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REVIEW

Candida auris: From Multidrug Resistance to Pan-Resistant Strains

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Abstract: *Candida auris* is an emerging multidrug-resistant fungus that is rapidly spreading worldwide. Currently, *C. auris* cases have been reported globally from >30 countries. Most reported infections involve critically ill patients in hospitals, mainly in intensive care unit settings. Infection with *C. auris* is associated with high mortality rates, and it is often resistant to multiple classes of antifungal drugs. Despite the rapid global spread, it is difficult to predict the actual burden of the infection as the standard laboratory methods fail to correctly identify the fungi. Longer stays in healthcare facilities, use of tracheostomies and percutaneous endoscopic gastrostomy tubes, ventilators in clinical care units and mobile equipment in healthcare settings are shown as major risk factors of *C. auris* infection. Due to its propensity to cause outbreaks and its antifungal resistance, *C. auris* poses a risk for patients in healthcare facilities. The emergence of pan-resistant *C. auris* strains in some areas is an alarming signal for the disease with limited treatment options, high mortality rates, and the ability of the pathogen to spread easily in healthcare settings. In this regard, susceptibility testing on clinical isolates, mainly for patients treated with echinocandins, is needed. Increasing awareness about *C. auris* infection and advancing the diagnostic methods are also essential for early detection and control of the deadly fungal infection.

Keywords: *Candida auris*, multidrug resistance, pandrug resistance, risk factors, challenges

Background

C. auris is one of the few species of the genus *Candida* which cause candidiasis in humans. It is one of the emerging fungus that can cause invasive infections. As it was detected in the external ear canal of the patient, it was named as *Candida auris*. Auris is the Latin word for ear. Currently, *C. auris* has emerged globally as a multidrug-resistant nosocomial pathogen and it is considered a major threat to healthcare settings. Worldwide reports of *C. auris* have considerably increased within a decade.[1,2] The aim of this review is, therefore, to describe the current status of *C. auris*, mainly focusing on the current challenges in clinical and laboratory diagnosis, emergence of pan-drug resistance and possible ways of preventing and controlling the spread of the infection. For this purpose, a systematic search of bibliographical databases was done using the search engines: Google Scholar, Google search, Scopus and PubMed Central. The following key words (phrases) were used in the search engine including but not limited to *C. auris*, mechanisms of drug resistance, risk factors, diagnosis, treatment, prevention and control. Peer-reviewed research articles, reviews and short communications by international organizations were included. The search was restricted to English language and duplicates were removed.

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Trends in *C. auris* Occurrence

C. auris was first described in Japan in 2009.[2] Then, *C. auris* isolates have started to be identified and reported across five continents as agents of hospital-associated infections.[3] To mention but a few reports, twelve isolates of *C. auris* were identified in India from 2009 to 2011.[4] In 2011, three cases of *C. auris* fungemia were reported from South Korea of which two isolates were obtained during a 2009 study and a third one was discovered in a stored sample from 1996.[5] The first outbreak of *C. auris* in Europe was reported in 2016 in Royal Brompton Hospital, a London cardio-thoracic hospital.[6] *C. auris* began spreading in the United States (U.S) in 2015 and a total of 77 *C. auris* cases were reported in 2017.[7] According to the 2019 CDC report, *C. auris* has been isolated and reported globally from >30 countries (Figure 1) from which multiple cases of *C. auris* have been reported from Australia, Bangladesh, Canada, China, Colombia, France, Germany, India, Israel, Japan, Kenya, Kuwait, Malaysia, the Netherlands, Oman, Pakistan, Panama, Russia, Saudi Arabia, Singapore, South Africa, South Korea, Spain, the United Kingdom (UK) and the United States.[8] Indeed, the real prevalence and the epidemiology of *C. auris* still remain uncertain mainly due to the limited accuracy of available conventional diagnostic tools.[9,10]

The phylogenetics of *C. auris* suggests distinct genotypes exist in different geographical regions with substantial genomic diversity. Whole-genome sequencing and analyses of isolates from Pakistan, India, South Africa, Venezuela, Japan and previously sequenced *C. auris* genomes deposited in the National Center for Biotechnology Information's (NCBI) sequence read archive identified a distinct geographic distribution of genotypes.[11,12] In this regard, four distinct clades were identified, namely South American clade, African clade, South Asian clade and East Asian clade. These clades segregated geographically to South Asia (India and Pakistan), South Africa, Venezuela and Japan.[12,13] Recently, however, an isolate representative of a potential fifth clade, separated from the other clades by >200,000 single-nucleotide polymorphisms, was identified in a 14-year-old patient in Iran who had never traveled outside the country.[14,15] In some areas such as the US, isolated cases cluster to all four *C. auris* clades, likely introduced through international travel and subsequent spread in healthcare facilities.[16]

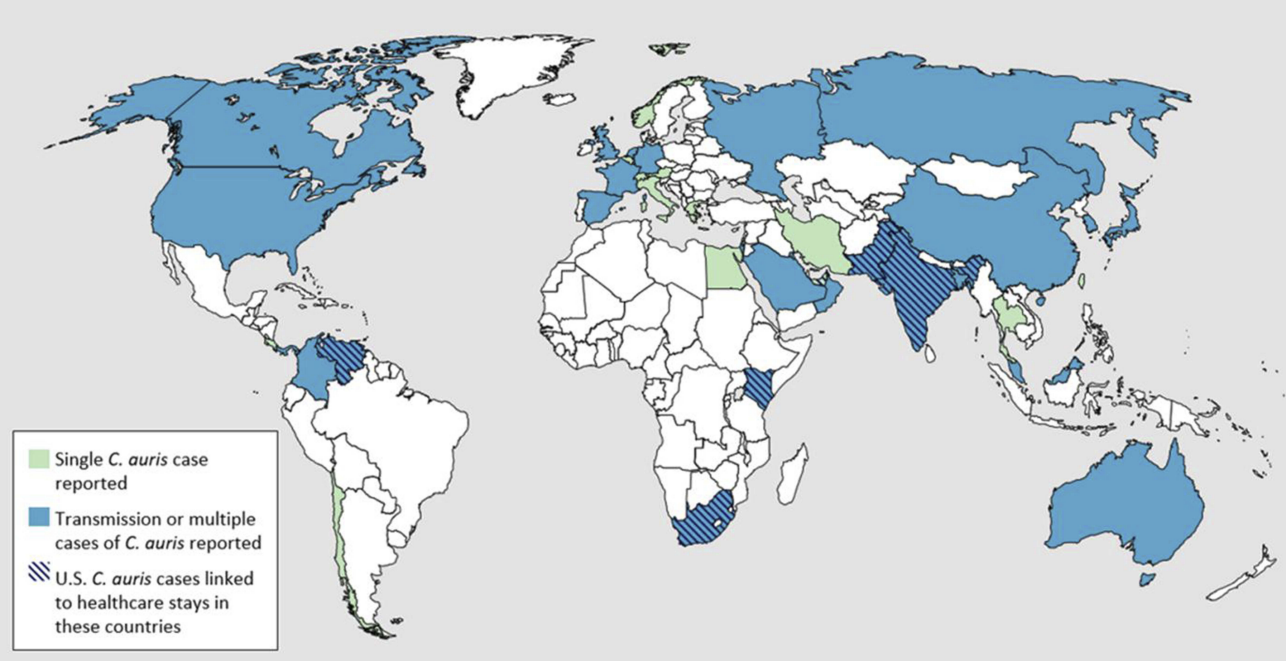

Figure 1 Countries from which *Candida auris* cases have been reported, as of December 31, 2019.
Notes: Reproduced from CDC. *Candida auris*: A Drug-resistant Germ That Spreads in Healthcare Facilities. Available at: https://www.cdc.gov/fungal/candida-auris/tracking-c-auris.html. Accessed on 15 January 2020.[8] Content source: Centers for Disease Control and Prevention, National Center for Emerging and Zoonotic Infectious Diseases (NCEZID), Division of Foodborne, Waterborne, and Environmental Diseases (DFWED). Use of the material, including any links to the materials on the CDC, ATSDR or HHS websites, does not imply endorsement by CDC, ATSDR, HHS or the United States Government; reference to specific commercial products, manufacturers, companies, or trademarks does not constitute its endorsement or recommendation by the US Government, Department of Health and Human Services, or Centers for Disease Control and Prevention. The material is otherwise available on the agency website for no charge.

Risk Factors of *C. auris* Infection

Usually, longer stays in certain types of post-acute care facilities such as intensive care units (ICUs) is considered as a major risk factor of *C. auris* infection. For instance, the first and only *C. auris* candidemia case in Kuwait was a patient in the ICU with chronic renal failure.[17] In India, more than two-thirds of ICUs (19 out of 27 ICUs) were found to have *C. auris* isolates.[18] In Spain, an average length of stay of 25 days in healthcare institutions was associated with developing *C. auris* infection.[19] This might be attributed to the nature of disease transmission which mostly involves exposure to contaminated facilities in healthcare institutions.[7] *C. auris* colonizes both biotic (skin and other body sites) and abiotic surfaces. Notably, its ability to adhere to surfaces and plastic materials (eg, catheters), biofilm formation, and salt tolerance facilitate the acquisition of the fungus in healthcare settings such as ICUs.[20] The majority of *C. auris* infected patients have had a recent exposure to an indwelling device or have undergone some invasive procedures.[21] Infections have been observed several days to weeks after hospitalization in susceptible patients, suggesting exogenous sources of infection.

In agreement with this, patients with tracheostomies and percutaneous endoscopic gastrostomy (PEG) tubes are more likely to acquire *C. auris* infection.[22] Ventilators in clinical care units were reported to spread *C. auris* infection. In this regard, the prevalence of *C. auris* in nursing home units with ventilator beds was 7.7% compared to regular nursing homes without ventilator (0.7%).[23] Mobile equipment's in healthcare settings has also been implicated in the transmission of *C. auris* infection.[23] Furthermore, the incidence of *C. auris* increases among patients with primary or acquired altered immune response, therapeutic management of broad-spectrum antibiotics, transplantation, patients with different comorbidities, and other conditions requiring immunosuppressive agents.[24,25]

C. auris has been isolated from patients of both sexes and of all age groups. Though the reported *C. auris* isolates were mostly isolated from males,[13] no reason has been provided yet for the sexual differences in terms of frequency of *C. auris* infections.

Current Challenges of *C. auris* Infection

Non-Specific Clinical Presentations

C. auris can cause severe invasive infections. However, clinical conditions associated with *C. auris* are non-specific and it is often difficult to differentiate between other types of systemic infections.[10] Clinical conditions associated with most of the reported *C. auris* cases include bloodstream infections, urinary tract infection, otitis, surgical wound infections, skin abscesses, myocarditis, meningitis, bone infections and wound infections.[18,26] According to the CDC report,[8] fever and chills that do not improve after antibiotic treatment for a suspected bacterial infection are usually considered among the common symptoms of invasive *C. auris* infection. However, none of the aforementioned clinical conditions provide definitive diagnosis, and laboratory investigation should be considered for confirmation.

Misidentification by Conventional Diagnostic Tests

Early detection of *C. auris* infections has been shown to be beneficial as earlier initiation of appropriate antifungal therapy saved many lives.[27] However, identification of *C. auris* remained challenging because most phenotypic methods misidentify *C. auris*. Until the sequence analysis correctly identified isolates as *C. auris*, they were initially misidentified as other *Candida* species.[5] So far, culture and microscopy characteristics have been used to differentiate different *Candida* species. In view of this, *C. auris* cells are ellipsoid in shape, an ovoid to elongate budding yeast, which seldom forms rudimentary pseudohyphae and typically appears as pink. *C. auris* also grows as yeast and forms smooth, shiny, whitish-gray, viscous colonies on growth media and it has high tolerance for salinity and heat.[10,28] However, these features may not provide definitive diagnosis for *C. auris* as there are other *Candida* species, such as *C. haemulonii*, with the most similar phenotypic characteristics.[29]

It was confirmed by molecular techniques that conventional diagnostic tests using biochemical typing often misidentify *C. auris*.[30] *C. auris* isolates have been misidentified as a range of other *Candida* species with phenotypic and biochemical methods (Table 1), including API 20C, Vitek 2 (bioMérieux), Phoenix (BD), and MicroScan.[28,31,32] As recommended by CDC (Table 1), correct identification of *C. auris* can be done using accepted diagnostic methods such as matrix-assisted laser desorption ionization–time of flight (MALDI-TOF) platforms.[33] Moreover, molecular identification techniques like polymerase chain reaction, sequencing, and amplified fragment length polymorphism fingerprinting will detect *C. auris* and differentiate it

Table 1 Identification of *Candida auris* by Different Diagnostic Methods

Tests Which Misidentify *C. auris* as *OtherCandida* Species[1,28,30-32,55]	**Tests Which Correctly Identify *C. auris***[33,34]
API 20CAUX	Bruker Biotyper MALDI-TOF (RUO libraries (v 2014[5627] and CA system library (v claim4))
API Candida	bioMerieux VITEK MS MALDI-TOF (ROU library (Saramis v 4.14))
Phoenix (BD Diagnostics)	VITEK 2 YST (Software v 8.01)
Vitek	Polymerase chain reaction (PCR)
MicroScan (Beckman Coulter)	Amplified fragment length polymorphism fingerprinting
Vitek MS (bioMerieux)	

from closely related species such as *C. haemulonii, C. duobushaemulonii*, or *C. lusitaniae*.[34]

It has to be noted that isolations from non-sterile body sites such as lungs, urinary tract, skin and soft tissue, and genital apparatus may represent colonization rather than infections.[26,35] Hence, the presence of signs and symptoms of *C. auris* infections should be considered to differentiate simple colonization from infection.[36] Certainly, it is important to identify *C. auris* even from a non-sterile body site because colonization poses the risk of transmission, which requires implementation of infection control precautions.[10]

Multidrug Resistance and Emergence of Pan-Resistant Strains

C. auris is characterized by high rate of antifungal resistance with reduced susceptibility to azoles, polyenes, and echinocandins.[37] In vitro, more than 90% of *C. auris* isolates have shown resistance to fluconazole.[38] *C. auris* resistance to voriconazole and amphotericin B was shown to be 3–73% and 13–35%, respectively.[21,27] In the US, more than 99% of the *C. auris* isolates were shown to be resistant to fluconazole, nearly two-thirds were resistant to amphotericin B, and roughly 4% were resistant to echinocandins.[39] A systematic review and meta-analysis from Sekyere et al also reported that most of *C. auris* isolates are resistant to fluconazole (44.29%), followed by amphotericin B (15.46%), voriconazole (12.67%), caspofungin (3.48%) and flucytosine (1.95%).[13] Thus, higher resistance to fluconazole in a *Candida* non-albicans species has become one of the distinguishing characteristics indicative of a potential *C. auris* infection.[40]

Indeed, echinocandins are the first-line therapy for *C. auris* infection. As synergistic interactions have a better efficacy, a combination therapy of an echinocandin and liposomal amphotericin B is prescribed in cases of unresponsiveness to echinocandins.[41–43] However, most recently in US, three cases of pan-resistant *C. auris* with resistance to all three classes of commonly prescribed antifungal drugs have been reported.[39] In the same report, it was mentioned that a total of 801 patients with *C. auris* were identified in New York as of June 28, 2019. Among these patients, three of them developed resistance to all antifungal medications, including echinocandins.[39] In fact, echinocandin-resistant *C. auris* isolates have been previously described[44]; however, the isolates were susceptible to azoles. Chowdhary et al also reported 14 (4%) pan-azole-resistant *C. auris* cases[9]; however, this data was limited to only micafungin and anidulafungin. Although the overall numbers of pan-resistant cases reported so far are few, it is an alarming signal for the disease with limited treatment options, high mortality rates, and the ability of the pathogen to spread easily in healthcare settings.

Data regarding the molecular mechanisms of resistance of *C. auris* to antifungal agents are scarce, and the precise mechanism of resistance in isolates is not well known. As shown by some studies (Table 2), *C. auris* escapes from the microbicidal effect of all the classes of anti-fungal agents through different mechanisms, including but not

Table 2 Mechanism of Antifungal Resistance by *C. auris*

Antifungal	**Resistance Mechanism**	**References**
Polyenes	Mutations, 5 SNPs in different genome loci	[28,56]
Azoles	Point mutations in the lanosterol 14 α-demethylase (ERG11) gene	[21,24,57]
	ERG 11 up-regulation due to mutation in Upc2 TF	
	Up-regulation of efflux pump genes	
Nucleoside analogs	Amino acid substitution (F211) in FUR1	[58]
Echinocandin	Mutation in FKS1/2 gene	[10]

limited to mutations in ERG3 and ERG11 genes, up-regulation of efflux pump genes and single-nucleotide polymorphisms (SNPs) in different genome loci.[13] The South Asia clade is shown to exhibit increased antifungal resistance compared to other clades of *C. auris*.[9] Likewise, the reported U.S. pan-resistant cases emerged in New York where the South Asia clade (clade 1) predominates.[45]

Increased Risk of Mortality

Invasive infections of *C. auris* are fatal unless early detection and treatment is initiated. The ability of *C. auris* to develop resistance to commonly used antifungal agents is responsible for its high rates of mortality.[37] In fact, the reported mortality rates due to *C. auris* vary. The 30-day mortality rate of *C. auris* in Colombia was 35.2%.[46] Mortality rates in Asia, Far East, and the United States is estimated to be more than 50% for those with invasive infections.[5,47,48] In Spain, a thirty-day mortality rate was reported to be 41.4%.[19] In general, the crude in-hospital mortality rate for *C. auris* candidemia is estimated to range from 30% to 72%.[10]

Awareness About the Infection

C. auris is a newly emerging fungus and has subsequently been associated with invasive infections and outbreaks in healthcare settings worldwide. Lack of awareness about this drug-resistant *Candida* could lead to unnoticed transmission and outbreaks in healthcare settings.[40] In this regard, the healthcare workers should be aware of this fatal invasive infection and need to adapt the laboratory testing strategies and implement enhanced control measures early enough to prevent healthcare outbreaks.[49] So far, there is no concrete evidence on the current state of knowledge of the public and healthcare workers regarding *C. auris* infection. CDC itself claimed that CDC fungal experts had never heard and received a report describing a Candida infection resistant to all antifungal medications before 2016. It was after hearing the news that CDC sounded the alarm in the US about *C. auris*.[50] Currently, only few countries worldwide (about 30 countries) have reported *C. auris*,[8] suggesting that the infection is either undetected or unreported in the majority of countries. However, there is no much information whether the disease does not actually exist in those countries where *C. auris* is not reported yet. In this regard, the awareness of health workers about the whole picture of *C. auris* infection including the diagnostic challenges could not be underestimated as most of the routine diagnostic methods miss the fungus and the infection may continue to be unreported.

Prevention and Control

C. auris strains are characterized by their ability to form a biofilm structure on biotic and abiotic surfaces.[20] Patients are often indefinitely colonized by *C. auris* primarily on skin, nares and other body sites. Indeed, there is no currently known decolonization strategy and colonization may persist for months leading to invasive infection and transmission to others.[51] *C. auris* also persists in the environment for months, and persistent environmental contamination, contaminated medical equipment and other fomites are believed to play a role in nosocomial *C. auris* transmission.[52] In view of this, rigorous attention to environmental cleaning is important for preventing transmission within a healthcare facility. Indeed, common disinfectants such as quaternary ammonia compounds do not work.[8] But, surface disinfectants such as chlorine and hydrogen peroxide were shown to have good efficacy against *C. auris*.[53,54]

C. auris was made nationally notifiable at the 2018 Council for State and Territorial Epidemiologists (CSTE) Annual Conference.[8] Hence, detected cases have to be reported to local or state health departments. Patients with confirmed infections or suspected to have *C. auris* infections should be kept in separate wards under strict contact precautions.[8] Patients or healthcare workers coming in close contact with infected persons should also be placed under strict contact precautions until they are proven to be negative for confirmatory diagnostic tests. Moreover, it is recommended to thoroughly disinfect the wards of patients found to be colonized or infected with *C. auris*. Cleaning and disinfection of shared medical equipment is encouraged.[6]

Conclusion

Infections by *C. auris* are progressively emerging in hospitals and ICU settings. *C. auris* with high mortality rates, multi-drug resistance, environmental resilience, difficulty in microbiological identification and horizontal transmission has become an issue in clinical practice. Most reported infections of *C. auris* involved critically ill patients. The emergence of pan resistance is an alarming signal and controlling the spread of the resistance strain is needed. Because of the potential for the development of resistance, patients on antifungal treatment for *C. auris* should be monitored closely for clinical improvement. Susceptibility testing should also be conducted, especially in patients treated with echinocandins. Moreover, increasing awareness about the infection and

advancing the diagnostic methods is essential to control *C. auris* infection.

Abbreviations

AFLP, amplified fragment length polymorphism; ICU, intensive care unit; MALDI-TOF, matrix-assisted laser desorption/ionization–time of flight mass spectrometry; RUO, research use only.

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Author Contributions

Both authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare no competing interests.

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