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CANDIDA AURIS: A BRIEF REVIEW ON NOTORIOUS NOSOCOMIAL MULTIDRUG-RESISTANT CANDIDA SPECIES AS AN EMERGING FUNGUS GLOBALLY

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INTRODUCTION

Infections in today's world are one of the most important mortality and morbidity cause more so in low and lower-middle income countries,[1,2] Intensive care units (ICUs) have been an important source of infections, worldwide, especially bacterial.[3-7] Studies conducted in Europe and North America have reported that primary (at the time of admission) as well as secondary (nosocomial, ventilator-associated, device-related, and others) infections are common in ICUs.[6] Recent studies from different areas of the country have reported that both primary and secondary infections with gram-positive and gram-negative bacteria are widespread.[8-12] Fungi have recently emerged as a major cause of human diseases, especially among patients who are hospitalized for a long duration or are immunocompromised.[13] The most common fungi involved in invasive disease in humans are opportunistic yeasts like *Candida albicans* or filamentous fungi like *Aspergillus* Spp. fungi such as *Candida* (except C. *albicans*), *Fusarium*, *Trichosporon* and *Malassezia* spp., which were previously considered to be non-pathogenic for humans or were only causing human diseases sporadically are now emerging as leading nosocomial fungal pathogens have become a source of concern. *Candida* spp. belong to the normal microbiota of an individual's mucosal oral cavity, gastrointestinal tract, and vagina.[14] *Candida* spp. is the only opportunistic fungi; that exist both as a commensal and pathogen. It is also unique among the mycotic pathogens as it causes a broad spectrum of clinical manifestations ranging from mere mucocutaneous overgrowth to life threatening systemic infections.[15] Over past two decades, there has been a change in the distribution of *Candida* species causing nosocomial infections from *C. albicans* to Non-albicans *Candida* (NAC) species such as *C. tropicalis, C. glabrata, C. parapsilosis, C. krusei*, and *C. lusitaniae*.[16]

Candida auris (*C. auris*) is a newly emerged member of the *Candida/Clavispora* clade, first isolated in Japan in 2009 from the ear discharge of a female patient. In the past decade, infections caused by *C. auris* have become a global threat due to its rapid emergence worldwide and multidrug resistance (MDR) properties.[17]

Taxonomy

The first isolate of *Candida auris* (type strain JCM:15448; CBS:10913; DSM:21092) had several attributes that distinguished it from its closest known relatives, warranting its demarcation as a new species.[17]

Taxonomy ID: 498019

Current name: *Candida auris* Satoh & Makimura, 2009 culture from type material of *Candida auris*: JCM:15448; CBS:10913; DSM:21092; CDC:B11220 includes: *Candida* sp. KM-143.[18]

Table 1: Scientific classification.[18]

Kingdom	Fungi
Phylum	Ascomycota
Class	Saccharomycetes
Order	Saccharomycetales
Family	Metschnikowiaceae
Genus	*Clavispora*
Clade	*Clavispora/Candida* clade
Species	*C. auris*

Epidemiology and Genetic Analyses

Candida auris, belonging to the *Candida haemulonii* complex of the Metschnikowiaceae family, was first described in 2009 when it was isolated from the ear canal (auris means "ear" in Latin) of a Japanese female patient, who was a patient at Tokyo Metropolitan Geriatric Hospital (Tokyo, Japan).[17,19] Subsequently, it was recovered from 15 ear samples from 5 Korean hospitals and identified as a causative agent of otitis media.[19] These yeast isolates had phenotypic similarity to *C. haemulonii* and were less susceptible to amphotericin B (AMB) and fluconazole (FLU) than most other *Candida* spp.[19,20] However, a retrospective review of *Candida*

strain collections in South Korea revealed that the earliest known strain of *C. auris* dated back to 1996 and was isolated from the blood of a paediatric patient.[19,21] In 2011, 15 isolates of *C. auris* were recovered from 15 patients in a tertiary care hospital in Northern India.[22] These isolates were initially identified as *C. haemulonii*, but were later confirmed as *C. auris* upon sequencing. Further reports have been published regularly from health care centres from North India and some centres in Southern India.[23-26] Infection and colonization have been detected mainly in critical care patients and affect both paediatric and adult populations.[23,27]

Genetic analyses have shown a striking divergence of *C. auris* from some *Candida* species, while it remains more closely related to others. When percent nucleotide identities of various yeast species compared to *Candida auris* (South Asian clade), calculated over the 285-bp D1-D2 portion of the *C. auris* 28S ribosomal DNA gene, it remains more closely related to *Candida lusitaniae* and *Candida haemulonii* whereas least resemblance is seen with *Candida rugosa*.[28,29,30]

Since 2009, five genetically diverse clades have been discovered from various places; India and Pakistan (South Asian; Clade I), Japan (East Asian; Clade II), South Africa (African; Clade III), Venezuela (South American; Clade IV).[28] and most recently in 2019, Iran (Clade V).[31] Over the past decade, isolates of *C. auris* have also been detected across all major continents, including elsewhere in Asia, Europe, the Middle East, Africa, Australia, and North and South America.[17,28,31,32-52]

The spread of *C. auris* within and between hospital settings has been demonstrated by at least clades I, III and IV.[42,51,53] so it might be possible that abiotic factors could explain the emergence. For example, human activities such as deforestation, expansion of farmland, and coastal ecosystem disruption could have allowed an ecological jump.[54] *C. haemulonii* causes clinical infections, is also found in the GI tract and skin of marine animals.[55] Also, *C. auris* has been shown to persist on a wide variety of hospital equipment.[51] Thus, it seems likely that *C. auris* may also have an environmental niche (plants or aquatic). The widespread use of fungicidal agents, especially triazoles in agriculture could have been responsible for *C. auris* to become more prominent in the environment, as it shows high levels of antifungal resistance. And also, increased human travel, trade or other anthropogenic factors may have simply led to the globalization and emergence of *C. auris*.[54]

Identification

The analysis of rDNA sequences of 28S D1/D2 and 18S internal transcribed spacer (ITS) regions and 50 protein sequences indicates that *C. auris* belongs to the Metschnikowiaceae family within the *Candida/Clavispora* clade.[17,29,56] *C. auris*, like other species of the *Candida/Clavispora* clade, is a member of the CTG clade. Species in this clade translate the CTG codon as serine rather than leucine.[57]

C. auris can be easily misidentified as *C. haemulonii, C. lusitaniae or* other yeast species (like *Rhodotorula* species) using conventional phenotypic and biochemical methods.[58,59] The growth of *C. auris* on commercial CHROMagar medium at temperatures up to 42℃ results in white, pink, or dark purple colonies [60-62]. *C. auris* generally does not form hyphae or pseudohyphae on corn meal agar (CMA). Unlike other *Candida* species, *C. auris* grows well at 42℃, and therefore this thermal tolerance property is being utilized to differentiate *C. auris* from other *Candida* species.[63] Matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) devices can accurately differentiate between *C. auris* and other fungal species; however, the accurate identification of *C. auris* is dependent on the reference data- bases included in the MS device.[58,64,65] Polymerase chain reaction (PCR) and molecular techniques can also be used for *C. auris* identification. Molecular methods based on sequencing of genetic loci, such as the D1/D2 region of the 28S rDNA or the ITS region of rDNA, can accurately detect *C. auris* isolates.[39,66-69]

Table 2: Some identification methods for *C. auris*.[70]

Identification method	Database/software, (in case applicable)	*C. auris* confirmed (if it is the primary identification)	*C. auris* may have been misidentified in case of given identifications (needs further identification)
BioMerieux VITEK MS MALDI- TOF	RUO library (with Saramis Version 4.14 database and Saccharomycetaceae update) & IVD library (v3.2)	*C. auris*	n/a
VITEK 2 YST	Software version 8.01	*C. auris* (if initial identification is *C. lusitaniae* or *C. famata*; confirm by CMA)	*C. haemulonii* *C. duobushaemulonii* *Candida* spp. not identified
	Older versions	n/a	*C. haemulonii* *C. duobushaemulonii* *Candida* spp. not identified
GenMark ePlex BCID-FP Panel		*C. auris*	n/a

C. auris ferments sugars such as glucose sucrose, trehalose (weak) and does not ferment galactose, maltose, lactose or raffinose. It assimilates carbon sources like Glucose, sucrose, maltose, D-trehalose, D-raffinose, D-melezitose, inulin (weak), soluble starch, ribitol (weak), galactitol, D-mannitol, sorbitol and citrate, N-acetyl-D-glucosamine (NAG) and does not assimilate D-galactose, L-sorbose, D-cellobiose, lactose, melibiose, D-xylose, L-arabinose, D- arabinose, ribose, L-rhamnose, D-glucosamine, NAG, methanol, ethanol, glycerol, erythritol, α-methyl-D- glucoside, salicin, D-gluconate, DL-lactate, succinate, inositol, hexadecane, 2-keto-D-gluconate and xylitol. It utilizes nitrogen sources like Ammonium sulfate, cadaverine, L-lysine and does not utilize Sodium nitrite, potassium nitrate and ethylamine. Growth in vitamin-free medium, 50% glucose, and 10% NaCl/5% glucose medium is observed. Starch formation, urease activity and diazonium blue B reaction is negative. Growth in the presence of 0.1% and 0.01% cycloheximide is negative. Hyphae formation is negative. Some strains form pseudohyphae occasionally, but most strains do not. Little adherence to catheter material (as compared to *Candida albicans*). Phospholipases and proteinases production were strain-dependent and relatively lower than *C. albicans*. Most strains form biofilms to different degrees while some do not form biofilms at all. Cells are ovoid, ellipsoidal to elongate, (2.0–3.0) × (2.5–5.0) µm, single, in pairs, or in groups/aggregates. No chlamydospores or chlamydoconidia are formed on cornmeal agar. Genomic features are: 12.3–12.5 Mb genome, GC content = 44.8%–45.3%, Coding sequence = 6675, 5.8S rRNA, 184 tRNA, 3262 repetitive elements.[71]

Risk Factors

C. auris is an opportunistic pathogen. The available data indicates that the risk factors for *C. auris* infections are similar to the risk factors associated with infections due to other species of *Candida*. These are: diabetes mellitus, presence of indwelling medical device (central venous catheter), immunocompromised state, neutropenia, exposure to broad-spectrum antibiotics and/antifungal agents, parenteral nutrition, blood transfusion, haemodialysis, surgery within 30 days, intensive care, previous antifungal agents within 30 days, concomitant bacteremia, concomitant candidemia, indwelling urinary catheter, candiduria, chronic kidney disease, and chemotherapy. Infections have been reported in the patients of all ages, from preterm infants to the elderly. Various studies suggest a diverse set of risk factors associated with *C. auris* infections.[22,72]

Virulence Factors

C. auris shares many virulence factors with *C. albicans* such as nutrient acquisition, histidine kinase-2 component system, iron acquisition, tissue invasion, enzyme secretion (Saps and lipases), multidrug efflux, and genes/pathways involved in the cell wall modelling and nutrition acquisition. *C. auris* is closely related phylogenetically to *C. krusei*, *C. haemulonii*, and *C. lusitaniae*, which are known to have intrinsic and inducible resistance to fluconazole, Amphotericin B, or both.[28] Survival of *C. auris* in the hospital environments may be enhanced by its capacity for salt tolerance and cell aggregation into large and difficult to disperse aggregates. Also the isolates exhibit thermotolerence up to 42°C and do not form biofilms on intravascular catheters that might act as an added advantage for survival and pathogenesis. A draft genome sequence of *C. auris* also revealed that a large percentage of its genes are devoted to central metabolism, a property that is important for adaptation to highly divergent environments.[20,23]

Clinical Manifestations

C. auris has been isolated from multiple infection sites throughout the body and is generally hospital acquired. *C. auris* has been reported to be isolated from clinical conditions including bloodstream infections (Candidaemia), urinary tract infection, otitis, surgical wound infections skin abscesses related to insertion of the catheter, infection of the heart muscle, meningitis,

bone infections, and wound infections (colonization and infection in burns). *C. auris* has also been reported to be isolated from urine and the respiratory tract samples, but it is difficult to differentiate whether these are due to true infections or just colonization.[28,72-74] *C. auris* is mainly hypothesized to predominantly colonize the skin; however, in some rare instances, it has also been isolated from the gut, oral, and oesophageal mucosa of infected individuals. In clinical settings, *C. auris* is seen to be most commonly associated with bloodstream infections.[64] A study pointed out that approximately 5% of candidemia cases in intensive care units (ICUs) in India were caused by *C. auris*.[75] Invasive infections caused by *C. auris* occur more commonly in critically ill patients in ICUs. Similar to the other invasive *Candida* infections, invasive *C. auris* infections are associated with high global mortality rates ranging from 30% to 60%.[28,76,77]

Treatment and Antifungal Resistance

The successful treatment of *C. auris* infection depends highly on its accurate identification. In early stages of infection, the symptoms are non-specific and blood cultures typically remain negative.[78] So the first-line therapy remains an echinocandin, pending specific susceptibility testing, which should be done as soon as possible.[79] However, the antifungal agent of choice will depend on the drug susceptibility report of the organism isolate. One of the important reason that *C. auris* is considered to be a "superbug" and is increasingly becoming an emerging threat to human health is its intrinsic resistance to one or more classes of antifungal agents available.[64,80] Based upon the conservative antifungal agent break points for *C. albicans* and other *Candida* species, most of the isolates of *C. auris* are resistant to fluconazole. One of the subset of *C. auris* isolates has high minimum inhibitory concentrations (MICs) than that of amphotericin B and echinocandin compounds, and some of the *C. auris* strains are resistant to all available classes of antifungal drugs.[25,28] An available comparative study of European Committee on Antimicrobial Susceptibility Testing (EUCAST) and Clinical and Laboratory Standards Institute (CLSI) methods suggested that *C. auris* isolates have a remarkably similar fluconazole resistance but a wide range of MICs for the other antifungal drug classes.[81] Although isolates of *C. auris* that are resistant to fluconazole and amphotericin B are commonly seen, echinocandin-resistant isolates (e.g., caspofungin) are relatively rare.[82] Some clinicians prefer to use >1 antifungal drug to treat these MDR (multidrug resistant) invasive organisms. There is currently no evidence or experience available to support combination therapy in invasive infections with this organism, and clinicians are advised to make decisions on a case-by-case basis. Duration of antifungal treatment is same to that used for infections caused by other *Candida* spp. Treatment for candidemia should be continued for 14 days after documented clearance of *Candida* from the bloodstream and resolution of symptoms attributing to candidemia. The time to clearance of infection after starting treatment is not clear; however, persistent fungemia for up to 3 weeks has been observed by few authors.[23,28] However wherever feasible, an effort should be made to remove indwelling medical devices such as central venous catheters and urinary catheters. If an isolate is found to be resistant to azoles, echinocandins, or amphotericin B, the laboratory should also conduct test for susceptibility to Flucytosine, Nystatin, and Terbinafine. For the treatment of any further MDR strains, a regimen incorporating oral Terbinafine could also be considered.[83]

Infection Prevention and Control

Candida previously has been thought to be a colonizer within the gastrointestinal tract, and later acquired into the hospital environment. The early evidence is suggestive of the organism might be spreading through contact with contaminated environmental surfaces or equipment, or from person to person. The majority of the infected patients might have had a recent exposure to an indwelling medical device or might have undergone some invasive procedures.[28] Infections have been observed from several days to weeks (average 19 days) after hospitalization in susceptible patients, suggesting an exogenous source associated with breach in infection control practices.[74] Apart from direct transmission from fomites (blood pressure cuffs, stethoscopes, and other equipment in contact with the patient), infections can be transmitted indirectly via the contaminated hands of health care workers. Infection due to *C. auris* is usually sporadic and is caused by the genetically distinct, endogenous isolates that are normal colonizers in the patient's skin and mucosal surfaces.[83,84]

Route cause analysis following the London outbreak revealed that the minimum contact period for the transmission of infection with a positive case or a contaminated environment was more than or equals 4 h. The persistence and propagation of fungus in spite of all the infection prevention measures indicate an innate resilience of *C. auris* for survival and persistence in the environment, high transmissibility, and the ability to rapidly colonize the patient's skin and environment.[85]

Wherever possible, the equipment used for infected/colonized patient should not be shared with other patients on the ward unless between-patient cleaning has been assured. Improved adherence to central line-associated bloodstream infection, catheter-associated urinary tract infection care bundles, as well as tracheostomy site care should be strictly followed. All patients colonized or infected with the organism should be preferably isolated in a single room. Strict adherence to standard precautions including hand hygiene using soap and water followed by alcohol hand rub. Use of personal protective equipment (gloves, aprons, and gowns) by healthcare workers should also be encouraged. These should be donned after hand washing and before entering the room and should be removed and

discarded in the room followed by a thorough hand wash and application of alcohol hand rub. Visitors of such patients need to be briefed about the infection and infection prevention and control precaution (IPC). Contact isolation of all patients transferred from other affected hospitals or a hospital abroad until screening results are available. Clinicians and the ancillary health professionals should be trained regarding IPC recommendations.

Although there is limited evidence supporting routine screening for *C. auris* at the time of hospital admission, screening policies can also be designed based on the local risk assessment and prevalence of infections. Nose, throat, groin, urethral, perineal, sputum/endotracheal, drain fluids, wound and cannula entry swabs can be taken for screening if indicated. All screen-positive patients should be isolated. A series of three negative screens taken 24 hours apart is suggested before deisolating the patient.[85]

Colonization of inpatients has been reported from the affected hospitals around the world. Clinical studies till date have shown that the colonization is difficult to eradicate and that it tends to persist making infection prevention and control strategies even more important. Colonized patients could present opportunities for contamination of the health care environment both during admission as well as post discharge follow-ups. For decolonization of skin, patients can be prescribed twice-daily 2% chlorhexidine gluconate-containing wipes or aqueous 4% chlorhexidine formulations.[85] Oral decolonization can be done by using 0.2% chlorhexidine mouthwash or 1% chlorhexidine dental gel in patients on ventilator support. Oral nystatin has been used in oropharyngeal colonization. Chlorhexidine-impregnated protective disks for central vascular catheter exit sites have been used to reduce line- associated *C. auris* bloodstream infections.[73,84,85]

Once the patient has left the environment, a terminal cleaning should also be undertaken either by using 1,000 ppm chlorine- based product or by using hydrogen peroxide vapours. All equipment should be thoroughly cleaned in accordance with manufacturer's instructions, and where relevant returned to the company for cleaning. Particular attention should be paid to cleaning of multiple-use equipment (e.g., blood pressure cuffs, thermometers, computers on wheels, ultrasound machines) from the bed space of an infected/colonized patient.

Candida auris is a notifiable condition. Report any possible or confirmed *C. auris* cases immediately to your facility's infection prevention and control department and follow your facility's process for reporting to public health departments. Consider identifying the species of *Candida* isolates from both sterile and non-sterile sites and conduct antifungal susceptibility. Continue surveillance for at least one month or until there is no evidence of transmission.[70] In India, according to Indian Council of Medical Research (ICMR) advisory; Whenever there is a suspected or confirmed case of *C. auris* infection or *C. auris* colonization in the hospital, the details should be notified to Mycology Reference Laboratory, Department of Medical Microbiology, PGIMER, Chandigarh. The suspected *C. auris* isolates can be sent to labs at PGIMER Chandigarh and/or Vallabhbhai Patel Chest Institute, University of Delhi for identification and characterisation.[86]

CONCLUSION

C. auris is an emerging fungus that poses a serious threat to global health. The organism is difficult to identify using conventional biochemical methods. Thus, accurate identification of this species is important to determine the actual prevalence of this underreported pathogen. Newer methods such as molecular methods and MALDI-TOF can determine it with most accuracy. *C. auris* is commonly multi-drug resistant; because of its reduced susceptibility to azoles; with a few strains even resistant to all these three classes of antifungals. To date, infections with *C. auris* have been largely acquired in hospital settings, and horizontal spread of the pathogen has been demonstrated through the clonality of isolates within a hospital. Therefore, implementation of strict infection prevention and control measures for all positive *C. auris* cases along with the regular audits for compliance should be undertaken.[28,85]

Further research needs to be done to better understand the factors promoting environmental resilience, transmission of infection, development of resistance mechanisms to antifungal drugs/disinfectants, and risk factors contributing to host colonization and infection.

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