REVIEW / DERLEME

DOI: 10.4274/mjima.galenos.2022.2022.28
Mediterr J Infect Microb Antimicrob 2022;11:28
Erişim: http://dx.doi.org/10.4274/mjima.galenos.2022.2022.28

Candida auris: Microbiological Characteristics and Laboratory Diagnosis of the Hidden Pathogen

Candida auris: Gizli Patojenin Mikrobiyolojik Özellikleri ve Laboratuvar Tanısı

Esra YILDIRIM SERVİ[1], Meltem UZUN[2]

[1]*İstanbul University, Institute of Health Sciences, Department of Medical Microbiology; İstanbul Sabahattin Zaim University, Food and Agriculture Research and Application Center, İstanbul, Turkey*
[2]*İstanbul University, İstanbul Faculty of Medicine, Department of Medical Microbiology, İstanbul, Turkey*

Abstract

Candida auris was first isolated in Japan in 2009. It has since been reported in more than 25 countries worldwide. This species, which can cause invasive infections with high mortality rates, is difficult to identify with traditional biochemical methods. *C. auris* can be transmitted among hospitalized patients by colonizing the skin. Resistance to fluconazole and amphotericin B is common in this species, and resistance to echinocandins, which are preferred in the treatment in some countries, is seen to develop. Studies have shown that resistance to antifungals is acquired, not intrinsic, and primary resistance mechanisms against echinocandins and azoles have been identified. This species is difficult to control because of its multidrug resistance, even the emergence of pan-resistant strains, misidentification with conventional methods in clinical microbiology laboratories, and long-term persistence in the hospital environment. In order to prevent infections with infection control measures, advanced laboratory methods that allow accurate diagnosis is needed. In addition, new antifungal agents should be researched and included in practice in order to ensure success in treatment. In this short review, current information about the epidemiology, infections, microbiological features and laboratory diagnosis of *C. auris* is mentioned.
Keywords: *Candida auris*, diagnosis, antifungal drug resistance, *Candida*

Öz

Candida auris ilk olarak 2009 yılında Japonya'da izole edilmiş ve o zamandan bu yana dünya çapında 25'ten fazla ülkede rapor edilmiştir. Yüksek ölüm oranlarına sahip invazif enfeksiyonlara neden olabilen bu türün geleneksel biyokimyasal yöntemler ile tanımlanması zordur. *C. auris* deride kolonize olarak hastanede yatan hastalar arasında bulaşabilir. Bu tür içinde flukonazole ve amfoterisin B'ye direnç yaygındır ve bazı ülkelerde tedavide tercih edilen ekinokandinlere karşı da direncin geliştiği görülmektedir. Yapılan çalışmalarda, antifungallere karşı oluşan direncin intirensek değil kazanılmış olduğu gösterilmiş, ekinokandin ve azollere karşı birincil direnç mekanizmaları belirlenmiştir. Çoğul ilaca dirençli olmaları, hatta pan-rezistan suşların ortaya çıkması, klinik mikrobiyoloji laboratuvarlarında geleneksel yöntemlerle yanlış tanımlanmaları ve hastane ortamında uzun süre kalabilmeleri nedeniyle bu türün kontrol altına alınması zordur. Enfeksiyon kontrol önlemleri ile enfeksiyonların önlenebilmesi için doğru tanı konulabilmesine olanak sağlayan gelişmiş laboratuvar yöntemlerine ihtiyaç vardır. Ayrıca tedavide başarının sağlanması için yeni antifungal ilaçların araştırılması ve uygulamaya dahil edilmesi gerekmektedir. Bu kısa derlemede, *C. auris*'in epidemiyolojisi, oluşturduğu enfeksiyonlar, mikrobiyolojik özellikleri ve laboratuvar tanısı hakkında güncel bilgilere değinilmiştir.
Anahtar Kelimeler: *Candida auris*, tanı, antifungal ilaç direnci, *Candida*

Cite this article as: Yıldırım Servi E, Uzun M. *Candida auris*: Microbiological Characteristics and Laboratory Diagnosis of the Hidden Pathogen. Mediterr J Infect Microb Antimicrob. 2022;11:28.

Address for Correspondence/Yazışma Adresi: Esra YILDIRIM SERVİ MD, İstanbul University, Institute of Health Sciences, Department of Medical Microbiology, İstanbul, Turkey
Phone: +90 555 572 31 94 **E-mail:** esrayildirim.yl@gmail.com **ORCID ID:** orcid.org/0000-0001-5094-5828
Received/Geliş Tarihi: 08.02.2022 **Accepted/Kabul Tarihi:** 25.04.2022

Published: 16 May 2022

Introduction

Invasive fungal infections increase the mortality rate in hospitalized patients with underlying diseases and especially in immunocompromised patients[1-4]. *Candida* spp. is the most frequently isolated species among invasive fungal infections. These yeasts are commensal in healthy humans and can cause systemic infections in case of immunosuppression due to their ability to adapt easily to different hosts. The genus *Candida* includes approximately 500 species, and at least 30 species infect humans. More than 90% of invasive infections are caused by *C. albicans, C. glabrata, C. parapsilosis, C. dubliniensis, C. tropicalis* and *C. krusei*. However, *C. auris*, which has been resistant to multiple drugs in recent years, also poses a threat to public health[5-7]. Studies on the sequencing of the 28S D1/D2 and 18S ITS regions show that *C. auris* belongs to the *Metscnikowiaceae* family. *C. auris* is a member of the CTG lineage, such as *C. albicans, C. tropicalis, C. haemulonii* and *C. lusitaniae* species of the genus *Candida/Clavispora*[8]. *C. auris* was first isolated from the outer eardrum of a patient in Japan in 2009 and was named *C. auris* because of the Latin word "auris" meaning "ear"[9]. After a long process, the second patient was detected in Japan in 2017 and five more *C. auris* strains were isolated in 2018[10,11].

Although initially assumed to be a rare pathogen, less than 10 years after its initial isolation, it has begun to be detected in increasing numbers all over the world. However, since this species is difficult to identify using conventional and biochemical methods, data on its incidence and prevalence are not yet clear[12,13]. This review aimed to provide information about the epidemiology, infections, laboratory diagnosis and antifungal drug sensitivity of *C. auris*.

Epidemiology and Risk Factors

C. auris was first isolated from the ear secretion of a 70-year-old patient in Japan in 2009. However, in a retrospective study of *Candida* strains in South Korea, it was reported that the oldest known *C. auris* strain was isolated from the blood of a child in South Korea in 1996 and was initially misidentified as *C. haemulonii*[8,14,5]. As of August 2016, the CDC began collecting epidemic data in the United States, and seven new patients were registered within the first month. In the latest CDC report, as of 2020, one patient with *C. auris* was reported from Austria, Belgium, Chile, Costa Rica, Egypt, Greece, Italy, Iran, Norway, Poland, Switzerland, Taiwan, Thailand and the United Arab Emirates; while multiple patients with *C. auris* were reported from Australia, Bangladesh, Canada, China, Colombia, France, Germany, India, Israel, Japan, Kenya, Kuwait, Malaysia, Netherlands, Oman, Pakistan, Panama, Russia, Saudi Arabia, Singapore, South Africa, South Korea, Spain, Sudan, the United Kingdom, the United States, and Venezuela. In Turkey, Kurt et al.[16] reported the first *C. auris* isolation from an 81-year-old patient with fungemia, Bölükbaşı et al.[17] reported the first *C. auris* isolation from a Coronavirus disease-2019 positive patient, and Kömeç et al.[18] reported three patients with *C. auris* in another study.

In genome analysis studies to determine the clonal link between *C. auris* strains in epidemic and sporadic patients, it has been observed that the strains are clonally close but have slight differences from each other, and therefore the emergence of *C. auris* is independent and each one spreads locally[19].

Based on the genomic information and the regions where the first strains were isolated, four main clades of *C. auris* were identified as South Asia (I), East Asia (II), South Africa (III), and South America (IV). There are very few single nucleotide polymorphisms (SNPs) in each segment. Recently, a new *C. auris* line (Clade V) has been reported in Iran and this clade differs from the others by more than 200 000 SNPs. Whole genome sequencing (WGS) analyzes revealed that the first four genetically distinct clades of *C. auris* appear independently and almost simultaneously in different regions on three continents[8,20]. While the East Asian clade is seen to infect only the ear, other clades are known to cause invasive infections, hospital-acquired infections and epidemics[20].

Although *C. auris* is closely related to other *Candida* species in nature, its isolation from environmental sources has not been found. In a study conducted in the Netherlands, it was reported that *C. auris* was isolated from swimming pools, but it was reported that this situation was caused by pool visitors. On the other hand, some studies have suggested that the emergence of *C. auris* may have resulted from climate change, especially global warming, and that wetlands may have natural ecological niches due to their resistance to high temperature and salt concentration[8,20].

The risk factors for infections due to *C. auris* are generally similar to those of infections with the genus *Candida*. Suppression of the immune system, use of broad-spectrum antibiotics and antifungal drugs, presence of important medical comorbidities (diabetes mellitus, lung disease, cardiovascular disease, chronic kidney disease, presence of malignancy), presence of central venous catheter/urinary catheter/post-operative drain, parenteral nutrition, bacteremia, candiduria, chemotherapy, blood transfusions, hemodialysis, bone marrow suppression, prolonged stay in the intensive care unit are among these risk factors[21-25]. Intensive care patients, premature newborns and elderly patients are risky groups. Candidemias due to *C. auris* typically occur several weeks after hospitalization. Mortality rates due to infection range from 30% to 72%. Variability in mortality rates depends on the extent of infection, age and

age-related risk factors, and various factors such as comorbid conditions. Studies have shown that the increase in *C. auris* colonization or infection is associated with diarrhea and the use of tetracycline, a broad-spectrum antibiotic, and the use of minocycline and tigecycline, which are second-generation tetracycline derivatives, and that infections are more common in males[8,24,26].

Its Virulence Factors and Infections it Causes

C. auris has many virulence features similar to *C. albicans*. Pathways involved in enzyme secretion, nutrient uptake, siderophore-based iron uptake, tissue invasion, the bicomponent histidine kinase system, and cell wall modeling are some of these similarities. Virulence factors may vary depending on the strain. Studies have shown that different *C. auris* strains secrete different levels of phospholipase and proteinase, can evade the attack of neutrophils and innate immunity, and have a lower ability to stimulate cytokine release and phagocytosis compared to *C. albicans*. Although it can form a biofilm that allows it to adhere to various surfaces, this feature varies depending on the strain. Due to the rarity of pseudohyphae formation, its ability to form biofilms and adhere to tissue is less than *C. albicans*. *C. auris* is divided into two groups according to its aggregation feature. As a result of the inability of the daughter cells to separate from the mother cell after budding, a large cell aggregation occurs, which is difficult to break down with disinfectants. Non-clustered strains have been shown to be more pathogenic than aggregates and *C. albicans*. Aggregation, thermotolerance and osmotolerance are the properties of *C. auris* that contribute to its longevity and viability on biotic and abiotic surfaces. Its persistence on surfaces is important because it is one of the factors leading to in-hospital contamination[8,25].

The clinic of *C. auris* infections is similar to that of other *Candida* infections. *C. auris* is isolated from body parts such as nose, pharynx, lung, pleural cavity, heart, liver, abdominal cavity, ear, vagina, armpit, bone, groin, brain, and clinical specimens such as blood, sputum, feces, urine, surgical tissue. Studies have shown that strains isolated from the genitourinary system, skin, soft tissue and lungs are the representatives of the colonized group rather than the actual infection[12,27-30].

Complications of invasive *C. auris* infections vary depending on the extent of infection, host comorbidities, and resistance patterns[25]. *C. auris* can cause fungemia, myocarditis, vulvovaginitis, urinary tract infection, surgical wound infections, burn infections, skin abscesses, malignant otitis, meningitis, complicated intra-abdominal infections, pericarditis and bone infections[15,31-33].

C. auris, which most commonly causes fungemia, spreads to different organs by hematogenous route and causes multi-organ dysfunction. On the contrary, dissemination of a localized infection causes multi-organ system failure and death[25].

C. auris can be easily transmitted from person to person. Patients colonized with this strain are a source of contamination for other patients. Colonization occurs a few hours to several days after contact with the microorganism, while invasive infection occurs within days or months after colonization. Colonization with *C. auris* can continue for months or even indefinitely. Therefore, identifying asymptomatic colonized patients is very important in terms of taking additional precautions during surgical interventions in these patients[34-36]. *C. auris* can also be spread from infected or colonized patients by contact with contaminated surfaces. Studies have shown that *C. auris* is isolated from patient rooms, corridors outside patient rooms, chairs, beds, windowsills, benches, electrocardiogram cables, infusion pumps and ventilators. Common patient equipment such as thermometer, sphygmomanometer and oximeter also act as a reservoir for *C. auris*. It has been shown that the persistence of *C. auris* on moist and dry surfaces is between seven days and four weeks[37-39]. In hospitals, patients colonized by or infected with *C. auris* should be placed in single rooms. If single rooms are not available, cohorts should be performed. Disposable equipment should be used. Disinfection of contacted areas and surfaces should be done using both detergent and disinfectant. Substances with sporicidal properties (peracetic acid or hydrogen peroxide) should be used for disinfection. In addition, disinfection techniques that do not require contact, such as UV and hydrogen peroxide vapor, are also suitable. Patient rooms should be disinfected at least once a day. Healthcare workers who come into contact with the patient should provide appropriate hand hygiene. Routine screening of healthcare workers and the environment for *C. auris* is not recommended. However, based on epidemiological evidence, screening may be considered in cases where there is a relationship between health workers and the environment with transmission or where transmission is detected despite recommended precautions[24]. For this reason, it is of great importance to take the necessary precautions to prevent transmission.

Identification

C. auris is phylogenetically closely related to *C. krusei*, *C. haemulonii* and *C. lusitaniae*[40]. It is a haploid yeast. The genome size ranges between 12.1 and 12.7 Mb and it has seven chromosomes. Based on genomic and RNA sequencing information, it is estimated to have approximately 5,500 genes[8,20].

They can be seen singly, in pairs or in groups in microscopic examination and reproduce by budding like other species. It is oval shaped and 2.5-5.0 µm in size. The germ tube test is negative and does not produce pseudohyphae. However, pseudohyphae

can form in environments with high salt concentrations and in the case of heat shock protein depletion, suggesting that this morphological change may also occur under stress conditions[8,41]. While they grow as smooth-edged, white/cream colonies on sabouraud dextrose agar, they form beige, pink, pale rose or pale purple colored colonies on commercial chromogenic media including CHROMagar *Candida*, BBL CHROMagar *Candida*, CAN2 chromogenic, *Candida* ID and Brilliance *Candida* agar (Figure 1)[37,42]. Chromogenic agars are not used for primary identification, but can help differentiate *C. auris* strains, especially from mixed cultures[24]. *C. auris* grows well at 38 °C or 42 °C and its growth is inhibited in the presence of 0.01% or 0.1% cycloheximide[43].

The carbohydrate assimilation characteristics of *C. auris* are shown in Table 1[44].

C. auris cannot be identified phenotypically accurately with automated systems such as API 20C (bioMerieux, France), API ID 32C (bioMerieux, France), API *Candida* (bioMerieux, France) BD Phoenix (Becton, Dickinson and Company, USA), Microscan (Beckman Coulter, USA), RapID Yeast Plus (Remel, USA) and Vitek-2 YST ID (bioMerieux, France) as with conventional methods, and it is misidentified as *C. haemulonii*, *C. sake, C. famata*, *C. catenulata, Saccharomyces kluyveri* and *Rhodotorula mucilaginosa* (Table 2)[45-47].

Another method, matrix-assisted laser desorption ionization-time of flight mass spectro-metry (MALDI-TOF MS), is a fast and reliable method for the identification of *C. auris* from pure culture. *C. auris* strains can be identified at species level with 100% sensitivity and specificity using updated commercial MALDI-TOF MS database libraries. However, if the databases used are not sufficient for reliable identification, the result should be verified with other identification methods[13,24].

Molecular methods based on the sequencing of the D1-D2 region of 28S rDNA and the internally transcribed spacergen gene regions allow the accurate identification of *C. auris* and the establishment of its phylogenetic structure. Since DNA sequencing methods, which are time-consuming and expensive, cannot be found in all diagnostic laboratories, their applicability has been limited to developed countries. Polymerase chain reaction (PCR)-based methods have been developed to overcome this limitation. Polymerase chain reaction-based methods are generally divided into three groups. Methods in the first group are based on end-point PCR and range from a single PCR specific to *C. auris* only to multiplex PCR, which simultaneously identifies closely related and unrelated species. Since applications in this group require less equipment, their applicability is more possible in developing countries[49]. The second group is based on real-time PCR, which can only detect *C. auris* or species closely related to *C. auris*[50,51]. These methods are highly sensitive and advantageous as some can detect directly from clinical and environmental samples. However, its use is limited in countries with limited resources due to its high cost and requiring more equipment. The third group includes methods based on other technologies such as PCR-RFLP, loop-mediated isothermal amplification and T2 magnetic resonance system[42,52].

Methods such as amplified fragment length polymorphism analysis, multilocus sequence typing and variable area gel electrophoresis (pulsed-field gel electrophoresis) give successful results in distinguishing epidemic strains. However, WGS has a superior distinguishing feature between species. It is also preferred for simultaneous identification and genotyping of strains. While the WGS method gives results in a short time like 8-72 hours compared to other typing methods, it requires bioinformatics expertise and is more costly for laboratories[24].

Resistance to Antifungal Drugs

Liquid microdilution, E-test or VITEK2 methods are mostly used to determine the sensitivity of *C. auris* to antifungal drugs in clinical microbiology laboratories. While these methods are standard, they have some limitations such as the application steps are time consuming and at least 24 hours are required to read the results. However, the developed molecular methods allow accurate and rapid detection of antifungal susceptibility results[53].

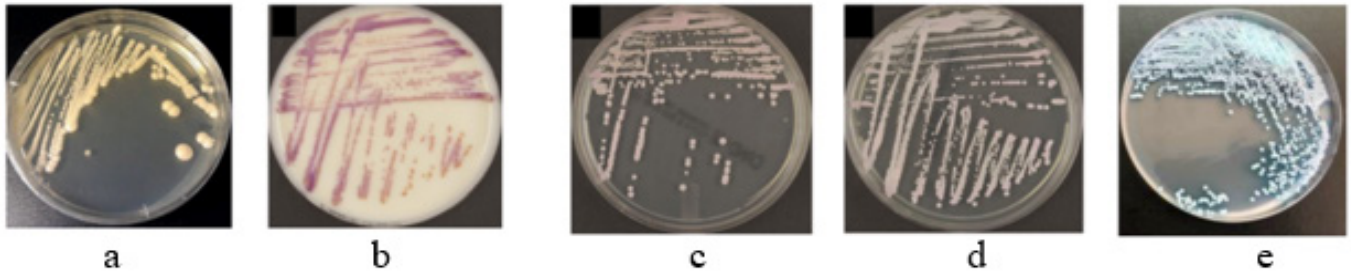

Figure 1. Colony morphologies of *C. auris* on different media; A) Saboraud dextrose agar (white-cream colony), B) Brilliance™ *Candida* agar (beige-pink colony), C) CHROMagar™ *Candida* (pale pink colony), D) CHROMID® *Candida* agar (pale pink colony), E) CHROMagar™ *Candida* Plus (blue colony)[37]

Table 1. Carbohydrate assimilation characteristics of *C. auris*[44]

Glucose	+	D-mannitol	+	L-sorbose	-
Sucrose	+	Sorbitol	+	D-cellobiose	-
Maltose	+	Citrate	+	D-glucosamine	-
D-trehalose	+	Inulin	+	D-xylose	-
D-raffinose	+	Ribitol	+/-	DL-arabinose	-
D-hybridosis	+	NAG	-	Ribose	-
Soluble starch	+	Lactose	-	L-rhamnose	-
Galactitol	-	D-galactose	-	Melibiosis	-
Methanol	-	Ethanol	-	Glycerol	-
α-methyl-D-glucoside	-	Erythritol	-	Salicin	-
D-gluconate	-	DL-lactate	-	Succinate	-
2-keto-D-gluconate		Hexadecane		Xylitol	

Table 2. Results of *C. auris* in automated systems[48]

Identification method	Incorrect identification result
Vitek-2 YST ID	*Candida haemulonii*
	Candida duobushaemulonii
API 20C	*Rhodotorula glutinis*
	Candida sake
API Candida	*Candida famata*
API ID 32C	*Candida sake*
	Saccharomyces kluyveri
BD Phoenix	*Candida haemulonii*
	Candida catenulata
Microscan	*Candida famata*
	Candida guilliermondii
	Candida lusitaniae
	Candida parapsilosis
	Candida tropicalis
RapID Yeast Plus	*Candida parapsilosis*

To date, no clinical threshold has been defined for *C. auris* in reference antifungal susceptibility testing methods. However, epidemiological threshold values have been proposed tentatively in some publications. In the studies performed, the limit values for fluconazole, voriconazole, flucytosine, amphotericin B, anidulafungin, micafungin and caspofungin were 32 mg/L, 2 mg/L, 128 mg/L, 2 mg/L, 4 mg/ L, 4 mg/L, and 2 mg/L[12,40]. Minimum inhibitory concentration (MIC) values determined for amphotericin B and caspofungin in VITEK2 YST AST and E-test method differ when compared to Clinical and Laboratory Standards Institute Standards. The MIC values determined by these methods need to be verified using the reference method[24].

One of the reasons why the emergence of *C. auris* is of such concern is that this strain is resistant to or has the potential to develop resistance to multiple antifungal drugs[54]. It has been reported that the sensitivity of *C. auris* to azole group antifungal agents, including voriconazole, posaconazole, itraconazole and isavuconazole, is decreased[40,54-57]. The widespread prevalence of reduced sensitivity to azole drugs is extremely worrying. Because azoles are the mainstay in the treatment of *Candida* infections. As a result of the studies, the idea has appeared about fluconazole resistance is acquired resistance[19]. Although it is known that resistance to fluconazole in *C. auris* is caused by mutations in ERG11, different mechanisms have been described that contribute to the formation of resistance. In addition, *C. auris* strains also show a variable susceptibility profile to amphotericin B. Concerns about developing resistance to azoles and amphotericin B led to the recommendation to use echinocandins as first-line therapy. However, the detection of high MIC values for one or more echinocandins in studies with *C. auris* strains was found to be alarming[58,59].

Whole genome sequencing studies have shown that *C. auris* possesses both ATP-binding cassette and major facilitator superfamily proteins. These proteins have a very similar homologue to MDR1 and CDR1/CDR2, as well as CDR4 and two SNQ2 homologs. Mutations in Hotspot1 S639 in FKS1 are responsible for echinocandin resistance. In addition, two different regions, called S639P and S639F, have been identified in *C. auris*. These regions cause a 4- to 8-fold increase in the MIC value of echinocandins. The molecular mechanism of resistance to amphotericin B has not been clarified yet[60,61]. In addition, mutations of F126T in the South African clade, Y132F in the South American clade, and Y132F and K143R mutations in the South Asian clade caused azole resistance. In addition, Y132F and K143R mutations were found to increase resistance to fluconazole[20].

The problem of resistance to antifungals has revealed the need to find new drugs that can be effective in treatment. Currently, there are publications on four new antifungal drugs whose efficacy against *C. auris* has been determined. The first of these drugs is ibrexafungerp (formerly SCY-078 or MK-3118). Ibrexafungerp is a triterpenoid antifungal drug that acts fungicidally by inhibiting 1,3-ß-D-glucan synthase, an important component of the fungal cell wall, similar to echinocandins. It shows broad-spectrum in vitro activity against various *Candida* species, including *C. auris* strains with the FKS mutation. It is also the first oral drug that is not included in the azole group in the treatment of vaginal candidiasis[62-64]. Another newly developed drug is rezafungin. Rezafungin (formerly CD101) is a new β-glucan synthase inhibitor chemically related to anidulafungin. Phase 3 clinical trials of the drug have been initiated. It has a low MIC for some echinocandin-resistant *C. auris* strains and a long half-life that allows once-weekly dosing[65]. Manogepix (APX0011A), on the other hand, is another broad-spectrum antifungal that inhibits a protein that plays an important role in fungal cell wall integrity, such as Gwt1p, and has been found to be effective against multi-drug resistant *C. auris* strains[66]. VT-1598 is a tetra-azole inhibitor of Cyp51, just like tri-azole-based Cyp51 inhibitors, they inhibit the conversion from lanosterol to ergosterol, disrupting the pathway of ergosterol biosynthesis. Due to its unique chemical structure, this antifungal agent is more specific to Cyp51 in the fungal cell compared to mammalian cytochrome P450 enzymes. In this way, drug-drug interactions that may be clinically important for triazoles such as fluconazole, voriconazole, posaconazole and isavuconazole can be avoided[67].

Conclusion

C. auris infections have high morbidity and mortality worldwide. Accurate and timely identification of the agent in clinical microbiology laboratories is critical for effective treatment and prevention of infection. In order to control the spread of *C. auris*, it is necessary to understand its epidemiology and to pay attention to infection control methods to minimize transmission between patients. The emergence of pan-resistant strains after multidrug-resistant strains is a signal to worry about the agent. For this reason, it is of great importance to investigate the effects of natural compounds, semi-synthetic and synthetic compounds, nanoparticles, and peptides with reported antifungal activities on *C. auris*, in terms of increasing treatment options.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: E.Y.S., M.U., Design: E.Y.S., M.U., Data Collection or Processing: E.Y.S., M.U., Analysis or Interpretation: E.Y.S., M.U., Literature Search: E.Y.S., M.U., Writing: E.Y.S.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Alangaden GJ. Nosocomial fungal infections: epidemiology, infection control, and prevention, Infect Dis Clin Nort Am. 2011;25:201-25.
2. Colombo AL, Guimarães T, Sukienik T, Pasqualotto AC, Andreotti R, Queiroz-Telles F, Nouér SA, Nucci M. Prognostic factors and historical trends in the epidemiology of candidemia in critically ill patients: an analysis of five multicenter studies sequentially conducted over a 9-year period. Intensive Care Med. 2014; 40:1489-98.
3. Giacomazzi J, Baethgen L, Carneiro LC, Millington MA, Denning DW, Colombo AL, Pasqualotto AC; Association With The LIFE Program. The burden of serious human fungal infections in Brazil. Mycoses. 2016;59:145-50.
4. de Cássia Orlandi Sardi J, Silva DR, Soares Mendes-Giannini MJ, Rosalen PL. *Candida auris*: Epidemiology, risk factors, virulence, resistance, and therapeutic options. Microbial Pathog. 2018;125:116-21.
5. Daniel HM, Lachance MA, Kurtzman CP. On the reclassification of species assigned to *Candida* and other anamorphic ascomycetous yeast genera based onphylogenetic circumscription. Antonie Van Leeuwenhoek. 2014;106:67-84
6. Brandt ME, Lockhart SR. Recent taxonomic developments with *Candida* and other opportunistic yeasts. Curr Fungal Infect Rep. 2012;6:170-7.
7. Silva S, Negri M, Henriques M, Oliveira R, Williams DW, Azeredo J. *Candida glabrata*. *Candida parapsilosis* and *Candida tropicalis*: biology, epidemiology, pathogenicity and antifungal resistance. FEMS Microbiol. 2012;36:288-305.
8. Du H, Bing J, Hu T, Ennis CL, Nobile CJ, Huang G. *Candida auris*: Epidemiology, biology, antifungal resistance, and virulence. PLoS pathog. 2020;16:e1008921.
9. Satoh K, Makimura K, Hasumi Y, Nishiyama Y, Uchida K, Yamaguchi H. *Candida auris* sp. nov., a novel ascomycetous yeast isolated from the external ear canal of an inpatient in a Japanese hospital. Microbiol Immunol. 2009;53:41-4.
10. Iguchi S, Mizushima R, Kamada K, Itakura Y, Yoshida A, Uzawa Y, Arai Y, Umeyama T, Miyazaki Y, Sekizuka T, Kuroda M, Makimura K, Kikuchi K. 2051. Detection of *Candida auris* Among Previously Unidentified Yeasts Isolated from Ear Discharge Specimens in Japan. In Open Forum Infect Dis. 2018;5(Suppl 1):598-9.
11. Iguchi S, Mizushima R, Kamada K, Itakura Y, Yoshida A, Uzawa Y, Arai Y, Takaoka M, Sato S, Goto A, Karasawa T, Tsuruoka N, Totsuka D, Ono E, Nonaka M, Makimura K, Kikuchi K. The second *Candida auris* isolate from aural discharge in Japan. Jpn J Infect Dis. 2018;71:174-5.
12. Sarma S, Upadhyay S. Current perspective on emergence, diagnosis and drug resistance in *Candida auris*. Infect Drug Resist. 2017;10:155-65.
13. Mizusawa M, Miller H, Green R, Lee R, Durante M, Perkins R, Hewitt C, Simner PJ, Carroll KC, Hayden RT, Zhang SX. Can multidrug-resistant *Candida auris* be reliably identified in clinical microbiology laboratories? J Clin Microbiol. 2017;55:638-40.
14. CDC. Centers for Disease control and Prevention. Recommendations for identification of *Candida auris*. Last Accessed Date: 12 November 2018. Available from: https://www.cdc.gov/fungal/candida-auris/recommendations.html
15. Lee WG, Shin JH, Uh Y, Kang MG, Kim SH, Park KH, Jang HC. First three reported cases of nosocomial fungemia caused by *Candida auris*. J Clin Microbiol. 2011;49:3139-42.

16. Kurt AF, Kuskucu MA, Balkan II, Baris A, Yazgan Z, Serife Oz A, Tosun AI, Mete B, Tabak F, Aygun G. *Candida auris* Fungemia and a local spread taken under control with infection control measures: First report from Turkey. Indian J Med Microbiol. 2021;39:228-30.

17. Bölükbaşı Y, Erköse Genç G, Orhun G, Kuşkucu MA, Çağatay A, Önel M, Öngen B, Ağaçfidan A, Esen F, Erturan Z. First Case of COVID-19 Positive *Candida auris* Fungemia in Turkey. Mikrobiyol Bul. 2021;55:648-55.

18. Kömeç S, Karabıçak N, Ceylan AN, Gülmez A, Özalp O. Three *Candida auris* Case Reports from Istanbul, Turkey. Mikrobiyol Bul. 2021;55:452-60.

19. Lockhart SR, Berkow EL, Chow N, Welsh RM. *Candida auris* for the clinical microbiology laboratory: not your grandfather's *Candida* species. Clin Microbiol Newsl. 2017;39:99-103.

20. Rhodes J, Fisher MC. Global epidemiology of emerging *Candida auris*. Curr Opin Microbiol. 2019;52:84-9.

21. CDC. Clinical Alert to U.S.. Healthcare facilities, June 2016, fungal diseases, 2017. Last Accessed Date: December 9, 2017. Available from: https://www.cdc.gov/fungal/diseases/ candidiasis/candida-auris-alert.html

22. Azar MM, Turbett SE, Fishman JA, Pierce VM. Donor-derived transmission of *Candida auris* during lung transplantation. Clin Infect Dis. 2017;65:1040-2.

23. Snyder GM, Wright SB. The epidemiology and prevention of *Candida auris*. Curr Infec Dis Rep. 2019;21:19.

24. Ong CW, Chen SC, Clark JE, Halliday CL, Kidd SE, Marriott DJ, Marshall CL, Morris AJ, Morrissey CO, Roy R, Slavin MA, Stewardson AJ, Worth LJ, Heath CH; Australian and New Zealand Mycoses Interest Group (ANZMIG); and the Healthcare Infection Control Special Interest Group (HICSIG); both of the Australasian Society for Infectious Diseases (ASID). Diagnosis, management and prevention of *Candida auris* in hospitals: position statement of the Australasian Society for Infectious Diseases. Intern Med J. 2019;49:1229-43.

25. Sikora A, Zahra F. *Candida auris*. [Updated 2021 Sep 10]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; Last Accessed Date: Jan 2021. Available from: https://www.ncbi.nlm.nih.gov /books/NBK563297/

26. Jeffery-Smith A, Taori SK, Schelenz S, Jeffery K, Johnson EM, Borman A; *Candida auris* Incident Management Team, Manuel R, Brown CS. *Candida auris*: a review of the literature. Clin Microbiol Rev. 2018;31:e00029-17.

27. Bradley SF. *Candida auris* Infection. JAMA. 2019;322:1526.

28. Lone SA, Ahmad A. *Candida auris*-the growing menace to global health. Mycoses. 2019;62:620-37

29. Cortegiani A, Misseri G, Fasciana T, Giammanco A, Giarratano A, Chowdhary A. Epidemiology, clinical characteristics, resistance, and treatment of infections by *Candida auris*. J Intensive Care. 2018;6:69.

30. Jung J, Kim MJ, Kim JY, Lee JY, Kwak SH, Hong MJ, Chong YP, Lee SO, Choi SH, Kim YS, Woo JH, Kang WS, Chung JW, Kim MN, Kim SH. *Candida auris* colonization or infection of the ear: A single-center study in South Korea from 2016 to 2018. Med Mycol. 2020;58:124-7.

31. Ruiz Gaitán AC, Moret A, López Hontangas JL, Molina JM, Aleixandre López AI, Cabezas AH, Mollar Maseres J, Arcas RC, Gómez Ruiz MD, Chiveli MÁ, Cantón E, Pemán J. Nosocomial fungemia by *Candida auris*: first four reported cases in continental Europe. Rev Iberoam Micol. 2017;34:23-7.

32. Dahiya S, Chhillar AK, Sharma N, Choudhary P, Punia A, Balhara M, Kaushik K, Parmar VS. *Candida auris* and Nosocomial Infection. Curr Drug Targets. 2020;21:365-73.

33. Uppuluri P. *Candida auris* Biofilm Colonization on Skin Niche Conditions. mSphere. 2020;5:e00972-19.

34. Biswal M, Rudramurthy SM, Jain N, Shamanth AS, Sharma D, Jain K, Yaddanapudi LN, Chakrabarti A. Controlling a possible outbreak of *Candida auris* infection: lessons learnt from multiple interventions. J Hosp Infect. 2017;97:363-70.

35. Horton MV, Johnson CJ, Kernien JF, Patel TD, Lam BC, Cheong JZA, Meudt JJ, Shanmuganayagam D, Kalan LR, Nett JE. *Candida auris* Forms High-Burden Biofilms in Skin Niche Conditions and on Porcine Skin. mSphere. 2020;5:e00910.

36. Spivak ES, Hanson KE. *Candida auris*: an Emerging Fungal Pathogen. J Clin Microbiol. 2018;56:e01588-17.

37. Keighley C, Garnham K, Harch SAJ, Robertson M, Chaw K, Teng JC, Chen SC. *Candida auris*: Diagnostic Challenges and Emerging Opportunities for the Clinical Microbiology Laboratory. Curr Fungal Infect Rep. 2021:1-11.

38. Kumar J, Eilertson B, Cadnum JL, Whitlow CS, Jencson AL, Safdar N, Krein SL, Tanner WD, Mayer J, Samore MH, Donskey CJ. Environmental Contamination with *Candida* Species in Multiple Hospitals Including a Tertiary Care Hospital with a *Candida auris* Outbreak. Pathog Immun. 2019;4:260-70.

39. Cortegiani A, Misseri G, Giarratano A, Bassetti M, Eyre D. The global challenge of *Candida auris* in the intensive care unit. Crit Care. 2019;23:150.

40. Lockhart SR, Etienne KA, Vallabhaneni S, Farooqi J, Chowdhary A, Govender NP, Colombo AL, Calvo B, Cuomo CA, Desjardins CA, Berkow EL, Castanheira M, Magobo RE, Jabeen K, Asghar RJ, Meis JF, Jackson B, Chiller T, Litvintseva AP. Simultaneous emergence of multidrug-resistant *Candida auris* on 3 continents confirmed by whole-genome sequencing and epidemiological analyses. Clin Infect Dis. 2017;64:134-40.

41. Bidaud AL, Chowdhary A, Dannaoui E. *Candida auris*: an emerging drug resistant yeast - A mini-review. J Mycol Med. 2018;28:568-73.

42. Mahmoudi S, Agha Kuchak Afshari S, Aghaei Gharehbolagh S, Mirhendi H, Makimura K. Methods for identification of *Candida auris*, the yeast of global public health concern: A review. J Mycol Med. 2019;29:174-9.

43. Kathuria S, Singh PK, Sharma C, Prakash A, Masih A, Kumar A, Meis JF, Chowdhary A. Multidrug-Resistant *Candida auris* Misidentified as *Candida haemulonii*: Characterization by Matrix-Assisted Laser Desorption Ionization-Time of Flight Mass Spectrometry and DNA Sequencing and Its Antifungal Susceptibility Profile Variability by Vitek 2, CLSI Broth Microdilution, and Etest Method. J Clin Microbiol. 2015;53:1823-30.

44. Gülmez D. *Candida auris*: The Fungal Pathogen That Managed to Spread Around the World in a Decade. FLORA. 2019;24:263-71.

45. Tsay S, Kallen A, Jackson BR, Chiller TM, Vallabhaneni S. Approach to the investigation and management of patients with *Candida auris*, an emerging multidrug-resistant yeast. Clin Infect Dis. 2018;66:306-11.

46. Lu PL, Liu WL, Lo HJ, Wang FD, Ko WC, Hsueh PR, Ho MW, Liu CE, Chen YH, Chen YC, Chuang YC, Chang SC. Are we ready for the global emergence of multidrug-resistant *Candida auris* in Taiwan? J Formos Med. 2018;117:462-70.

47. Saris K, Meis JF, Voss A. *Candida auris*. Curr Opin Infect Dis. 2018;31:334-40.

48. Iguchi S, Itakura Y, Yoshida A, Kamada K, Mizushima R, Arai Y, Uzawa Y, Kikuchi K. *Candida auris*: a pathogen difficult to identify, treat, and eradicate and its characteristics in Japanese strains. J Infect Chemother. 2019;25:743-9.

49. Ruiz-Gaitán AC, Fernández-Pereira J, Valentin E, Tormo-Mas MA, Eraso E, Pemán J, de Groot PWJ. Molecular identification of *Candida auris* by PCR amplification of species-specific GPI protein-encoding genes. Int J Med Microbiol. 2018;308:812-8.

50. Asadzadeh M, Ahmad S, Al-Sweih N, Khan Z. Rapid and Accurate Identification of *Candida albicans* and *Candida dubliniensis* by Real-Time PCR and Melting Curve Analysis. Med Princ Pract. 2018;27:543-8.

51. Leach L, Zhu Y, Chaturvedi S. Development and Validation of a Real-Time PCR Assay for Rapid Detection of *Candida auris* from Surveillance Samples. J Clin Microbiol. 2018;56:e01223-17.

52. Yamamoto M, Alshahni MM, Tamura T, Satoh K, Iguchi S, Kikuchi K, Mimaki M, Makimura K. Rapid Detection of *Candida auris* Based on Loop-Mediated Isothermal Amplification (LAMP). J Clin Microbiol. 2018;56:e00591-18.

53. Hou X, Lee A, Jiménez-Ortigosa C, Kordalewska M, Perlin DS, Zhao Y. Rapid detection of ERG11-associated azole resistance and FKS-associated echinocandin resistance in *Candida auris*. Antimicrob Agents Chemother. 2019;63:e01811-8.

54. Chowdhary A, Anil Kumar V, Sharma C, Prakash A, Agarwal K, Babu R, Dinesh KR, Karim S, Singh SK, Hagen F, Meis JF. Multidrug-resistant endemic clonal strain of *Candida auris* in India. Eur J Clin Microbiol Infect Dis. 2014;33:919-26.

55. Arendrup MC, Prakash A, Meletiadis J, Sharma C, Chowdhary A. Comparison of EUCAST and CLSI reference microdilution MICs of eight antifungal compounds for *Candida auris* and associated tentative epidemiological cutoff values. Antimicrob Agents Chemother. 2017;61:e00485-17.

56. Ben-Ami R, Berman J, Novikov A, Bash E, Shachor-Meyouhas Y, Zakin S, Maor Y, Tarabia J, Schechner V, Adler A, Finn T. Multidrug-resistant *Candida haemulonii* and *C. auris*, Tel Aviv, Israel. Emerg Infect Dis. 2017;23:195-203.

57. Ruiz-Gaitán AC, Cantón E, Fernández-Rivero ME, Ramírez P, Pemán J. Outbreak of *Candida auris* in Spain: a comparison of antifungal activity by three methods with published data. Int J Antimicrob Agents. 2019;53:541-6.

58. Kordalewska M, Perlin DS. Molecular diagnostics in the times of surveillance for *Candida auris*. J Fungi (Basel). 2019;5:77.

59. Rudramurthy SM, Chakrabarti A, Paul RA, Sood P, Kaur H, Capoor MR, Kindo AJ, Marak RSK, Arora A, Sardana R, Das S, Chhina D, Patel A, Xess I, Tarai B, Singh P, Ghosh A. *Candida auris* candidaemia in Indian ICUs: analysis of risk factors. J Antimicrob Chemother. 2017;72:1794-801.

60. Vatanshenassan M, Boekhout T, Meis JF, Berman J, Chowdhary A, Ben-Ami R, Sparbier K, Kostrzewa M. *Candida auris* identification and rapid antifungal susceptibility testing against echinocandins by MALDI-TOF MS. Front Cell Infect Microbiol. 2019;9:20.

61. Lockhart SR. *Candida auris* and multidrug resistance: Defining the new normal. Fungal Genet Biol. 2019;131:103243.

62. Jallow S, Govender NP. Ibrexafungerp: A First-in-Class Oral Triterpenoid Glucan Synthase Inhibitor. J Fungi (Basel). 2021;7:163.

63. Gamal A, Chu S, McCormick TS, Borroto-Esoda K, Angulo D, Ghannoum MA. Ibrexafungerp, a Novel Oral Triterpenoid Antifungal in Development: Overview of Antifungal Activity Against *Candida glabrata*. Front Cell Infect Microbiol. 2021;11:642358.

64. Ghannoum M, Arendrup MC, Chaturvedi VP, Lockhart SR, McCormick TS, Chaturvedi S, Berkow EL, Juneja D, Tarai B, Azie N, Angulo D, Walsh TJ. Ibrexafungerp: a novel oral triterpenoid antifungal in development for the treatment of *Candida auris* infections. Antibiotics (Basel). 2020;9:539.

65. Ham YY, Lewis JS, Thompson GR. Rezafungin: a novel antifungal for the treatment of invasive candidiasis. Future Microbiol. 2021;16:27-36.

66. Arendrup MC, Chowdhary A, Jørgensen KM, Meletiadis J. Manogepix (APX001A) In Vitro Activity against *Candida auris*: Head-to-Head Comparison of EUCAST and CLSI MICs. Antimicrob Agents Chemother. 2020;64:e00656-20.

67. Wiederhold NP, Patterson HP, Tran BH, Yates CM, Schotzinger RJ, Garvey EP. Fungal-specific Cyp51 inhibitor VT-1598 demonstrates in vitro activity against *Candida* and Cryptococcus species, endemic fungi, including Coccidioides species, Aspergillus species and Rhizopus arrhizus. J Antimicrob Chemother. 2018;73:404-8.