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Review Article

Unveiling the rise of *Candida auris*: Latest developments and healthcare implications

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ABSTRACT

Candida auris, a fungus that is resistant to multiple drugs, has become a major global healthcare concern in recent years. The pathogen quickly disseminates within healthcare facilities, colonizes many surfaces, and leads to recurrent infections despite frequent disinfection measures. Automated systems frequently misidentify it, resulting in a delayed diagnosis. Inadequate hand hygiene, the use of multiple antibiotics, and contaminated medical equipment are the main causes of infections that primarily target critically ill patients in hospital intensive care units (ICUs). *Candida auris* isolates are resistant to commonly used antifungal drugs like fluconazole, amphotericin, and echinocandins. This review article thoroughly examines the current understanding of *Candida auris* infections, encompassing its epidemiology, clinical symptoms, diagnosis, treatment options, and prevention measures. It additionally summarizes a recent literature review on emerging diagnostic techniques and treatment options. Gaining a comprehensive understanding of the difficulties presented by this pathogen and staying informed of the most recent developments is essential for healthcare providers and policymakers in order to efficiently counteract its transmission and limit its detrimental impact on patient health.

1. Introduction

Candida auris is the first fungal pathogen to be classified as a public health threat because of its ability to easily inhabit the skin, rapidly transmit among patients, induce severe illness, resistance to numerous antifungal medications, and the ability to cause substantial healthcare-related infections.[1] This specific strain of yeast, first identified in Japan in 2009 in the external ear canal of a Japanese patient, has now spread to healthcare facilities worldwide, leading to outbreaks and a significant increase in illness and death rates.[2]

Researchers have detected *C.auris* in various anatomical locations of the human body, including the skin (most common), urogenital tract (common), and respiratory tract (rare). This occurrence has been linked to the emergence of serious conditions such as blood stream infections, cardiac infections, pneumonia and urinary tract infections.[3] C. auris can survive on dry and moist environmental surfaces in healthcare facilities due to its ability to produce virulence factors and form biofilms, leading to persistent colonization of human skin and the environment.[4]

It has been noted to affect both children and adults, with a higher occurrence among critically ill patients in high-dependency units. Despite antifungal therapy, the impaired innate immune response to *C. auris* may be a contributing factor to its increased mortality rates.[1] The fungus has become a widespread nosocomial disease that is challenging to manage and has an unacceptably high mortality rate of up to 70%.[5]

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This particular fungus is known as a "super fungus" due to its high transmissibility among patients, resistance to numerous antifungal medications, and ability to withstand frequently used cleaning methods in hospital settings.[6] The World Health Organization Fungal Priority Pathogens List (WHO-FPPL) has included this organism in the "Critical Priority Group" as a major global health concern due to challenges in its identification, the implications for infection prevention and control, and the significant rise in the number of regions and countries reporting cases of *C. auris*.[7]

Access to conventional diagnostic techniques is rather limited, which poses a challenge in accurately identifying the organism using conventional procedures. Several Candida species, such as *C. auris* and *C. haemulonii*, are frequently overlooked because their identification process is difficult.[8] Clinical strains of *C.auris* display diverse colony and cellular morphologies, encompassing yeast, filamentous, aggregated, and elongated forms. The observed phenotypic diversity is a common trait of *C. auris*, which was seen in 8 isolates from patients in in a study and they belong to 4 major genetic clades. 9 Distinct clades of *C. auris* are linked to various categories of illnesses, whereas Clade I, III, and IV are responsible for severe infections and transmission inside healthcare settings, whilst Clade II is specifically related with ear infections.[4] The various cell types of *C. auris* display unique characteristics of resistance to antifungal agents and pathogenicity.[9]

C.auris is known for its high drug resistance and various resistance mechanisms. Echinocandins are typically the primary treatment for invasive candidiasis, although azoles may be considered if in vitro susceptibility is established. In 2021, the Essential Medicines List (EML) included echinocandins. It exhibits a high level of resistance, reaching up to 93%, to at least two out of the three primary categories of antifungal medications: azoles, echinocandins, and polyenes. However, in many countries, both diagnostic techniques and drugs remain inaccessible.[5]

C.auris has a restricted range of treatment choices and can lead to severe infections, frequently in combination with additional problems such as COVID-19. *C.auris* possesses a significant capacity to trigger a "novel pandemic" as a result of its resistance to several drugs and its elevated rates of mortality.[10] The article aims to provide a thorough examination of existing literature on *C.auris* infections, together with recent advancements in diagnostic methods and treatment choices for this condition.

2. Methodology

To ascertain any fresh developments on *C. auris* subsequent to a prior literature study, a comprehensive search of articles published between the years 2019 and 2023 was conducted, employing a snowballing technique to uncover any additional noteworthy studies. The search encompassed databases such as Medline, Embase, Scopus, NICE Evidence Search, with a restriction to papers written in English. The search phrases "*Candida auris*", "*C. auris*"," Drug resistant *C.auris*" were employed. Articles were deduplicated and excluded if they lacked any mention of *C. auris* or if they did not include information pertaining to the important topics of the review, as previously indicated.

Table 1: Risk factors for acquiring *C.auris* infection

1	The presence of invasive medical instruments like endotracheal tubes, enteral feeding tubes, intravenous catheters, and urine catheters.
2	Individuals with weakened immune systems
3	Extended duration of hospitalization
4	Preexisting respiratory or neurological conditions or chronic renal disease
5	History of extended antibiotic usage
6	Previous surgical procedure
7	Prolonged duration of stay in the critical care unit (ICU)
8	Colonization of multiple sites

Table 2: Misidentification of *C.auris* by various methods

Identification Method	**Organism *C. auris* can be misidentified as**
Vitek 2 YST	*Candida haemulonii* *Candida duobushaemulonii*
API 20C	*Rhodotorula glutinis* *Candida sake* Candida intermedia
API ID 32C	*Candida sake* *Saccharomyces kluyveri*
BD Phoenix yeast identification system	*Candida haemulonii* *Candida catenulata* *Candida famata*
MicroScan	*Candida guilliermondii* *Candida lusitaniae* Candida parapsilosis
RapID Yeast Plus	*Candida parapsilosis*

Adapted from CDC website (https://www.cdc.gov/fungal/candida-auris/pdf/Testing-algorithm_by-Method_508.pdf)45

3. Discussion

3.1. Etiology-about the fungus

Candida auris, a yeast species belonging to the Candida genus derives its name from its initial identification from the external ear canal of a patient at a hospital in Japan. The genetic analysis of yeast revealed a new species that is very similar to *Candida ruelliae*, *Candida haemulonii*, *C. duobushaemulonii*, and *C. pseudohaemulonii* in terms of how it evolved.[20]

C. auris reproduces through a process called budding. Its cells can exist as a single cell, in pairs or in groups. The cells are oval, varying from ellipsoidal to elongated, with a dimension of 2.5–5.0 micrometres. *C. auris* generally lacks

Table 3: MIC breakpoints of various drugs used for treating *C.auris* infections

Class	Drugs	Tentative MIC Breakpoints (μg/mL)	Comment
Triazoles	Fluconazole	≥32	Isolates with MICs ≥32 were shown to have a resistance mutation in the Erg11 gene, making them unlikely to respond to fluconazole.
	Voriconazole and other second generation triazoles	N/A	Fluconazole susceptibility can be used as an alternative for evaluating the susceptibility of second generation triazoles. Nevertheless, strains that exhibit resistance to fluconazole may occasionally exhibit a response to other triazoles. The decision to administer an alternative triazole will depend on the individual case.
Polyenes	Amphotericin B	≥2	If the Etest is used to assess the minimum inhibitory concentration (MIC) of amphotericin B and a result of 1.5 is obtained, it should be rounded up to 2.
Echinocandins	Anidulafungin	≥ 4	The tentative breakpoints are determined by analyzing the most common distribution of echinocandin from around 100 isolates collected from various geographic areas.
	Caspofungin	≥ 2	-
	Micafungin	≥ 4	-

Table 4: Newer therapeutic options for treating *C.auris* infections

Class of newer formulations	Compound name	Mechanism of activity against *C.auris*
Antimicrobial peptides	Cathelicidin LL-37	disrupts the cell membrane integrity of *C. auris*, triggers oxidative stress, and arrests the cell cycle in the S-phase, leading to cell death.[11]
	Cm-p5	can inhibit the formation of *Candida auris* biofilms and stop the maturation of existing biofilms.[12]
Immunotherapy	Monoclonal antibodies (mAbs) -C3.1 (anti-β-Man3) and cocktails of 6H1 (anti-Hwp1) and 9F2 (anti-Pgk1)	Target Candida cell surface antigens. mAb-based immunotherapy can be used as an effective alternative to antifungal drugs for treating multidrug-resistant *C. auris* infections.[13]
Metals and nanoparticles	Silver, carbon, zinc oxide, titanium dioxide, polymer, and gold	can alter the essential functions of *C. auris* cells by modulating their transcriptome, epigenome, and metabolism.[14]
Natural compounds	Compound 6f	blocks the cell cycle of *C. auris* at the S and G2/M phases and inhibits the expression and activity of antioxidant enzymes in *C. auris*, leading to the production of reactive oxygen species.[15]
Novel antifungal agents	Benzoanilide compound, A1	blocks the biosynthesis of virulence factors and fungal cell walls by inhibiting GPI and GPI-anchored proteins.[16]
	Myriocin (a serine palmitoyltransferase inhibitor) and flucytosine	Synergistic effect on killing the fungus.[17]
	Compound 2b, a Schiff base of sulphonamides	promising activity against C. glabrata and fluconazole-resistant *C. auris*, with MICs of 4-16 μg/ml.[18]
Repurposed drugs	Antiparasitic drugs, (miltefosine), Anticancer drugs (e.g., alexidine dihydrochloride)	Effective against biofilm formation of *C.auris*.[19]

the ability to form hyphae, pseudo hyphae, or germ tubes.[21] Nevertheless, elevated levels of salt stress, specifically on Yeast extract, Tryptone, and Dextrose(YTD) plus 10% NaCl, and a lack of heat-shock proteins (HSP), can induce the formation of pseudo hyphae-like structures.[22]The *C. auris* strain exhibits rapid proliferation at 40 ^{0}C but displays sluggish proliferation at 42^{0}C.[20] The proliferation of fungus in a culture medium is dependent upon the particular medium employed. When cultivated on Sabouraud agar, *C.auris* will produce smooth colonies that are white to cream-colored. On CHROMagar, colonies can grow as coloured colonies, ranging from pale to deep pink and sometimes beige.[23]

3.2. Epidemiology

Following the pathogen's initial discovery in 2009, South Korea identified fifteen more ear isolates collected between 2004 and 2006. The previous classification of these isolates as *Candida haemulonii* was incorrect.[24] Since then, reports of invasive isolates in blood and other specimens have emerged, leading to the identification of *C. auris* on every inhabited continent. Its prevalence continues to increase, with mortality rates varying from 30 to 72%.[25]

The genomic study of *C. auris* isolates has identified four distinct geographical clades: clade I (South Asian), clade II (East Asian), clade III (South African), and clade IV (South American). Recently, a new clade V has been described in Iran. The genetic variants discovered among the clades suggest that *C. auris* most likely evolved independently in the specified geographical regions.[26]

The worldwide occurrence of *C.auris* infection is uncertain and probably underestimated due to the absence of commercially accessible diagnostic methods and its similarity to other Candida species.

Candida auris can readily spread among individuals as a result of conditions such as a dense population, pollution, elevated urban temperatures, inadequate hygiene, and frequent foreign travel.[27] A study in the USA found that between 2017 and 2022, *C. auris* caused a total of 192 hospitalizations. Out of these, 38 cases (20%) were bloodstream infections. For these infections, the estimated crude fatality rate was 34%.[28] A study conducted in the United Arab Emirates revealed a substantial rise in the occurrence of *C. auris* cases from 2018 to 2021. Each year, the likelihood of reporting a positive *C. auris* case increased by 161.5%.[29] The species poses a significant risk to human health in Africa due to its rapid dissemination and potent resistance to antifungal medications, particularly in settings with limited resources. In Africa, the incidence of *C. auris* is 8.74%, and it is associated with a high mortality rate of 39.46%.[30]

As of March 2020, the Centre for Disease Control and Prevention (CDC) had documented the presence of *C. auris* isolates in 41 countries. Over the past decade, the CDC have documented a total of 5,754 clinical cases and 13,163 screening cases as of December 2022. On March 20, 2023, the centre issued a warning about the rapid dissemination of this fungus in healthcare facilities across the United States. The CDC has categorized this specific strain as an "urgent antimicrobial resistance threat."[31]

3.3. Pathogenesis

In outbreaks, *C. auris* colonizes patients' skin by 37.5% to 86%. When the skin barrier breaks, *C. auris* skin colonization increases the risk of invasive disease.[32] It may persist on surfaces for two weeks, causing nosocomial epidemics.[33]*C. auris* invades the host's respiratory system, unlike other *Candida* species. Virulence and morphologies vary widely in *C. auris*, with certain aggregative phenotypes resembling less dangerous *Candida* species.[34] Compared to C. albicans, *C. auris* reduces neutrophil phagocytosis and death.[32]*C. auris* elicits a greater cytokine response in human mononuclear cells than C. albicans, suggesting it is an innate immune system inducer. However, *C. auris* has a lesser macrophage lysis capacity than *C. albicans*, suggesting the innate immune system may clear it less effectively.[34] Cell wall mannan- *C. auris* possesses a specific cell surface mannan with a high β-1,2 linkage content, unlike other *Candida* species. This unusual mannan structure interacts well with the blood and sweat gland immune proteins IgG and mannose-binding lectin. C. auris mannan binds IgG 12–20 times stronger than C. albicans mannan.[35] Because of cell wall mannosylation, *C. auris* can avoid neutrophils, which are essential for fungal immunity. Breaking the mannosylation pathway in *C. auris* led to a decrease in mannan in the outer cell wall. This revealed immunostimulatory components and made it easier for neutrophils to interact, phagocytose, and kill the fungus. Other *Candida* species, including *C. albicans* and C. glabrata, did not exhibit neutrophil evasion by cell wall mannosylation like *C. auris*.[36] Extracellular vesicles (EVs) - made by *C. auris* are not the same as those made by *Candida albicans* in terms of molecular structure and biological activity. *C. auris* EVs helped the fungus adhere to epithelial cells and survive in macrophages, suggesting they contributed to its pathogenicity. In contrast, C. albicans EVs primed macrophages to attack the fungus.[37] Thermotolerance, Osmo tolerance, filament development, biofilm formation, and hydrolytic enzyme synthesis make *C. auris* pathogenic.[38] *C. auris*, which is more thermotolerant than comparable *Candida* species, may have emerged because of global warming and climate change. A study implies that climate change caused an environmental ancestor of *C. auris* to become pathogenic through temperature adaptation and spread globally by an intermediate host. It emphasizes the necessity to understand *C. auris* ecological niches and transmission cycles, including the possibility of a marine or freshwater

intermediate host.[39,40] Based on the "global warming emergence hypothesis," it is believed that *C. auris* was present in the environment before it was clinically recognized and became dangerous to humans as a result of adapting to climate change. In order for this theory to be considered valid, it is essential to obtain a sample of *C. auris* from the isolated Andaman Islands. The growth rate of one environmental isolate was slower at mammalian temperatures compared to clinical strains, providing evidence that the progenitor of C. auris has recently undergone adaptation to higher temperatures.[41,42] Biofilm formation -Researchers have created many models to examine *C. auris* biofilm formation. They have developed crucial in vivo and ex vivo models for studying *C. auris* biofilms. The fact that the main signalling pathways in *C. auris, C. albicans*, and *S. cerevisiae* are all the same suggests that orthologous pathways may help explain how biofilms form and how diseases happen *C. auris* biofilm-forming abilities may explain its unusually high hospital spread, as biofilm cells are less susceptible to antifungal treatments.[43] A novel aggregating *C. auris* strain with higher cell-cell adhesion forms biofilms more effectively. Amplification of the cell surface adhesin ALS4 gene increases adhesion and biofilm formation. A lot of the clinical isolates of *C. auris* had changes in the copy number of ALS4, which suggests that the sub telomeric region is not stable.[44,45]

3.4. Resistance to disinfectants

Efficient decolonization methods and disinfection procedures are critical for preventing and managing *C. auris* transmission. However, there is currently a lack of reliable methods for removing *C. auris* from the skin, and certain disinfectants are not efficient against this pathogen.[46] Disinfectants such as quats and chlorhexidine have poor effectiveness against *C. auris*. However, mixing them with another biocidal agent can enhance their efficiency. *C. auris* exhibits a distinct susceptibility to disinfectants in comparison to *Candida albicans* and other *Candida* species. Disinfectants that are efficacious against *C. albicans* may not demonstrate the same effectiveness against C. auris. The distinctive aggregating phenotype of *C. auris* may be a factor in its diminished susceptibility to disinfectants, although further investigation is required to fully comprehend this phenomenon.[47]

3.5. Risk factors

C. auris primarily affects people who have significant underlying medical issues and require complex medical interventions. Hospitals, nursing homes, and long-term care facilities have documented outbreaks. Pathogens' ability to colonize the skin, environmental surfaces, and medical equipment facilitates the transmission of infections in healthcare settings. The risk factors are succinctly outlined in (Table 1).[48]

The fungus colonizes several anatomical areas, including the axilla, groin, nares, respiratory tract, and urinary tract, especially in persons receiving medical attention in a hospital setting. Researchers conducted a study, examining the surfaces, environment, clothing, and equipment in the patient's room, and found that the fingerprinting patterns of C. auris isolates matched. This implies that colonized patients have dispersed *C. auris* into their immediate environment.[49]

Researchers have also shown that *C. auris* thrives on reusable axillary temperature probes used on the skin surface. This discovery aligns with the observed rise in *C. auris* isolation from the armpit of colonized individuals, compared to other body parts. The epidemic in a neurologic critical care unit in England was attributed to the use of reusable axillary temperature probes.[50]

Healthcare professionals and those living in the same household, for example, have a lower probability of contracting *C. auris.*

Screening for *C. auris* colonization is an essential infection control strategy. This involves using composite skin swabs taken from the axilla (armpit) and groin. Healthcare facilities should implement protocols to evaluate patients who have undergone medical treatment in foreign hospitals.[51]

3.6. Clinical manifestations

C. auris infections present in various clinical forms, variety of infections from superficial (skin) infections to more severe, life-threatening infections including bloodstream infections, wound infections, ear infections, and invasive candidiasis.[52] Invasive infections can lead to high mortality rates, making early diagnosis and intervention critical.[53]

3.7. Specimen collection

There are two methods by which medical professionals can ascertain the presence of infection or colonization with *C. auris* in a patient. The process of colonization screening involves a healthcare clinician collecting a sample from the patient's skin by gently rubbing a swab in the armpits and groin. This swab is then sent to a laboratory for further analysis and testing.[50]

Clinical specimen testing involves collecting a clinical sample, such as blood or urine, from a patient exhibiting signs of an infection with an unidentified aetiology. Testing procedures often screen for a comprehensive range of infections, including bacterial ones. The test results may indicate that the patient has *C. auris*.[52]

Conducting retesting on patients infected or colonized with *C. auris* is not advisable, as this practice does not guarantee the absence of the pathogen on the patient's skin

or other bodily locations, nor does it mitigate the risk of transmission to others.[51]

3.8. Laboratory diagnosis

Precise identification of *C. auris* is crucial for delivering optimal healthcare to patients, prescribing appropriate treatment for those with invasive infections, and identifying colonized persons to implement infection prevention and control measures. Normal phenotypic methods have a hard time diagnosing *Candida auris* infections because it looks a lot like other *Candida* species, like *Candida haemulonii, Candida duobushaemulonii*, *Candida sake*, and Rhodotorula glutinis. Thus, it is crucial to analyse any *Candida* spp. isolates at the species level. If *Candida* spp. is detected, more investigation should be conducted to confirm that they are not C. auris.[20]

3.8.1. Microscopy

When observed under a microscope, *C. auris* appears quite similar to other *Candida* species. This is a budding yeast that does not produce germ tubes. However, certain strains of *C. auris* can develop basic pseudo hyphae when grown on cornmeal agar.[21]

3.8.2. Culture

C. auris thrives at temperatures ranging from 42 to 45 degrees Celsius. This characteristic can be utilized to distinguish it from various other *Candida* species, particularly *Candida haemulonii*, which it is sometimes mistaken for. Most *C. auris* isolates display a pale purple or pink hue when grown on CHROMagar™ *Candida*, a chromogenic agar medium, resembling several non-C. albicans species. Therefore, the use of chromogenic agars is not appropriate as the main method of identification. Chromogenic agars are useful for conducting screenings to identify suspicious colonies within mixed cultures, such as the presence of *C. albicans*. If non-*C. albicans* species are found on chromogenic agar, it is advised to transfer them to Sabouraud's agar and identify them using the protocols set by the local laboratory. Novel chromogenic media have been created to enhance the process of identifying *C. auris*.[22] *C. auris* can be erroneously recognized as several species when employing yeast identification techniques including VITEK 2 YST, API 20C, BD Phoenix yeast identification system, and Micro Scan as shown in (Table 2).[54]

To avoid misidentification, it is advisable to confirm the accurate identification of all clinical isolates classified as *C. haemulonii*, *C. duobushaemulonii*, C. famata, and *C. auris* using matrix-assisted laser desorption ionization time-of-flight mass spectroscopy (MALDI-TOF MS) or DNA sequencing techniques. When used with up-to-date databases covering all phylogenetic clades or databases certified by the United States Food and Drug Administration (FDA), MALDI-TOF MS systems, such as the Bruker-Daltonics MALDI Biotyper and VITEK MS by bioMeriaux, can accurately identify *C. auris*. Polymerase chain reaction (PCR) amplification of the internal transcribed spacer (ITS) region of ribosomal DNA (rDNA) and/or PCR sequencing of either the ITS region or the D1/D2 domains of rDNA achieve a definitive identification.[54]

3.8.3. Non-culture methods

Recently, there have been developments in culture-independent approaches that allow for the rapid identification of *C. auris* within a few hours. These technologies have been developed to expedite the quick detection of patients who are colonized by the virus. The latest developments in the diagnosis of *C. auris* have played a crucial role in enhancing the detection and treatment of infections caused by this highly resistant fungal disease. The progress in this field has been driven by the demand for expedited, more precise, and economically efficient diagnostic techniques. Here are some recent significant advancements in the field of C. auris diagnosis:

1. Loop-Mediated Isothermal Amplification (LAMP): LAMP is a rapid nucleic acid amplification technique that has been adapted for the detection of *C. auris*. LAMP assays provide results within a short time frame (typically less than an hour) and are particularly valuable in resource-limited settings.
2. Nanopore Sequencing: The MinION platform and similar devices from Oxford Nanopore Technologies have enabled real-time sequencing of *C. auris* genomes. This technology has the potential to rapidly identify *C. auris* strains and their genetic characteristics, including resistance mechanisms, aiding in outbreak investigation and treatment decisions.
3. CRISPR-Based Detection: Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) technology is being harnessed for the specific and sensitive detection of *C. auris* DNA. CRISPR-based assays offer the benefit of highly precise and rapid diagnostics.
4. Next-Generation Sequencing (NGS): The identification and characterization of *C. auris* isolates increasingly rely on NGS technologies. Whole-genome sequencing (WGS) can provide detailed insights into the genetic makeup of different strains, aiding in tracking the spread of the pathogen and understanding its resistance profiles.
5. Multiplex PCR Assays: Multiplex PCR assays have been developed to simultaneously detect multiple fungal pathogens, including *C. auris*. These assays are valuable for differentiating between various *Candida* species and other fungi in clinical specimens.
6. Enhanced Antifungal Susceptibility Testing (AST): AST methods have been refined to assess the

susceptibility of *C. auris* to a broader range of antifungal agents. These improvements help clinicians select the most effective treatment options, especially given the pathogen's multidrug resistance.

7. Biosensors: Novel biosensor technologies are being explored for *C. auris* detection. These devices can offer rapid and point-of-care diagnostics, making them suitable for use in a variety of healthcare settings.
8. Machine learning and artificial intelligence: Machine learning algorithms and AI systems are being developed to analyse clinical data and predict *C. auris* infections. These systems can identify patterns and risk factors, enabling early intervention.
9. Improved Sample Collection and Transport Kits: Innovations in sample collection and transport kits have been introduced to ensure the stability and integrity of specimens during transit to diagnostic laboratories, reducing the risk of false-negative results.
10. Global Surveillance Networks: The establishment of global surveillance networks and information-sharing platforms has enhanced the timely reporting and tracking of *C. auris* outbreaks, improving overall diagnostic efforts.

These recent advances in *C. auris* diagnostics are essential for accurate and timely identification of infections, enabling healthcare providers to implement appropriate infection control measures and tailor treatment to individual patient needs. As our understanding of this pathogen evolves, ongoing research and development efforts will further enhance diagnostic capabilities.[55]

3.9. Antifungal susceptibility testing

The Clinical and Laboratory Standards Institute (CLSI) has created guidelines for evaluating the efficacy of antifungal drugs using susceptibility testing. These guidelines offer recommendations for assessing the vulnerability of yeasts, such as *C. auris,* to antifungal medications.

Currently, there are no officially defined susceptibility breakpoints specific to *C. auris*. Thus, breakpoints are determined by considering the standards set for closely related *Candida* species as well as expert judgment as shown in (Table 3). The relationship between microbiologic breakpoints and clinical outcomes is yet unknown.[56]

3.10. Antifungal resistance mechanisms

A major cause for concern regarding *C. auris* is its ability to withstand several antifungal medications, such as fluconazole, amphotericin B, and echinocandins. The presence of multidrug resistance makes therapy more difficult, resulting in a limited range of effective therapies and longer hospital stays. Resistance development in *Candida* has progressed from cross-resistance to multiresistance, resulting in the appearance of *Candida* species that are resistant to multiple drugs, including multidrug-resistant (MDR), extensively drug-resistant (XDR), and pan drug-resistant (PDR) strains.[57]

Developing novel antifungal medicines is a pressing goal in the fight against this infection. Approximately 90% of *C. auris* isolates exhibit resistance to fluconazole, while 30% are resistant to amphotericin B, and 2-10% show resistance to echinocandins.[58]

Azole resistance is primarily caused by genetic changes in the ERG11 gene and increased drug efflux pump production.[59] Resistance to Amphotericin B, a rare phenomenon in fungi, affects approximately 30% of *C. auris* isolates and is associated with mutations in the ERG6 gene. The ERG6 mutations stop the production of ergosterol and cause sterols that are similar to cholesterol to build up. This makes the pathogen more than 32 times less sensitive to amphotericin B.[60]

The *C. auris* isolates from COVID-19 positive and negative patients in Qatar had a high level of clonality, which suggests that there was a clonal outbreak and is still spreading through healthcare institutions. More than 70% of the isolates exhibited resistance to both fluconazole and amphotericin B, which are two commonly used antifungal medications. The isolates exhibited changes in genes linked to resistance against azoles, echinocandins, and amphotericin B. Notably, a distinct isolate (CAS109) demonstrated resistance to all three classes of antifungal medications.[61]

A study found a new FKS1 R1354H mutation in a clinical strain of *C. auris* that is not sensitive to caspofungin. The study also observed that this mutation enhanced caspofungin resistance in both laboratory conditions and in a mouse model of widespread candidiasis. The FKS1 genotype was a more reliable way to show how well a treatment worked in living things than the minimum inhibitory concentration (MIC) that was seen in the lab.[62]

Two isolates that didn't respond to any of the drugs tested had a deletion in the FUR1 gene, which stopped them from making uracil phosphoribosyl transferase.[63] When *C. auris* was treated with caspofungin, it became resistant to it. This was shown by higher MIC50 values, slower growth, higher chitin content, upregulation of caspofungin target genes, and resistance to fluconazole. Exposure to caspofungin caused the cells of *C. auris* to adhere to one another and form a biofilm. The use of zinc oxide nanoparticles in caspofungin formulations inhibited the emergence of phenotypic alterations associated with resistance in *C. auris*.[64]

In order to combat antifungal resistance, it is of utmost importance to refrain from excessive use of antifungal medications. Instead, it is necessary to carefully choose the right drug, dosage, and duration of treatment. Additionally, implementing antifungal stewardship programs that take into account aspects that contribute to resistance, such

as species-level identification and susceptibility testing, is essential.[57]

3.11. Treatment

Treatment of *C. auris* infections is challenging and often requires a multidisciplinary approach. Combination therapy, when feasible, is often recommended. The choice of antifungal agents should be guided by susceptibility testing, though susceptibility data may be limited. Echinocandins are the mainstay of treatment but concern of resistance is increasing.

New antifungal agents, such as rezafungin, ibrexafungerp, and fosmanogepix, are being developed and tested as potential treatments for *C. auris* infections.[65] Rezafungin could allow once-weekly outpatient treatment for echinocandin-susceptible *C. auris* while reducing selective pressure on new drug classes. Oral formulations of these novel antifungals could enable step-down therapy, early discharge, or avoid hospitalization for mild/non-invasive *C. auris* infections.[66]

3.11.1. Newer treatments

Several novel antifungal chemicals and approaches, including antimicrobial peptides, combination therapy, immunotherapy, metals and nanoparticles, natural compounds, and repurposed medicines, are now being investigated and demonstrate promising efficacy against *C. auris* and elaborated in (Table 4).[60]

4. Prevention

Infection control measures, including patient isolation and strict adherence to hand hygiene, are crucial in preventing further transmission. Preventing *C. auris* infections hinges on robust infection control practices. Healthcare facilities must implement strict isolation precautions, environmental cleaning protocols, and active surveillance. Health authorities and organizations should prioritize public awareness campaigns and education for healthcare workers to reduce the risk of transmission.[67]

5. Limitations of the Study

The article includes literature review of the past and present knowledge about the *C. auris* pathogen. However Infection control and prevention has not been covered in detail as it is beyond the scope of this article.

6. Conclusion

C. auris infections have emerged as a formidable challenge in healthcare settings, primarily due to their resistance to antifungal agents, ease of transmission, and the limited diagnostic tools available. Early detection, stringent infection control measures, and the development of new antifungal therapies are crucial in addressing this growing public health concern. As *C. auris* continues to spread, collaboration among healthcare providers, researchers, and policymakers is essential to effectively combat this multifaceted threat. Ongoing surveillance, research, and international cooperation will be vital in the battle against *C. auris* infections.

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8. Conflicts of Interest

The author declares no conflicts of interest.

References

1. Nett JE. Candida auris: An emerging pathogen “incognito”? *PLOS Pathog*. 2019;15(4):1007638. doi:10.1371/journal.ppat.1007638.
2. Rhodes J, Fisher MC. Global epidemiology of emerging Candida auris. *Curr Opin Microbiol*. 2019;52:84–9. doi:10.1016/j.mib.2019.05.008.
3. Corsi-Vasquez G, Ostrosky-Zeichner L. Candida auris: what have we learned so far? *Curr Opin Infect Dis*. 2019;32(6):559–64.
4. Ciurea CN, Mare AD, Kosovski IB, Toma F, Vintilă C, Man A, et al. Candida auris and other phylogenetically related species – a mini-review of the literature. *Germs*. 2021;11(3):441–8.
5. de Jong A, Hagen F. Defend and Persist: How the Fungal Pathogen Candida auris was Able to Emerge Globally in Healthcare Environments. *Mycopathologia*. 2019;184(3):353–65.
6. Bensusan EC, Soares JA, Giorgetti L, and PD. Candida auris: Multidrug resistance and new treatment strategies. *Rev Bras Ciênc Bioméd*. 2022;3(1). doi:10.46675/rbcbm.v3i1.68.
7. WHO fungal priority pathogens list to guide research, development and public health action. Geneva: World Health Organization; 2022. Available from: https://www.who.int/publications/i/item/9789240060241.
8. Fan S, Yue H, Zheng Q, Bing J, Tian S, Chen J, et al. Filamentous growth is a general feature of Candida auris clinical isolates. *Med Mycol*. 2021;59(7):734–40.
9. Thatchanamoorthy N, Devi VR, Chandramathi S, Tay ST. Candida auris: A Mini Review on Epidemiology in Healthcare Facilities in Asia. *J Fungus*. 2022;8(11):1126. doi:10.3390/jof8111126.
10. Chaves A, Costa VM, Brito M. Candida auris: imminence of a new pandemic? *Revista Científica Multidiscip*. 2021;2(4):24287. doi:10.47820/recima21.v2i4.287.
11. Rather IA, Sabir JSM, Asseri AH, Ali S. Antifungal Activity of Human Cathelicidin LL-37, a Membrane Disrupting Peptide, by Triggering Oxidative Stress and Cell Cycle Arrest in Candida auris. *J Fungi*. 2022;8(2):204. doi:10.3390/jof8020204.
12. Kubiczek D, Raber H, Gonzalez-García M, Morales-Vicente F, Staendker L, Otero-Gonzalez AJ, et al. Derivates of the Antifungal Peptide Cm-p5 Inhibit Development of Candida auris Biofilms In Vitro. *Antibiotics (Basel)*. 2020;9(7):363. doi:10.3390/antibiotics9070363.
13. Rosario-Colon J, Eberle K, Adams A, Courville E, Xin H. Candida Cell-Surface-Specific Monoclonal Antibodies Protect Mice against Candida auris Invasive Infection. *Int J Mol Sci*. 2021;22(11):6162. doi:10.3390/ijms22116162.
14. Bandara N, Samaranayake L. Emerging and future strategies in the management of recalcitrant Candida auris. *Med Mycol*. 2022;60(4):myac008. doi:10.1093/mmy/myac008.
15. Wani MY, Ahmad A, Aqlan FM, Al-Bogami AS. Modulation of key antioxidant enzymes and cell cycle arrest as a possible antifungal mode of action of cinnamaldehyde based azole derivative. *Bioorg Med Chem Lett*. 2022;73:128922. doi:10.1016/j.bmcl.2022.128922.

16. Tu J, Zhu T, Wang Q, Yang W, Huang Y, Xu D, et al. Discovery of a new chemical scaffold for the treatment of superbug Candida auris infections. *Emerg Microbes Infect*. 2023;12. doi:10.1080/22221751.2023.2208687.
17. Izadi A, Paknia F, Roostaee M, Mousavi S, Barani M. Advancements in nanoparticle-based therapies for multidrug-resistant candidiasis infections: a comprehensive review. *Nanotechnology*. 2024;55(33):332001.
18. Hamad A, Chen Y, Khan MA, Jamshidi S, Saeed N, Clifford M, et al. Schiff bases of sulphonamides as a new class of antifungal agent against multidrug-resistant Candida auris. *Microbiologyopen*. 2021;10(4):e1218. doi:10.1002/mbo3.1218.
19. Izadi A, Gharehbolagh SA, Sadeghi F, Talebi M, Darmiani K, Zarrinnia A, et al. Drug repurposing against Candida auris: A systematic review. *Mycoses*. 2022;65(8):784–93.
20. Satoh K, Makimura K, Hasumi Y, Nishiyama Y, Uchida K, Yamaguchi H. Candida auris species a novel ascomycetous yeast isolated from the external ear canal of an inpatient in a Japanese hospital. *Microbiol Immunol*. 2009;53(1):41–4.
21. Chowdhary A, Sharma C, Duggal S, Agarwal K, Prakash A, Singh PK, et al. New clonal strain of Candida auris, Delhi, India. *Emerg Infect Di*. 2013;19(10):1670–3.
22. Kim SH, Iyer KR, Pardeshi L, Muñoz JF, Robbins N, Cuomo CA. Genetic Analysis of Candida auris Implicates Hsp90 in Morphogenesis and Azole Tolerance and Cdr1 in Azole Resistance. *mBio*. 2019;10(1):e02529–18. doi:10.1128/mBio.02529-18.
23. Cortegiani A, Misseri G, Fasciana T, Giammanco A, Giarratano A, Chowdhary A, et al. Epidemiology, clinical characteristics, resistance, and treatment of infections by Candida auris. *J Intensive Car*. 2018;6:69. doi:10.1186/s40560-018-0342-4.
24. Kim MN, Shin JH, Sung H, Lee K, Kim EC, Ryoo N, et al. Candida haemulonii and closely related species at 5 university hospitals in Korea: identification, antifungal susceptibility, and clinical features. *Clin Infect Dis*. 2009;48(6):57–61.
25. De Gaetano S, Midiri A, Mancuso G, Avola MG, Biondo C. Candida auris Outbreaks: Current Status and Future Perspectives. *Microorganisms*. 2024;12(5):927. doi:10.3390/microorganisms12050927.
26. Chow NA, De Groot T, Badali H, Abastabar M, Chiller TM, Meis JF, et al. Potential Fifth Clade of Candida auris, Iran, 2018. *Emerg Infect Dis*. 2018;25(9):1780–1.
27. Thakur S. State of the globe: Candida auris-a global healthcare threat. *J Glob Infect Dis*. 2022;14(4):129–30.
28. Benedict K, Forsberg K, Gold J, Baggs J, Lyman M. Candida auris-Associated Hospitalizations. *Emerg Infect Dis*. 2023;29:2017–2022.
29. Thomsen J, Abdulrazzaq NM, Oulhaj A, Nyasulu PS, Alatoom A, Denning DW. Emergence of highly resistant Candida auris in the United Arab Emirates: a retrospective analysis of evolving national trends. *Front Public Health*. 2024;11:1244358. doi:10.3389/fpubh.2023.
30. Yerbanga IW, Diallo SN, Rouamba T, Ouedraogo DF, Lagrou K, Oladele R, et al. Clinical Features and Antifungal Resistance Profile ofCandida auris in Africa: Systematic Review. *J Biosci Med*. 2024;12(1):126–49.
31. Tracking C. auris [Internet]. Candida Auris (C. Auris); 2024. Available from: https://www.cdc.gov/candida-auris/tracking-c-auris/index.html.
32. Horton MV, Holt AM, Nett JE. Mechanisms of pathogenicity for the emerging fungus Candida auris. *PLOS Pathog*. 2023;19(12):e1011843. doi:10.1371/journal.ppat.1011843.
33. Desoubeaux G, Coste AT, Imbert C, Hennequin C. Overview about Candida auris: What's up 12 years after its first description? *J Mycol Med*. 2022;32(2):101248. doi:10.1016/j.mycmed.2022.101248.
34. Garcia-Bustos V, Pemán J, Ruiz-Gaitán A, Cabañero-Navalon MD, Cabanilles-Boronat A, Fernández-Calduch M, et al. Host-pathogen interactions upon Candida auris infection: fungal behaviour and immune response in Galleria mellonella. *Emerg Microbes Infec*. 2021;11(1):136–46.
35. Yan L, Xia K, Yu Y, Miliakos A, Chaturvedi S, Zhang F, et al. Unique Cell Surface Mannan of Yeast Pathogen Candida auris with Selective Binding to IgG. *ACS Infect Dis*. 2020;6(5):1018–31.
36. Bruno M, Kersten S, Bain JM, Jaeger M, Rosati D, Kruppa MD, et al. Transcriptional and functional insights into the host immune response against the emerging fungal pathogen Candida auris. *Nat Microbiol*. 2020;5(12):1516–31.
37. DZamith-Miranda, Heyman HM, Couvillion SP, Cordero RJB, Rodrigues ML, Nimrichter L. Comparative Molecular and Immunoregulatory Analysis of Extracellular Vesicles from Candida albicans and Candida auris. *MSystems*. 2021;6:e0082221. doi:10.1128/mSystems.00822-21.
38. Horton MV, Johnson CJ, Zarnowski R, Andes BD, Schoen TJ, Kernien JF, et al. Candida auris Cell Wall Mannosylation Contributes to Neutrophil Evasion through Pathways Divergent from Candida albicans and Candida glabrata. *mSphere*. 2021;6(3):e0040621. doi:10.1128/mSphere.00406-21.
39. Rapti V, Iliopoulou K, Poulakou G. The Gordian Knot of C. auris: If You Cannot Cut It, Prevent It. *Pathogens*. 2023;12(12):1444. doi:10.3390/pathogens12121444.
40. Garcia-Bustos V, Cabañero-Navalon MD, Ruiz-Gaitán A, Salavert M, Tormo-Mas M, Pemán J, et al. Climate change, animals, and Candida auris: insights into the ecological niche of a new species from a One Health approach. *Clin Microbiol Infect*. 2023;29(7):858–62.
41. Casadevall A, Kontoyiannis DP, Robert V. Environmental Candida auris and the Global Warming Emergence Hypothesis. *MBio*. 2021;12(2). doi:10.1128/mbio.00360-21.
42. Allert S, Schulz D, Kämmer P, Großmann P, Wolf T, Schäuble S, et al. From environmental adaptation to host survival: Attributes that mediate pathogenicity of Candida auris. *Virulence*. 2022;13(1):191–214.
43. Khari A, Biswas B, Gangwar G, Thakur A, Puria R. Candida auris biofilm: a review on model to mechanism conservation. *Expert Rev Anti Infect Ther*. 2023;21(3):295–308.
44. Bing J, Guan Z, Zheng T, Zhang Z, Fan S, Ennis CL, et al. Clinical isolates of Candida auris with enhanced adherence and biofilm formation due to genomic amplification of ALS4. *PLOS Pathog*. 2023;19:1011239. doi:10.1371/journal.ppat.1011239.
45. Brandt P, Mirhakkak MH, Wagner L, Driesch D, Möslinger A, Fänder P, et al. High-Throughput Profiling of Candida auris Isolates Reveals Clade-Specific Metabolic Differences. *Microbiol Spectr*. 2023;11(3):e0049823. doi:10.1128/spectrum.00498-2.
46. Carty J, Chowdhary A, Bernstein D, Thangamani S. Tools and techniques to identify, study, and control Candida auris. *PLOS Pathog*. 2023;19(10):1011698. doi:10.1371/journal.ppat.1011698.
47. Omardien S, Teska P. Skin and hard surface disinfection against Candida auris - What we know today. *Front Med (Lausanne)*. 2024;11:1312929. doi:10.3389/fmed.2024.1312929.
48. Shastri PS, Shankarnarayan SA, Oberoi J, Rudramurthy SM, Wattal C, Chakrabarti A, et al. Candida auris candidaemia in an intensive care unit - Prospective observational study to evaluate epidemiology, risk factors, and outcome. *J Crit Care*. 2020;57:42–8. doi:10.1016/j.jcrc.2020.01.004.
49. Ahmad S, Alfouzan W. Candida auris: Epidemiology, Diagnosis, Pathogenesis, Antifungal Susceptibility, and Infection Control Measures to Combat the Spread of Infections in Healthcare Facilities. *Microorganisms*. 2021;9(4):807. doi:10.3390/microorganisms904080.
50. Eyre DW, Sheppard AE, Madder H, Moir I, Moroney R, Quan TP, et al. A Candida auris Outbreak and Its Control in an Intensive Care Setting. *N Engl J Med*. 2018;379(14):1322–31.
51. Worth LJ, Harrison SJ, Dickinson M, Diemen A, Breen J, Harper S, et al. Candida auris in an Australian health care facility: importance of screening high risk patients. *Med J Aust*. 2020;212(11):510–1.
52. Johnson EM, Borman A, Manuel R, Jeffery-Smith A, Taori SK, Schelenz S, et al. Candida auris: A review of the literature. *Clin Microbiol Rev*. 2018;31(1):e00029–17. doi:10.1128/CMR.00029-1.
53. Lee WG, Shin JH, Uh Y, Kang MG, Kim SH, Park KH, et al. First three reported cases of nosocomial fungemia caused by Candida auris. *J Clin Microbiol*. 2011;49(9):3139–42.

54. Identification of C. auris [Internet]. Candida Auris (C. Auris); 2024. Available from: https://www.cdc.gov/candida-auris/hcp/laboratories/identification-of-c-auris.html.
55. Lorenzo-Villegas DL, Gohil NV, Lamo P, Bagiu IC, Vulcanescu DD, Horhat FG, et al. Innovative Biosensing Approaches for Swift Identification of Candida Species, Intrusive Pathogenic Organisms. *Life*. 2023;13(10):2099. doi:10.3390/life13102099.
56. Antifungal Susceptibility Testing for C. auris [Internet]. Candida Auris (C. Auris); 2024. Available from: https://www.cdc.gov/candida-auris/hcp/laboratories/antifungal-susceptibility-testing.html.
57. Paiva JA, Pereira JM. Treatment of invasive candidiasis in the era of Candida resistance. *Curr Opin Crit Care*. 2023;29(5):457–62.
58. Giacobbe DR, Mikulska M, Vena A, Pilato VD, Magnasco L, Bassetti M, et al. Challenges in the diagnosis and treatment of candidemia due to multidrug-resistant Candida auris. *Front Fungal Biol*. 2023;4:1061150. doi:10.3389/ffunb.2023.1061150.
59. Sharma C, Kadosh D. Perspective on the origin, resistance, and spread of the emerging human fungal pathogen Candida auris. *PLoS Patho*. 2023;19(3):1011190. doi:10.1371/journal.ppat.1011190.
60. Rybak JM, Barker KS, Muñoz JF, Parker JE, Ahmad S, Mokaddas E, et al. In vivo emergence of high-level resistance during treatment reveals the first identified mechanism of amphotericin B resistance in Candida auris. *Clin Microbiol Infect*. 2022;28(6):838–43.
61. Abid FB, Salah H, Sundararaju S, Dalil L, Abdelwahab AH, Salameh S, et al. Molecular characterization of Candida auris outbreak isolates in Qatar from patients with COVID-19 reveals the emergence of isolates resistant to three classes of antifungal drugs. *Clin Microbiol Infect*. 2023;29(8):1083.e1–e7.
62. Kiyohara M, Miyazaki T, Okamoto M, Hirayama T, Makimura K, Chibana H, et al. Evaluation of a Novel FKS1 R1354H Mutation Associated with Caspofungin Resistance in Candida auris Using the CRISPR-Cas9 System. *J Fungi*. 2023;9(5):529. doi:10.3390/jof9050529.
63. Jacobs SE, Jacobs JL, Dennis EK, Taimur S, Rana M, Patel D, et al. Candida auris Pan-Drug-Resistant to Four Classes of Antifungal Agents. *Antimicrob Agents Chemother*. 2022;66(7):e0005322. doi:10.1128/aac.00053-22.
64. Fayed B, Jayakumar MN, Soliman SSM. Caspofungin-resistance in Candida auris is cell wall-dependent phenotype and potential prevention by zinc oxide nanoparticles. *Med Mycol*. 2021;59(12):1243–56.
65. Wang S, Pan J, Gu L, Wang W, Wei B, Zhang H, et al. Review of treatment options for a multidrug-resistant fungus: Candida auris. *Med Mycol*. 2024;62(1):127. doi:10.1093/mmy/myad127.
66. Giacobbe DR, Magnasco L, Sepulcri C, Mikulska M, Koehler P, Cornely OA. Recent advances and future perspectives in the pharmacological treatment of Candida auris infections. *Expert Rev Clin Pharmacol*. 2021;14:1205–1225.
67. Infection Control Guidance: Candida auris [Internet]. Candida Auris (C. Auris); 2024. Available from: https://www.cdc.gov/candida-auris/hcp/infection-control/index.html#:~:text=auris%20spreads%20easily%20in%20healthcare,disinfection%20prevent%20and%20control%20outbreaks.

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