

Understanding *Candida auris*: A Snapshot of a Global Concern

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Abstract

The rising incidence of fungal infections, particularly from *Candida* species, highlights the urgent global threat posed by *Candida auris* (*C. auris*). This newly identified pathogen presents unique challenges due to its resistance to multiple antifungal agents and rapid spread within healthcare settings. Despite efforts to understand its characteristics, diagnostic and therapeutic difficulties persist in controlling the spread of the disease. Novel treatments are under investigation, emphasizing the need for proactive measures to mitigate its impact on public health.

Introduction

The frequency of human fungal infections is escalating at an alarming rate, with eukaryotic pathogens currently affecting billions of people globally resulting in over 1.5 million deaths annually. *Candida*, *Aspergillus*, and *Cryptococcus* species are responsible for approximately 90% of these fatalities. Among them, *Candida* spp. stand out as the leading cause of invasive infections, with mortality rates ranging from 46% to 75%, a statistic that has remained stagnant for decades. *Candida auris*, a newly identified pathogenic yeast, poses a particularly significant global threat. First identified as a novel ascomycetous yeast species in 2009 from a patient's ear canal in a Japanese hospital, *C. auris* has since sparked infectious outbreaks in over 45 countries, with mortality rates approaching 60%. This pathogen presents a major challenge in healthcare settings due to its resistance to multiple antifungal agents, difficulties in microbiological identification, and its rapid spread, especially among critically ill patients. In response to these challenges, healthcare professionals must remain vigilant and informed about the threat posed by *C. auris*. It is imperative to implement proactive measures to prevent and effectively manage its spread in clinical settings.

Microbiological characteristics of *C. auris*

This yeast reproduces through budding and can be found as single cells, pairs, or grouped, with shapes varying from oval to elongated, measuring between 2.5 and 5.0 μm . It has close evolutionary

connections with *C. ruelliae*, *C. haemulonii*, and *C. pseudohaemulonii*. Although it seldom forms hyphae or pseudohyphae and does not produce germ tubes, *C. auris* strains thrive in temperatures ranging from 40°C to 42°C. Exposure to high-salt conditions and decreased heat-shock proteins can trigger the formation of structures resembling pseudohyphae. On SDA, colonies typically appear smooth and creamy white, and they test negative for germ tube formation.

Transmission

Over ten years since its identification, *C. auris* has become a significant nosocomial pathogen worldwide. Unlike other pathogenic *Candida* species, *C. auris* does not typically inhabit mucosal surfaces or GIT as a commensal yeast. However, it exhibits a distinctive preference for skin and can persist on human skin for extended periods. Notably, it demonstrates persistent colonization of human skin and various surfaces within healthcare settings, leading to widespread transmission within and between hospitals and significant outbreaks. It is facilitated by easy transfer through direct skin-to-skin contact, particularly in healthcare environments. Furthermore, *C. auris* can survive and spread in treated wastewater, contributing to its dissemination among both humans and animals.

Epidemiology

C. auris poses a global challenge, spreading across every continent except Antarctica, and has been identified as a multidrug-resistant organism in healthcare facilities in over 30 countries worldwide within the last decade. Initial investigations suggest that *C. auris* likely originated independently in four distinct geographical regions, as evidenced by phylogenetic analyses revealing four major clades: the South Asian, East Asian, African, and South American, Iran and Indo-Malaysia clades, also referred to as clades I, II, III, IV, V and VI respectively. These clades display significant genetic diversity, differing by tens to hundreds of thousands of single nucleotide polymorphisms (SNPs), with nucleotide variation almost 17 times greater between clades than within them. Notably, the first documented candidemia outbreak in South Asia occurred in an Indian hospital in 2013. Recent findings have revealed

C. auris isolated from street dogs hospitalized in Delhi, highlighting its potential for interspecies transmission. Various clinical manifestations, including bloodstream infections, urinary tract infections, otitis, surgical wound infections, skin abscesses (often linked to catheter insertion), myocarditis, meningitis, bone infections, and wound infections, have been connected to *C. auris*. However, isolations from the lungs, urinary tract, skin, soft tissues, and genital organs are more likely suggestive of colonization rather than active infections.

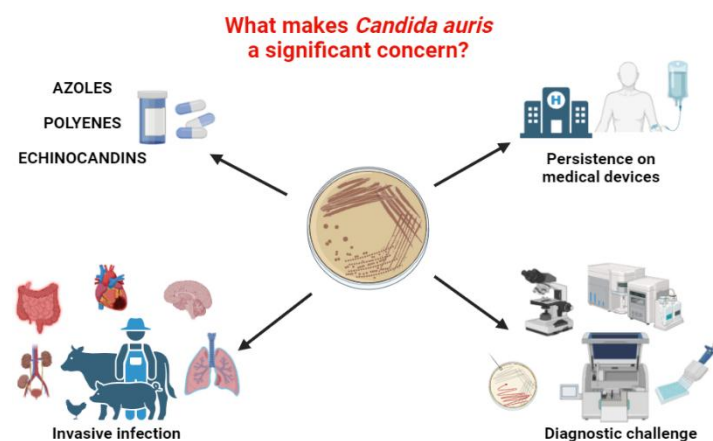


Fig 1 The rise of *Candida auris* as a global animal and human health concern

Diagnosis

Identification of *C. auris* can be achieved through various methods, including Phenotypic-Based Identification, Biochemical Identification, and Molecular-based approaches. However, despite these techniques, there remains a possibility of misidentifying species or strains. For example, differentiating between *C. auris* and its closely related counterparts, *C. haemulonii*, poses a challenge using traditional phenotypic assays. Nonetheless, the introduction of the new medium CHROMagar™ *Candida* Plus has significantly improved the presumptive identification of *C. auris*. This medium displays a unique coloration—light blue with a blue halo—allowing for reliable identification with a sensitivity and specificity of 100% after 36 hours of incubation. Molecular techniques, including sequencing of genetic loci and PCR/qPCR assays, antifungal susceptibility testing (AFST), and typing have emerged as effective tools. Additionally, matrix-assisted laser desorption ionization-time of flight mass spectrometry-based assays (MALDI-TOF) offer promising capabilities in defining susceptibility patterns of *C. auris* through species identification. These advancements collectively enhance the accuracy and efficiency of identifying and characterizing *C. auris* in clinical settings.

Antifungal resistance

The prevalence of antifungal resistance in *C. auris* is concerning, with a majority of clinical isolates showing resistance to main antifungal classes like azoles, polyenes, and echinocandins. Multidrug resistance to at least two classes is observed in over 40% of cases, and about 4% are resistant to all three classes. Azole resistance is primarily linked to increased activity of efflux pumps and mutations in the gene *Erg11* (the main target of azoles). Specific mutations in *Erg11*, like Y132F, K143R, and F444L, contribute to increased azole resistance. Polyene drugs, which bind to ergosterol, face resistance mechanisms that are not well understood but likely involve mutations in ergosterol biosynthesis. Echinocandins target β -1,3-glucan synthase, and resistance usually stems from mutations in genes like *FKS1* and *FKS2*. Resistance to pyrimidine analogue, such as 5-flucytosine often arises from mutations in the target gene *FCY1*. Transmission of pan-resistant and echinocandin-resistant *C. auris* isolates has been reported, indicating its high transmissibility in healthcare settings. The presence of different resistance gene alleles in related isolates suggests acquired rather than intrinsic resistance. Studies indicate clade-specific mutations associated with azole resistance have emerged recently, highlighting the evolving nature of resistance. Currently, the prevailing resistance pattern against *C. auris* reveals significant challenges in antifungal treatment. Resistance rates exceed 90% for fluconazole, approximately 50% for voriconazole, around 30% for Amphotericin B, and range from 7-10% for Echinocandins. Despite this knowledge, mechanisms of antifungal drug resistance in *C. auris* remain poorly understood. Given the limited antifungal classes and increasing resistance, there is a pressing need for more effective antifungal drugs.

Novel Treatments and Combination Therapies

To confront *C. auris* infections, urgent trials are ongoing for novel therapy methods, medications, and tools. At present, several new antifungal treatments are under clinical investigation, including VT-1598, a tetrazole-based inhibitor targeting fungal CYP51; rezafungin, an improved echinocandin derivative; and Manogepix (APX001A), which inhibits fungal Gwt1 gene and exhibits broad-spectrum antifungal activity. Emerging chemical structures like rocaglates, hydroxyquinolines, halogenated salicylanilides, pyrimidinediones, macrocyclic amidinoureas, oxadiazolylthiazoles, phenylthiazoles, and 2-

aryloxazolines are showing promising antifungal effects. These compounds demonstrate species-specific fungicidal actions, strong inhibition of biofilm formation, and broad-spectrum activity against drug-resistant strains, with limited toxicity to mammalian cells. Antimicrobial peptides such as Histatin 5 and LL-37 exhibit potent antifungal activity by disrupting cell membranes and synergizing with conventional antifungal agents. Presently, more than 100 combinations of drugs are being evaluated for their synergistic effects against *C. auris* infections. Compounds like sulfamethoxazole, lopinavir, and aprepitant enhance antifungal efficacy, while chlorhexidine acetate, miltefosine, and colistin demonstrate synergistic effects. Chemosensitizers, which enhance antifungal activity, offer promising avenues for treatment innovation. For example, Azoffluxin boosts fluconazole's effectiveness by inhibiting the Cdr1 efflux pump. At the same time, derivatives of carvacrol, farnesol, and haloperidol show potential for synergizing with antifungal agents, providing new strategies for combating *C. auris* infections.

Conclusion

In brief, *C. auris* poses a significant worldwide health challenge due to its rapid dissemination,

elevated mortality rates, and resistance to multiple drugs. Managing this threat necessitates enhanced surveillance, refined diagnostic methods, cautious antifungal administration, and continuous exploration of innovative treatment options to curb its public health impact.

References

- Chowdhary, A., Jain, K. and Chauhan, N., (2023). *Candida auris* genetics and emergence. *Annual Review of Microbiology*, 77, pp.583-602.
- Cortegiani, A., Misseri, G., Fasciana, T., Giammanco, A., Giarratano, A. and Chowdhary, A., (2018). Epidemiology, clinical characteristics, resistance, and treatment of infections by *Candida auris*. *Journal of intensive care*, 6, pp.1-13.
- Fasciana T, Cortegiani A, Ippolito M, Giarratano A, Di Quattro O, Lipari D, Graceffa D, Giammanco A. *Candida auris*: An overview of how to screen, detect, test and control this emerging pathogen. *Antibiotics* (Basel) (2020); 9:778.
- Yadav, A., Wang, Y., Jain, K., Panwar, V.A.R., Kaur, H., Kasana, V., Xu, J. and Chowdhary, A., (2023). *Candida auris* in dog ears. *Journal of Fungi*, 9(7), p.720.

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