencing, each of which exhibits genomic divergence at the level of DNA sequence and chromosome structure [63,64].

The reliable identification by molecular methods is based on, targeting the D1/D2 region of the 28S ribosomal DNA (rDNA), area of the 28s rDNA, or internal transcribed spacer (ITS) gene of *C. auris* enables TaqMan chemistry and SYBR green chemistry-based polymerase chain reaction (PCR) and/or real-time PCR assays to specifically identify *C. auris* and helps to differentiate it from other related species [9,43,65–67].

As a molecular target, a DNA fragment from the *C. auris* genome that encodes a gene for a pyruvate: ferredoxin oxidoreductase domain is used in loop-mediated isothermal amplification (LAMP) based identification of *C. auris* [68,69].

Another molecular test, T2 magnetic resonance technology makes use of target-specific primers and probes attached to super paramagnetic particles that recognize and amplify a signal associated with pathogens that can be identified by magnetic resonance technology [9,70].

Therapeutic options

Accurate detection and identification of *C. auris* pathogen is necessary for the effective treatment. It has been determined that *C. auris* antifungal agent resistance is acquired rather than inherent. The current worldwide findings conclude that susceptibility to fluconazole is the most decreased from *C. auris* isolates, followed by amphotericin B, and 5-fluorocytosine and echinocandins are also not 100% effective [43,44]. Most commonly reported resistance was found to the fluconazole then amphotericin B, and resistance to the echinocandins is emerging in some countries [71].

Because of high rate of therapeutic failures and limited availability of treatment choices, novel alternative antifungal strategies including combination therapy are needed to improve patient outcomes [72]. Therefore, *C. auris* is notable because of its resistance to azole antifungal agents and its potential for clonal transmission [10].

Vaious study reported that, application of synergistic therapies can represent success in the absence of efficient treatments. When used together, micafungin and voriconazole effectively responded to a variety of *C. auris* strains. As well as the combinations of micafungin and fluconazole, caspofungin, voriconazole and fluconazole showed indifferent synergistic results. Which indicates the possibility of effective therapy. The use of echinocandins in combination with other antifungal medications has recently received a lot of attention as a novel therapy option for *C. auris* infections [43,73–75].

Infection prevention and control

Candida auris has ability to be transmitted person-to-person by direct contact, form biofilms, persist on surfaces of hospital environment and on shared equipment, and resist chemical disinfection by certain products, therefore it has been associated with large healthcare-associated outbreaks and possibly persist longer time within the hospital environments [6,59,76]. *Candia auris* can survive on a different surface types, including dry, moist, and plastic surfaces, with organisms being viable for up to 14 days on plastic. It has been isolated for 3 months or more after initial detection in spite of negative screens and echinocandin treatment in the

intervening period. Contact with patients known to harbor *C. auris* or their environment is the major risk factor for the colonization. Multiple body sites has been detected as colonized with *C. auris* including nares, groin, axilla, and rectum [39]. Colonized or infected individuals shedding *C. auris* into their immediate environment is the source of potentially spreading to others and causing health care outbreaks, where it can persist for long periods of time on health care environments, including shared medical equipment and devices [77].

It is essential to thoroughly clean and disinfect reusable medical equipment as well as the surrounding environment to stop the spread of this organism and break the chain of transmission. Quaternary ammonium disinfectants and cationic surface-active agents have poor activity and are not effective against *C. auris* [78,79]. Skin disinfection at injection and surgical sites frequently involves the use of iodine-based disinfectants, which are categorized as intermediate-level disinfectants [79]. Currently, the CDC recommends the use of an Environmental Protection Agency (EPA)–registered hospital-grade disinfectant effective against *C. auris* [80]. Chlorine based disinfectants, hydrogen-peroxide based disinfectants and Ultraviolet light disinfection proven to have good disinfection efficacy and are showing highest reduction of *C. auris* [78,79,81].

Transmission based precautions or safety measures should be maintained in all health care settings,which contributes to reducing the possibilit y of transmission due to *C. auris* infection or coloni zation. Patients with *C. auris* infections or colonizations should be put on contact precautions, which include confining them to a single room, patient cohorting, wearing the proper personal protective equipment (PPE), proper treatment, allowing them to leave their room only for medically essential procedures and increse in awareness [67,82].

The challenge to identify and treatment of *C. auris* infections especially in resource- limited settings, where molecular techniques for identification are not available and limited access to antifungals treatment other than fluconazole may pose a significant threat. The dissemination of infection can be prevented by active case finding and surveillance, hand hygiene and environmental disinfection. Rapid detection is an essential component needed to prevent infection and guide to apply other measures to control dissemination [83].

Candida auris has all the makings of a superbug with its multidrug resistance, transmissibility and severe outcomes. Control of *C. auris* requires better understanding of the organism itself, accurate identification and vigilance, effective treatment and infection control measures with a coordinated public health response [5]. The early detection is necessary for prevention of further colonization, invasive infections and outbreaks of *C. auris*. Therefore, effective infection control strategies are crucial to prevent the emergence and spread of this pathogen, especially in intensive care units and health care settings. The decision to establish a systematic *C. auris* screening, identification and treatment policy should be assessed by each hospital on the basis of locality, risk and spread of infections encountered.

Conclusive remarks and future prospective

Candida auris is called "superbug fungus", due to its transmissibility, invasiveness, multidrug resistance and severe outcomes. It has variable resistance patterns to many typical antifungal agents used to treat other *Candida* infections and is considered a multi-drug resistant species. The exact reservoir of this pathogen has not been found, although it has been found almost exclusively in the hospital setting. The difficulty in laboratory identification, the ability to spread within healthcare settings, resistance to multiple antifungal agents with subsequent high mortality rates makes this *C. auris* is of particular cause of concern [33,59,84]. The difficulties in identification, multidrug resistance, persistence in hospital environments, broad range of infections, recognized in different geographic locations are the common factors involved to cause worldwide emergence and dissemination of *C. auris* infections [1,76]. *C. auris* is a global health threat because of its ability to persist in the environments, colonize skin, ability to cause nosocomial outbreaks, and causes severe disease with high mortality rates. These isolates are found MDR, with some strains having elevated MICs to drugs in major classes of antifungal drugs.

Candida. auris is an emerging healthcare-associated multi drug resistant pathogen. The biologic and epidemiologic variables could accelerate the global spread of *C. auris* infections. The outbreak response is more complicated by limited treatment options and inadequate

disinfection strategies, as well as by other issues of misidentification of this pathogen associated with application of commonly used diagnostic tools. Misdiagnosis of *C. auris* is common in many clinical and public health laboratories is due to incorporation of conventional diagnostic methodology. Due to antifungal resistance and limited treatment options, the already reported cases of *C. auris* from several countries worldwide suggest that *C. auris* has the propensity to cause outbreaks in health care environments. Therefore, a comprehensive study is needed to summarize and monitor the global epidemiology, drug resistance and therapeutic challenges, identification, nosocomial infection, colonization and spread of *Candida auris* infections.

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