**Candida auris** as a pathogen that can cause emerging infectious disease: a literature review

Ni Nyoman Nami Arthisari¹, Ni Nyoman Sri Budayanti², Ni Made Adi Tarini²

**INTRODUCTION**

The emerging fungal pathogen *Candida auris* is causing outbreaks of invasive disease in healthcare facilities around the world. *C. auris* can be multi-resistant to various antifungal classes commonly used to treat other Candida infections. Infection by *C. auris* ranges in severity from mild, localized infection (such as vaginitis) to invasive infection, namely candidemia. The incidence of candidemia is increasing worldwide, and *Candida* sp. is now recognized as a fourth cause of bloodstream infections, especially in the intensive care unit (ICU).¹ The Centers for Disease Control and Prevention (CDC) has paid particular attention to infections caused by *C. auris* for several reasons, namely *C. auris* is a species that is multi-resistant to various types of antifungals, difficult to identify by laboratories with standard methods, can cause outbreaks at the hospital quickly.²³ Furthermore, candidemia invasive fungal infection caused by *C. auris* is associated with high mortality and morbidity rates, with 15-35% mortality in adults and 10-15% in neonates. In addition, *C. auris* can colonize patients without signs of infection and survive in the environment around health facilities and medical equipment, thereby contributing to hospital outbreaks.¹²⁴

Identification methods for Candida fungi generally consist of phenotypic, serological, and molecular identification methods. Various studies mention phenotypic and biochemical identification methods, both conventional and automatic, for identifying *C. auris*. Misidentification often occurs with the species complex *Candida haemulonii*, *Candida famata*, *Candida glabrata*, *Candida sake*, *Candida kefyr*, *Candida albicans*, the Saccharomyces group, the Rhodotorula group and others. So that it will have an impact on inappropriate patient therapy management. Then various studies have also been conducted on molecular identification methods with various fungal gene targets to identify *C. auris* precisely and accurately; the time required is faster, and the cost is relatively inexpensive.⁴⁶

In Indonesia, studies on the identification of fungi down to the species level, for example, *C. auris* in standard laboratories in hospitals, especially Prof. Dr. I.G.N.G. Ngoerah Hospital in Denpasar, are still very rare, even though these species have become a concern in the world for their abilities as described above. Therefore, this literature review is compiled...
to understand the epidemiology, clinical manifestations, characteristics, virulence factors, methods of identification, therapy and prevention of infection control of C. auris species.

**Candida auris AS THE CAUSE OF EMERGING INFECTIOUS DISEASE**

In the world, an infection caused by the fungus *C. auris* is an emerging disease that threatens global health seriously. While candidiasis produced by other species normally develops from the patient's own microbiome, frequently from the gastrointestinal tract, the effective person-to-person transmission found for *C. auris* is startling. On the contrary to other Candida species, *C. auris* does not seem to effectively colonize the gastrointestinal tract; this is likely because it grows poorly in anaerobic environment.\(^1\)\(^-\)\(^3\) The emergence of *C. auris* is a concern for the CDC for a number of reasons, including the fact that this fungus is frequently resistant to several antifungal medications frequently used to treat Candida infections, some strains of *C. auris* are resistant to three classes of antifungals that are readily available, identification is challenging using standard laboratory methods and can happen in labs without special technology, identification errors can result in inappropriate management, and *C. auris* itself.\(^3\) *C. auris* has been isolated from several locations, including but not limited to the respiratory tract, muscles, and even reaching the central nervous system (CNS), in addition to numerous Candida infections that enter the bloodstream along with its ability to withstand heat (37 to 42°C), *C. auris* can also withstand high salinity and other environmental stresses, allowing it to flourish in a variety of habitats. As *C. auris* can survive longer outside of the human host, *C. auris* infections may develop from environmental sources such contaminated medical equipment or healthcare workers’ hands without first colonizing the diseased host.\(^7\)

**EPIDEMIOLOGY AND CLINICAL MANIFESTATION**

First report of *C. auris* as a novel pathogen was in 2009 by the Satoh et al study. These investigators reported one isolate from a specimen of external ear canal secretions from a 70-year-old female patient admitted to the Geriatric Hospital in Tokyo, Japan.\(^8\) Invasive strains of *C. auris* worldwide become common among hospitalized patients. It was found that the *C. auris* cases recorded in Japan looked to be largely ear infections; the fungus was discovered because of an ear infection, therefore the name “auris.” As the fungus did not enter the circulation in Japan, it did not seem to cause an invasive infection. However, the same strain of *C. auris* does in Korea.\(^7\)\(-\)\(^9\) The first instance to be reported in the United States came from a patient who was...
transferred from the United Arab Emirates in 2013. There has been 15 isolates identified as novel Candida sp. of patients with chronic otitis media collected from 2004 to 2006 in South Korea who were previously incorrectly identified as C. haemulonii, the isolate was confirmed by sequencing as C. auris.9 Six isolates from the first invasive infection of three patients (including 2 isolates from a bloodstream infection recovered from a 1-year-old girl in 1996) were also reported in South Korea in 2011.10

Since it was first isolated in 2009, within a decade of discovering C. auris infection as a pathogen in the bloodstream and other specimens, >4000 isolates have been reported in various countries. As of February 15, 2021, based on the CDC, 47 countries have reported single cases or clusters of cases or outbreaks of C. auris infection, including India, Pakistan, South Korea, Malaysia, South Africa, Oman, Kenya, Kuwait, Israel, United Arab Emirates, Saudi Arabia, China, Colombia, Venezuela, United States, Russia, Canada, Panama, United Kingdom, and continental Europe.11–13 685 multidrug resistant C. auris cases were documented in the United States in the beginning of 2019. In Illinois, New Jersey, and New York, respectively, the CDC has documented 195, 126, and 355 confirmed cases of drug-resistant C. auris as of June 30, 2019. Based on newly available data, the CDC indicated that the number of clinical cases of C. auris grew from 329 instances in 2018 to over a thousand in 2021. In the United States, 2,386 people were also found to have C. auris infection in 2021.12–14

The epidemiology of C. auris infection as a sporadic invasive infection changed drastically, replaced by many cases of nosocomial infection outbreaks from year to year. As a result of the increasing incidence of C. auris infection in recent years, C. auris is now recognized as a bloodstream pathogen more widely than C. glabrata or C. tropicalis in some health facilities.1 Many strains of C. auris have been identified using whole genome sequencing (WGS) analysis, then grouped into 4 C. auris clades based on region, C. auris (Africa: South Africa), C. auris (Asia: India and Pakistan), C. auris (East Asia: Japan), C. auris (Europe: Spain, Italy, United States, Russia, Canada, United Arab Emirates), C. auris (Canada, United Kingdom, and continental Europe), C. auris (South America: Venezuela), and finally in 2019 there is Clade V (Iran).11–14

In most cases, the clinical manifestations of C. auris infection are non-specific and are often difficult to distinguish from other systemic infections. Most of the cases reported in the last 5 years of C. auris infection were isolated from blood specimens and other sites of infection, including invasive medical devices.15 Infected patients are sometimes caused by C. auris include bloodstream infections (BSI), urinary tract infections (UTI), otitis, surgical wound infections, skin abscesses (associated with catheter insertion), myocarditis, meningitis, bone infections, and wound infections. In most cases, it is also reported that C. auris infection occurs in patients with critical conditions who are undergoing treatment in the ICU and using much invasive medical equipment such as ventilators, urinary catheters, central venous catheters, and others.15

Isolation from non-sterile body specimens such as lungs, urinary tract, skin, soft tissue, and genital organs is more likely to lead to colonization than infection. It is essential to identify C. auris even from non-sterile specimens because colonization can pose a risk of transmission, requiring the implementation of infection prevention and control measures as soon as possible.12

Figure 4. S. aureus colony growth on Sabouraud Dextrose Agar (SDA) media.14

Figure 5. Left: CHROMagar Candida media: C. glabrata (purple), C. tropicalis (navy blue), C. auris (white in red circle)). Middle: C. auris on CHROMagar Candida media. Right: C. auris on CHROMagar Candida media after being enriched with Salt Sab Dulcitol broth.14

Figure 6. CHROMagar Candida added to Pal’s supplements. Confluent growth with white colonies (A, B, and C). Poor growth with pink colonies on C. haemulonii var vulnera (d), C. duobushaemulonii (e), and C. haemulonii (f) after incubation at 37°C/24 hours (A), 37°C/ 48h (B). In figure (C) white colonies of C. auris (a,b) and no complex growth of C. haemulonii (c,d) after incubation at 42°C/48 hours.14
C. auris isolates fail to trigger the innate immune response and the synthesis of NETs by human neutrophils, while having less virulence than C. albicans isolates. This failure may contribute to the high death rate associated with this infection. The stages of tissue invasion by C. auris include adhesion to epithelial cells, vascular dissemination, and the ability to produce enzymes. Disseminated candidiasis occurs when Candida can evade the immune system, penetrate the vascular network, and enter the bloodstream. This pathogen can enter the blood through two routes, namely through the penetration of epithelial cells in the mucosa and through medical equipment, surgical wounds, and reduction in the number of natural microbiotas with the use of antibiotics that are not wise.

C. auris yeast cells are recognized by phagocytic cells, and then phagocytosis occurs. It is then placed into an intracytoplasmic vesicle called a phagosome. The fusion of phagosomes with lysosomes then lyses yeast cells, but some C. auris strains can avoid phagolysosomes so that lysis does not occur and they escape. C. auris cells then spread through the bloodstream, causing potentially fatal bloodstream infections.

MICROBIOLOGICAL IDENTIFICATION

C. auris detection can be done by combining several examination modalities such as microscopy, culture, and molecular biology technique. On microscopic examination with Gram stain, C. auris appears as yeast cells that are oval or round and elongated, single, in pairs and/or in groups. With a size of 2.5 – 5.0 micrometers. CDC recommends the identification of fungi down to the species level in the following situations:

a. If the patient is under clinical care, there is an indication.

b. When C. auris infection or colonization cases have been detected in a facility or unit.

c. If a patient has a history of hospitalization in a health care facility in the previous 6 months in a country with C. auris transmission.

The success of molecular identification of fungal isolates depends on the choice of a reliable target sequence or gene. The
**Table 1.** The MIC range of C. auris antifungals was determined by the broth microdilution method.\(^{19}\)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Tentative(^a) resistance breakpoints</th>
<th>MIC</th>
<th>MIC(_{50})</th>
<th>MIC(_{90})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluconazole</td>
<td>≥ 32</td>
<td>0.12 to ≥ 64</td>
<td>≥ 64</td>
<td>≥ 64</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>NA</td>
<td>0.032 to 16</td>
<td>0.5 to 2</td>
<td>2 to 8</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>NA</td>
<td>0.032 to 2</td>
<td>0.06 to 0.5</td>
<td>0.25 to 1</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>NA</td>
<td>0.015 to 16</td>
<td>0.016 to 0.5</td>
<td>0.125 to 0.25</td>
</tr>
<tr>
<td>Isavuconazole</td>
<td>NA</td>
<td>0.015 to 4</td>
<td>0.125 to 0.25</td>
<td>0.5 to 2</td>
</tr>
<tr>
<td>Anidulafungin</td>
<td>≥ 4</td>
<td>0.015 tp 16</td>
<td>0.125 to 0.5</td>
<td>0.5 to 1</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>≥ 2</td>
<td>0.03 to 16</td>
<td>0.25 to 1</td>
<td>1 to 2</td>
</tr>
<tr>
<td>Micafungin</td>
<td>≥ 4</td>
<td>0.015 to 8</td>
<td>0.125 to 0.25</td>
<td>0.25 to 2</td>
</tr>
<tr>
<td>Amphotericin</td>
<td>≥ 2</td>
<td>0.06 to 8</td>
<td>0.5 to 1</td>
<td>2 to 4</td>
</tr>
</tbody>
</table>

\(^{a}\) Patient’s body surface area as calculated by the Mosteller formula,\(^{46}\) which is: BSA (m\(^2\)) = √((height (cm) x weight (kg))/3600). ‡Option to use higher dose if inadequate initial response.

Table 2. Dosage of antifungal echinocandins for children and adults.\(^{31}\)

<table>
<thead>
<tr>
<th>Echinocandin</th>
<th>Adult dosing</th>
<th>Paediatric dosing (children 2 months to 17 years old)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anidulafungin</td>
<td>Loading dose 200 mg i.v., then 100 mg i.v. daily</td>
<td>Not approved in children</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>Loading dose 70 mg i.v., then 50 mg i.v. daily</td>
<td>Loading dose 70 mg/m(^2)/day i.v., then 50 mg/m(^2)/day i.v. (based on body surface area)</td>
</tr>
<tr>
<td>Micafungin</td>
<td>100 mg i.v. daily</td>
<td>Children ≤ 40 kg: 2-4 mg/kg/day i.v.,‡ Children &gt;40 kg: 100-200 mg/day i.v.‡</td>
</tr>
</tbody>
</table>

presumptive identification of the isolate usually influences the selection of gene targets, the technique used, and the level of identification being sought.\(^{18,19}\) Optimal gene targets have several characteristics, including:

a. Availability in multiple copies to provide good PCR sensitivity.

b. Relatively stable, especially when using primers for various types of fungi (pan fungal primers). Regarding amplification, the amplicon present in various regions should be specific for species or genus identification.

c. It has an optimum size (~500bp), short enough to be sequenced easily in an automated sequencer but long enough to provide sufficient information for identification.

d. Gene sequence information is contained in a database for reliable comparison and accurate interpretation of results.

The CDC recommends an identification method based on the D1/D2 region sequence of the 28S rDNA or ITS of the rDNA gene to identify C. auris. In choosing a PCR method, factors to consider include the sensitivity and specificity of the technique, availability of adequate laboratory capacity and equipment, and whether the method is clinically evaluated with similar clinical sample types, cost factors, and turnaround time for results.\(^{18}\)

A study by Denis et al, 2021 carried out C. auris identification checks using the polymerase chain reaction (PCR) and real-time PCR (qPCR) methods based on SYBR Green. The designed primers or amplicon include 5.8S, ITS2, and 28S fragments, which will selectively amplify the 163 bp gene product specific to C. auris.\(^{17}\) Moreover, primers for amplifying gene products from C. auris and closely related species (C. duobushaemulonii, C. haemulonii, and C. lusitaniae) were designed to produce PCR products of length 215 bp, 208 bp, 197 bp, and 203 bp respectively. A panel of 140 fungal clinical isolates was used in the assay, followed by electrophoretic or melting temperature analysis. This study resulted in a 100% match with the results of the DNA sequence, which obtained 93% sensitivity and 96% specificity for the identification of C. auris from 103 axillary or groin swab samples.\(^{19-25}\)

A study by Leach et al, 2018, carried out an identification examination of C. auris using the TaqMan-based real-time PCR method, which uses the target ITS2 region of the ribosomal gene.\(^{20}\) The performance of this test was evaluated using 365 patient swab samples and 258 environmental sponge samples. This method gave positive results from 49 swab samples with 89% sensitivity and 58 sponge samples with 100% sensitivity concerning positive culture results. Real-time PCR also detected C. auris from 1% swab samples and 12% sponge samples with negative culture results.\(^{20}\) This shows that real-time PCR can still detect C. auris genetic material that is not viable or when there are problems in the culture procedure. This examination gives results within 4 hours, significantly faster than the time needed for culture, which is 4 – 14 days.\(^{20,21,26-35}\) In addition to using rDNA primary targets (ITS and D1/D2), there is a study using glycosylphosphatidylinositol (GPI)-anchored protein target genes which are part of the C. auris cell wall (including IFF4, CSA1, PGA26, and PGA52 genes) and play a role in biofilm formation. This study examined using conventional PCR and real-time PCR with SYBR Green buffer. The results obtained were that for the conventional PCR method, the C. auris isolates examined were correctly identified using the primers of the GPI encoding genes. In contrast, all tested C. auris strains were accurately identified for the real-time PCR method.\(^{31}\)

Furthermore, current research showed six laboratories examined 100 coded sera for three serological tests for candidiasis: agar gel diffusion (AGD-1), whole cell agglutination (AGGL-1), and latex agglutination (LAT). AGD-2, AGD-3, AGGL-2, or one of three counterimmunoelectrophoresis (CEP) procedures (CEP-1, CEP-2, or CEP-3) were the tests that each of the six laboratories used. For a set of 53 “candida-involved” cases (33 proved, 14 presumptive, and 6 probable) and 47 negative controls (41
normal and 6 different disease states), the results are reported by laboratory. In the group with candida involvement, the AGD-1 test yielded an average of 85.1% positive outcomes and 5.0% positive outcomes in the control group. In the group with candida involvement, the LAT generated an average of 89.0% positive results, compared to 17.4% good results in the control group. In the candida-infected group, the average percentage of positive results from the AGGL-1 test was 63.8%, compared to 12.3% in the control group. The CEP-3 test (92.5% positives in the candida-involved group and 2.1% positives in controls) and CEP-1 test (88.7% positive in the candida-involved group and no positives in the controls) performed the best among the individual tests. The AGGL-2 and CEP-2 tests have the highest sensitivity (94.3 and 96.2%, respectively). The specificity of both tests was likewise the lowest (80.9 and 76.6%, respectively). The AGGL-1 produced significant laboratory-to-laboratory variation, although the AGD-1 was the most reproducible of the three typical tests.26

THERAPY, INFECTION PREVENTION, AND CONTROL

The antifungal susceptibility pattern of C. auris varies according to the clade, and this species shows 70% resistance to fluconazole and 5% resistance to echinocandins worldwide. There was 23% resistance to amphotericin B, an antifungal with very little resistance to Candida isolates. As much as 20% of Candida isolates showed resistance to 2 antifungal classes, and there were also pan-resistant isolates with high minimum inhibitory concentration (MIC) values for all available antifungal classes.15 Echinocandins are the first-line therapy for C. auris infection because most of these species are resistant to azole and amphotericin B. Several studies have also reported C. auris resistance to echinocandins. Patients should undergo very close follow-up and reassessment with microbiological culture studies to monitor the success of therapy or the development of resistance.12

C. auris is quite difficult to eradicate from the hospital environment because this species can survive in dry and humid conditions and on surfaces, including plastic, for up to 14 days. Some C. auris strains can tolerate cleaning agents such as sodium hypochlorite and parasitic acid.22-25 A study conducted by Escandon et al, 2019 and Kumar et al, 2019 who examined patients with their contacts, health and environmental workers in Colombia who reported outbreak cases, found that C. auris was detected in several different objects such as bedrails, patient bed controls, cellphones, hospital floors, chairs, medical equipment, toilets, door handles, alcohol dispensers and more.23,24

The CDC recommends using a United States Environmental Protection Agency (EPA) registered disinfectant that is effective against Clostridium difficile spores for surfaces contaminated with C. auris. Public Health England (PHE) recommends a product containing 1000 ppm hypochlorite to clean everything, even if another product has been used, such as Hydrogen peroxide or UV-C light. The European CDC (ECDC) recommends final cleaning using a disinfectant and a method certified for antifungal activity. The Pan American Health Organization/World Health Organization (PAHO/WHO) recommends cleaning with soap and water and disinfection using 0.1% bleach.25,33-35

CONCLUSION

C. auris is a multi-drug resistant pathogen that has become a concern worldwide because it has several characteristics, including resistance to many antifungal classes, difficult to identify using standard laboratory methods such as phenotypic and biochemical identification methods, therefore requires advanced identification methods such as molecular-based methods to be able to identify accurately. Furthermore, C. auris can cause invasive infections with a high mortality and morbidity rate. It should also be remembered that C. auris easily survives long enough in the surrounding environment to drive the rapid spread of outbreaks in healthcare facilities therefore it is essential to carry out C. auris identification checks down to the species level with molecular methods such as real-time PCR, which require a shorter time than conventional or culture methods to be able to properly manage patients and implement preventive measures and infection control as soon as possible.

CONFLICT OF INTEREST

There have been no competing interests regarding this manuscript.

FUNDING

The authors declared that no financial support or funding was obtained for this study.

ETHICAL STATEMENT

This review article has followed Committee on Publication Ethics (COPE) and International Committee of Medical Journal Editors (ICMJE) guidelines regarding publication ethics.

AUTHOR CONTRIBUTION

Design, intelligent content description, literature quest, data collection, data processing, manuscript writing, manuscript editing, and manuscript review are contributed by all authors. The corresponding author is the guarantor and constructs the concept of the manuscript.

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