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Review Article

Multidrug resistance mechanisms and therapeutic strategies in *Candida auris*

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ABSTRACT

In recent years, *Candida auris* has emerged as a formidable global health threat due to its multidrug resistance, high transmissibility in healthcare settings, and diagnostic challenges. Unlike most *Candida* species, *C. auris* can colonize the skin, persist on surfaces, and resist common antifungal agents including azoles, echinocandins, and polyenes. Its rapid global spread and association with high mortality in immunocompromised patients have drawn intense clinical and scientific attention. This review aims to consolidate current knowledge on the mechanisms underlying antifungal resistance in *C. auris*, including genetic mutations in target enzymes (e.g., ERG11, FKS1), overexpression of efflux pumps, biofilm formation, and stress response pathways. Additionally, it explores the pathogen's virulence factors, diagnostic challenges, and environmental resilience. We also provide a critical overview of emerging therapeutic strategies, including novel antifungal agents, combination therapies, and immunotherapeutic interventions. Special emphasis is given to the ongoing clinical trials and pipeline antifungals such as ibrexafungerp, manogepix, and rezafungin. The review concludes with future directions for research, highlighting the need for improved surveillance, molecular diagnostics, and antifungal stewardship to curb the rise of this deadly fungal pathogen.

Keywords: *C. auris*, Resistance, Multidrug resistance, Mechanisms therapeutic

INTRODUCTION

Fungal infections have become a significant public health concern, particularly among immunocompromised individuals and those in intensive care settings. Among the emerging threats is *Candida auris*, a multidrug-resistant fungal pathogen first identified in Japan in 2009 and now reported in over 50 countries.[1] Its emergence has been characterized by nosocomial outbreaks, high case-fatality rates, and an alarming ability to survive on surfaces and resist disinfection.[2] Unlike traditional *Candida* species such as *C. albicans*, *C. auris* poses unique diagnostic and therapeutic challenges, often leading to misidentification and treatment failure.

The rise of *C. auris* has coincided with increased global antifungal use, particularly in high-risk hospital populations. Several features contribute to its clinical threat: resistance to all three major antifungal classes (azoles, echinocandins, polyenes), ability to form robust biofilms, and genetic plasticity that facilitates rapid adaptation.[3] These characteristics make infections with *C. auris* difficult to treat and control, particularly in resource-limited settings.

Epidemiological studies have shown that *C. auris* comprises several genetically distinct clades (South Asian, East Asian, South African, South American, and Iranian), each associated with regional outbreaks and varying resistance patterns. The pathogen's ability to persist in hospital environments and colonize both patients and healthcare workers enhances its potential for widespread transmission.[4] Furthermore, the organism's resistance mechanisms-including ERG11 and FKS1 mutations,

upregulation of ATP-binding cassette (ABC) transporters, and biofilm-associated gene expression-further complicate treatment protocols.[5]

Given its increasing prevalence and impact, there is a critical need to consolidate current research and provide actionable insights for clinicians, microbiologists, and public health authorities. This review provides a comprehensive analysis of the resistance mechanisms, virulence traits, and emerging therapeutic options for *C. auris*, with the goal of informing future research and guiding clinical management strategies.

EPIDEMIOLOGY AND GLOBAL SPREAD OF *C. AURIS*

Since its 1st isolation in 2009 from the ear canal of a patient in Japan, *C. auris* has rapidly emerged as a global health threat.[6] The organism has been implicated in hospital outbreaks across Asia, Middle East, Africa, Europe, and Americas. Retrospective analyses have revealed that *C. auris* was misidentified in clinical laboratories as early as 1996, highlighting pathogen's long-standing but underrecognized presence in healthcare environments.

C. auris is classified into at least five genetically distinct clades based on WGS: South Asian (Clade I), East Asian (Clade II), South African (Clade III), South American (Clade IV), and a potential Iranian clade (Clade V). These clades exhibit significant genomic divergence, suggesting independent regional emergence rather than a single origin with global dissemination. Notably, each clade shows distinct antifungal resistance profiles and environmental persistence, complicating global surveillance and treatment guidelines.[2]

Healthcare-associated transmission is a hallmark of *C. auris* epidemiology. The pathogen can colonize patients' skin, survive on surfaces for extended periods, and resist routine hospital disinfectants. Outbreaks often occur in intensive care units (ICUs), where patients are exposed to broad-spectrum antibiotics, invasive devices, and prolonged hospitalization-all of which are known risk factors for colonization and invasive infection.

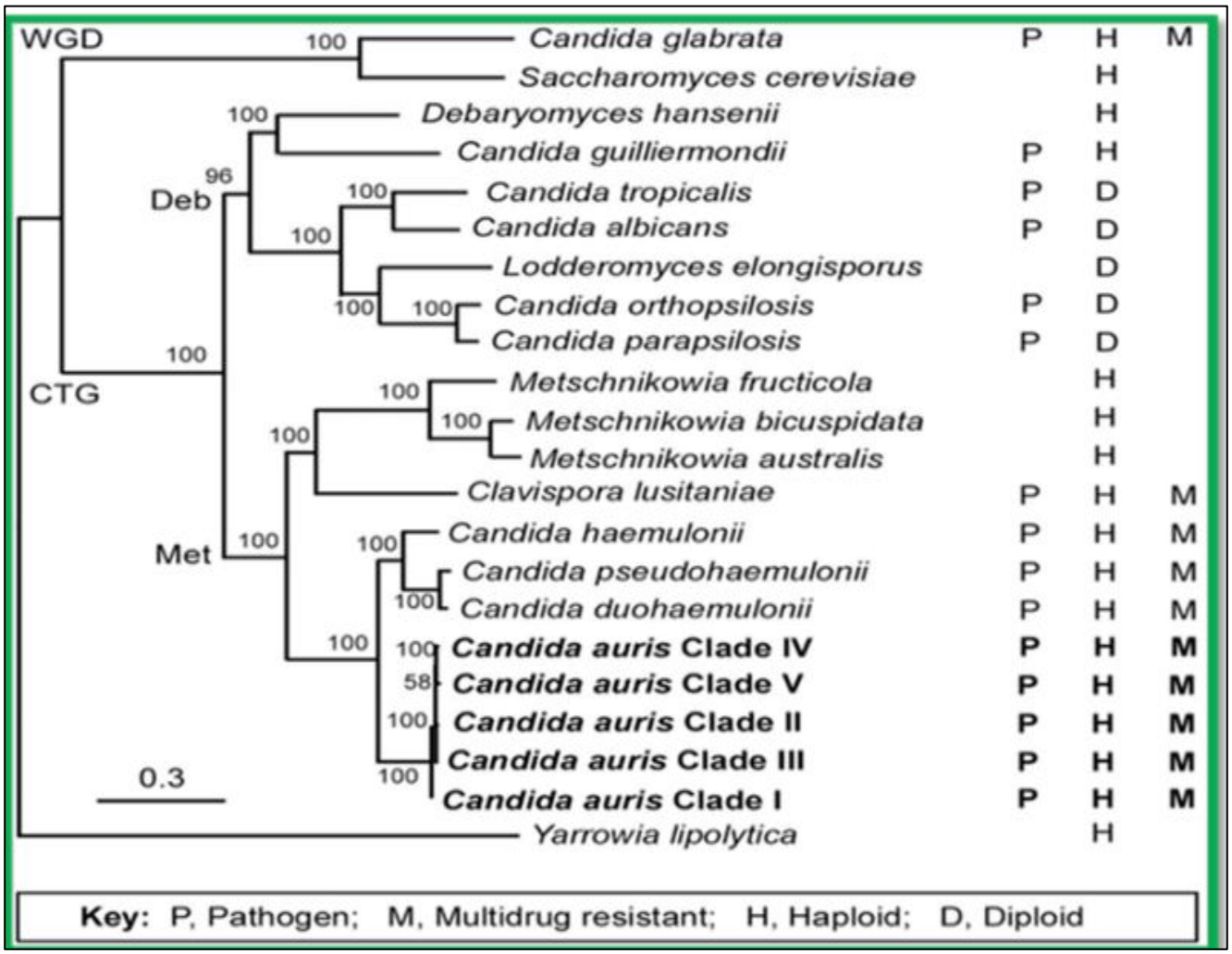

Figure 1: Maximum-likelihood phylogenetic tree based on whole genome sequencing (WGS) showing the genetic diversity and global distribution of the five major *C. auris* clades.

Each clade represents a regionally associated lineage.[7]

Global surveillance data from the centers for disease control and prevention (CDC) and world health organization (WHO) report a steady rise in *C. auris* cases, particularly in regions with limited infection control resources.[4,8] Mortality rates for *C. auris* candidemia have been reported to range from 30% to 60%, depending on host factors, treatment delays, and local antifungal resistance patterns.

The increasing number of outbreaks has triggered the inclusion of *C. auris* in the WHO fungal priority pathogens list.[8] Surveillance is further complicated by the organism's misidentification as *C. haemulonii* or *C. lusitaniae* by common diagnostic systems such as VITEK 2 and API 20C AUX, unless MALDI-TOF MS or PCR-based assays are employed.

Altogether, the global emergence of *C. auris* presents an urgent challenge to healthcare systems, necessitating coordinated responses in diagnostic capacity, infection prevention, and antifungal stewardship.

RESISTANCE MECHANISMS OF *C. AURIS*

Multidrug resistance is a defining feature of *C. auris*, contributing significantly to its classification as a global health threat.[9] Unlike other *Candida* species, *C. auris* exhibits intrinsic and acquired resistance to all three major classes of antifungal agents: azoles, echinocandins, and polyenes. Resistance mechanisms in *C. auris* involve genetic mutations in drug targets, overexpression of efflux transporters, alterations in membrane sterol composition, and enhanced biofilm formation.[5]

Resistance to azoles

Azoles, including fluconazole and voriconazole, inhibit lanosterol 14-α-demethylase enzyme encoded by ERG11 gene, which is essential for ergosterol biosynthesis. Mutations in ERG11, particularly Y132F, K143R and F126L, frequently observed in resistant *C. auris* isolates. These mutations reduce azole binding affinity, resulting in therapeutic failure.[3] Additionally, overexpression of ERG11 and upregulation of efflux pumps-such as ATP-binding cassette transporters (CDR1, CDR2) and major facilitator superfamily transporters (MDR1) contribute to decreased intracellular drug accumulation.[10]

Resistance to echinocandins

Echinocandins, which target the β-1,3-D-glucan synthase complex, are often the first-line treatment for invasive candidiasis. Resistance to echinocandins in *C. auris* is primarily due to point mutations in the FKS1 gene, especially within hotspot regions HS1 and HS2. The most clinically relevant mutations include S639F and R1354S, which alter the drug-binding site, reducing susceptibility to caspofungin, micafungin, and anidulafungin.[9]

Resistance to polyenes

Amphotericin B, a polyene antifungal, binds ergosterol in the fungal membrane to form pores that disrupt cell integrity. Reduced ergosterol content due to mutations or downregulation of the ERG2, ERG3, or ERG6 genes can lead to polyene resistance in *C. auris*. Additionally, lipid remodeling and oxidative stress response pathways are thought to mediate adaptive resistance.[11]

Biofilm-mediated resistance

Biofilm formation significantly enhances resistance to antifungals. *C. auris* biofilms exhibit a dense extracellular matrix and upregulation of efflux pumps, which together limit drug penetration and efficacy. Mature biofilms are up to 100-fold more resistant to fluconazole, exhibit reduced susceptibility to echinocandins and amphotericin B.[12]

Cross-resistance and multidrug resistance

Clinical isolates often show resistance to multiple antifungal classes simultaneously. Cross-resistance between azoles and amphotericin B has been observed in isolates with combined ERG11 mutations and biofilm-related gene upregulation.[13] This multidrug resistance severely limits treatment options, especially in ICU settings. Understanding these resistance mechanisms is vital for the development of effective therapeutic strategies and diagnostics. Continuous genomic surveillance is required to monitor emerging mutations and adapt treatment protocols accordingly.

VIRULENCE FACTORS AND PATHOGENICITY OF *C. AURIS*

Although *C. auris* shares several pathogenic traits with other members of the *Candida* genus, it displays unique virulence mechanisms that contribute to its survival in hospital environments and its capacity to cause invasive infections.[1] Its ability to colonize the skin, persist on abiotic surfaces, form biofilms, and resist host immune responses distinguishes it as a highly adaptable pathogen.[11]

Biofilm formation

Biofilm formation is a critical virulence trait of *C. auris*, enabling resistance to antifungal agents and immune evasion. Unlike *C. albicans*, which forms complex biofilms with hyphal structures, *C. auris* biofilms are composed primarily of aggregated yeast cells embedded in a dense extracellular matrix. These biofilms exhibit increased expression of efflux pump genes (CDR1, SNQ2) and cell wall integrity genes (FKS1, CHS2), conferring resistance to azoles, polyenes, and echinocandins.[12] Biofilm-associated cells are also protected from neutrophil-mediated killing and oxidative stress.[5]

Thermotolerance and osmotolerance

C. auris can thrive at temperatures exceeding 40 °C and in high-salinity environments, unlike most other *Candida* species. This thermotolerance allows it to survive febrile conditions and contributes to environmental persistence, particularly in hospital equipment and surfaces.[4] Additionally, its osmotolerance supports colonization in skin folds, catheter sites, and mucosal membranes.[13]

Surface adhesion and aggregation

The adhesion capacity of *C. auris* to plastic surfaces, epithelial cells, and medical devices facilitates nosocomial transmission. Certain isolates exhibit aggregative phenotypes, where cells form clumps that are difficult to dislodge and more resistant to antifungal treatment. These aggregates are thought to shield inner cells from both antifungals and immune effectors.[10]

Secreted hydrolytic enzymes

While less prominent than in *C. albicans*, *C. auris* produces proteases, lipases, and phospholipases, which assist in tissue invasion and nutrient acquisition. Studies indicate variability in enzyme production across different clades and isolates, suggesting strain-specific virulence modulation.[6]

Immune evasion and stress response

C. auris has been shown to resist oxidative and osmotic stress, as well as evade neutrophil-mediated killing. Its expression of stress response regulators such as HSP90 *and* SAP5, and the ability to suppress reactive oxygen species (ROS) generation, enhance its survival in the host.[12] In mouse models, *C. auris* exhibits reduced cytokine induction and delayed neutrophil recruitment compared to *C. albicans*, indicating a subdued host inflammatory response.[11]

Altogether, these virulence mechanisms contribute to the pathogen's resilience in clinical settings, its capacity to persist in colonized patients, and its ability to cause severe systemic infections with limited therapeutic options.

DIAGNOSTIC CHALLENGES AND IDENTIFICATION METHODS

Accurate and timely identification of *C. auris* is critical for initiating appropriate antifungal therapy and controlling nosocomial transmission. However, traditional diagnostic systems often misidentify *C. auris*, resulting in delayed diagnosis and suboptimal treatment.[2,14]

Misidentification in conventional systems

Routine biochemical identification systems, such as VITEK 2, API 20C AUX, and BD Phoenix, frequently misidentify *C. auris* as other closely related species, including *C. haemulonii*, *C. famata*, or *C. lusitaniae*.[13] This occurs due to overlapping metabolic profiles and incomplete databases in older systems. Misidentification not only hampers infection control but may lead to inappropriate antifungal selection, particularly when resistance is unrecognized.[2]

Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry

Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) offers rapid and accurate identification of *C. auris* when the database is appropriately updated. Several manufacturers have incorporated *C. auris* into their libraries, but performance varies between platforms. Laboratories must validate their systems using reference isolates to ensure reliability.[1,14]

Molecular diagnostics

PCR-based assays, including real-time PCR and loop-mediated isothermal amplification (LAMP), provide species-level identification and rapid turnaround times. Targeted sequencing of the D1-D2 region of the 28S rRNA gene or the ITS region of rDNA offers high accuracy and clade differentiation.[15] Commercial panels like the T2 *Candida* Panel and BioFire® FilmArray® may not yet reliably detect *C. auris*, though updates are in progress.[4]

Culture-based methods

C. auris grows well on sabouraud dextrose agar and CHROMagar *Candida* Plus, which can help presumptively distinguish it from other *Candida* species based on colony color and morphology. However, colony characteristics alone are insufficient for confirmation. Growth at 42 °C and tolerance to high salt concentrations (e. g., 10% NaCl) can also be supportive traits.[13]

Surveillance and screening

Because *C. auris* frequently colonizes patients asymptomatically, active screening in high-risk units such as ICUs is essential. Swabs from the axilla, groin, and nares are commonly used. Selective enrichment broths and chromogenic media can enhance detection. Genomic surveillance through WGS is also being adopted to track transmission and clade emergence.[2,4]

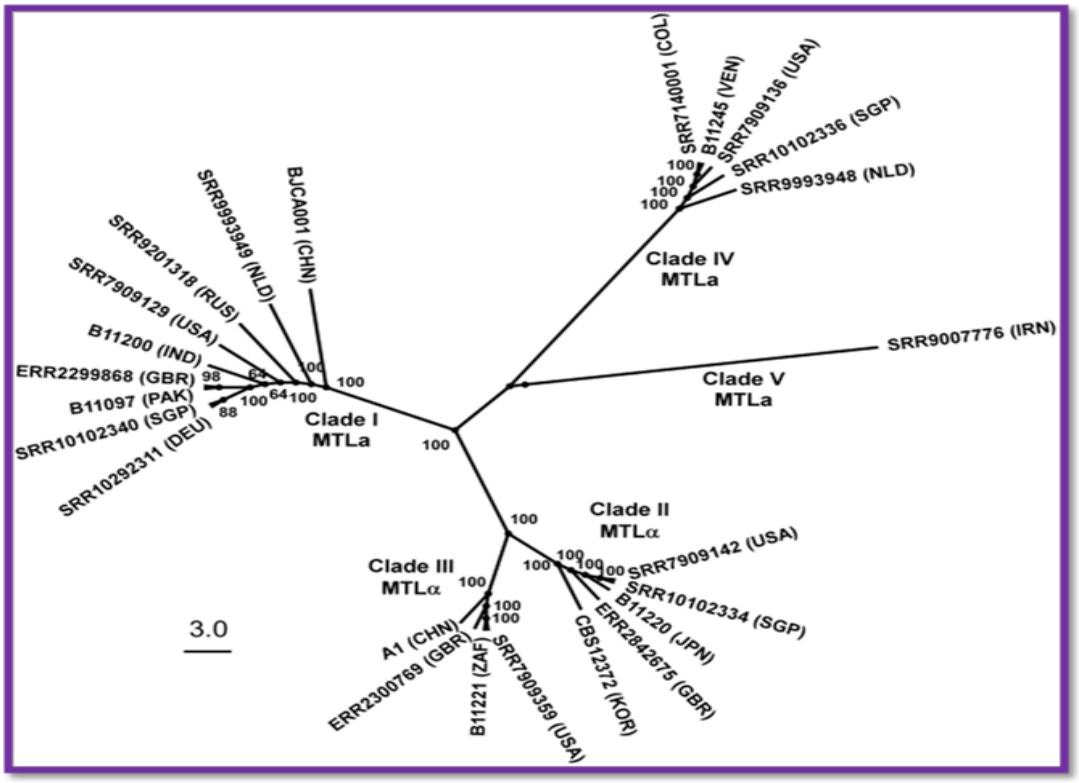

Figure 2: Global map depicting the spread of *C. auris* infections since its discovery, with annotations for country-level case numbers and distribution.

Data reflects CDC surveillance and regional outbreak reports.[4]

Epidemiology and mortality since its discovery, *C. auris* reported in over 40 countries (Figure 2). Crude mortality rates for *C. auris* bloodstream infections range from 30-72%, with outbreaks often linked to healthcare settings.

EMERGING THERAPEUTIC STRATEGIES AND ANTIFUNGAL PIPELINE

Treatment of *C. auris* infections is complicated by its frequent resistance to 1st-line antifungals and its ability to acquire resistance during therapy.[4,9] Despite these challenges, several promising therapeutic strategies and novel antifungal agents are in development/early clinical use.[14,15]

Current treatment options

Echinocandins, such as caspofungin, micafungin, and anidulafungin, remain the first-line treatment for *C. auris* infections.[4] However, treatment failures have been reported, especially in strains harboring FKS1 mutations.[6] Amphotericin B may be used as a second-line agent but carries risks of nephrotoxicity. High-dose liposomal amphotericin B is sometimes employed in refractory cases. Azoles are generally avoided unless susceptibility testing confirms sensitivity.[2]

Combination therapies

Given the high rates of multidrug resistance, combination therapy is an attractive strategy. Preclinical studies suggest that combining echinocandins with amphotericin B or azoles may enhance antifungal efficacy and reduce the likelihood of resistance development.[16] However, clinical data remain limited, and combination regimens are not yet standardized.

New antifungal agents

Several antifungal drugs with novel mechanisms of action are advancing through clinical development:

Ibrexafungerp (SCY-078): A triterpenoid glucan synthase inhibitor with oral bioavailability. It has demonstrated activity against *C. auris*, including echinocandin-resistant strains.[15]

Manogepix (APX001): Targets the fungal enzyme Gwt1, disrupting GPI-anchor biosynthesis. It shows potent activity against resistant *Candida* species.[14]

Rezafungin: A long-acting echinocandin with once-weekly dosing potential, effective against *C. auris* biofilms and resistant isolates.[17]

Fosmanogepix: A prodrug of manogepix, currently in phase 2 trials for invasive fungal infections, including *C. auris*.[18]

Immunotherapy and adjunctive treatments

Monoclonal antibodies targeting fungal antigens, immune checkpoint modulators and cytokine therapies are being explored.

Although still in experimental stages, these approaches may offer adjunctive benefits, particularly for immunocompromised patients.[19]

Antifungal stewardship

Optimizing antifungal use is critical to prevent further resistance development. Antifungal stewardship programs, rapid diagnostics, and susceptibility testing should be integrated into clinical practice, particularly in high-risk hospital settings.[4,16] The ongoing development of novel therapeutics and improved treatment strategies offers hope for managing multidrug-resistant *C. auris* infections.

Continued clinical trials and real-world data collection will be essential to guide evidence-based treatment recommendations.

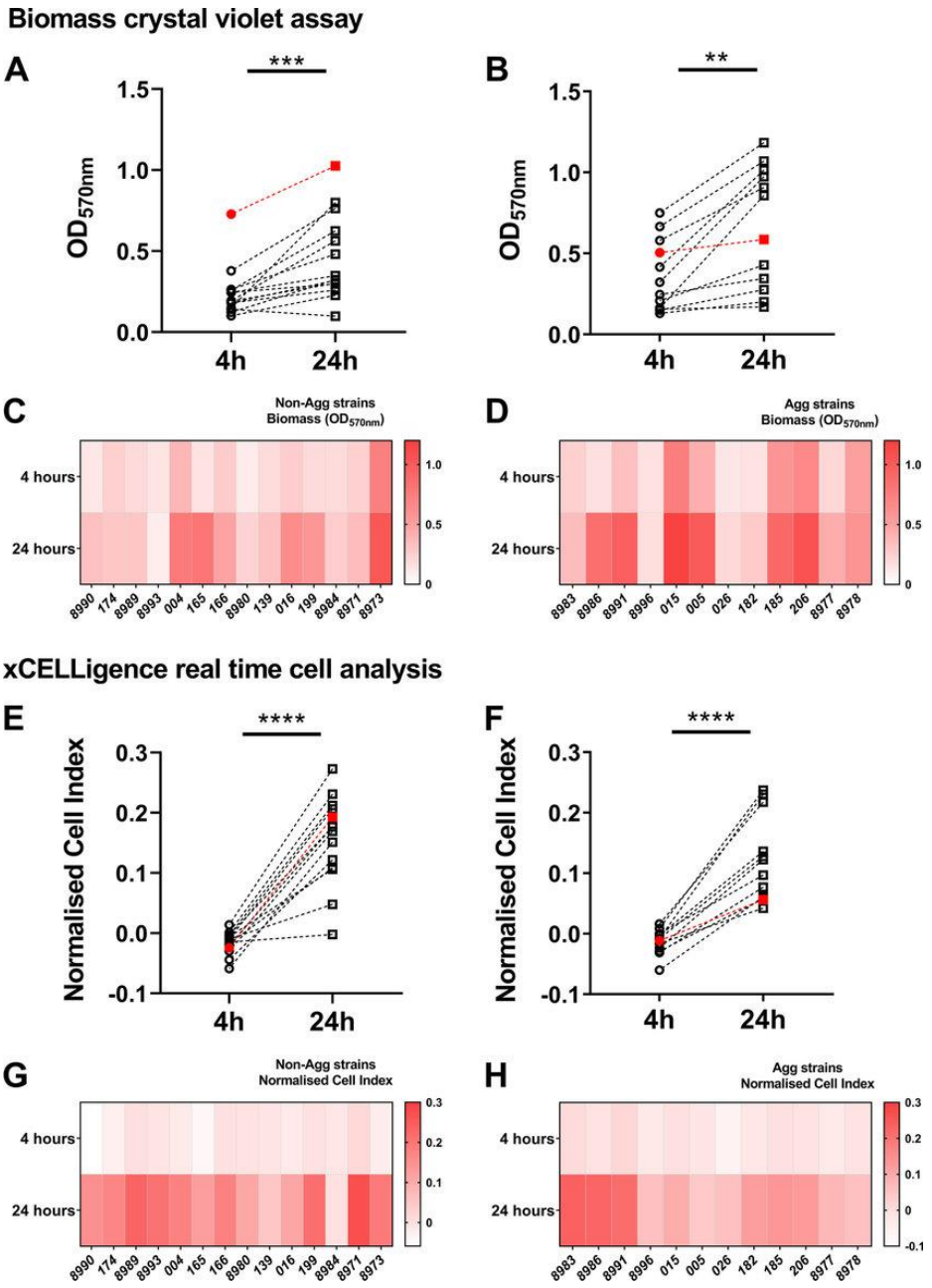

Figure 3: Biomass formation and real-time cell index assessment of non-aggregative and aggregative *C. auris* strains over 4- and 24-hours using crystal violet and xCELLigence impedance-based assays.
Significant increases in biofilm mass and cell index are observed over time. Data represent distinct strain behaviors.[12]

GENOMIC INSIGHTS AND MOLECULAR EPIDEMIOLOGY

The genomic characterization of *C. auris* has significantly advanced our understanding of its evolution, drug resistance, and epidemiological patterns. WGS and comparative genomics have revealed a high degree of genetic plasticity, enabling rapid adaptation and the emergence of multidrug resistance.[2,20]

Clade diversity and evolution

WGS analyses have identified at least five major clades of *C. auris*: South Asian (Clade I), East Asian (Clade II), South African (Clade III), South American (Clade IV), and a potential Iranian clade (Clade V).[21] These clades are genetically distinct, with thousands of single nucleotide polymorphisms (SNPs) separating them, indicating independent emergence rather than a single global spread. Notably, antifungal resistance profiles and virulence traits vary among clades, complicating treatment and infection control efforts.[7]

Resistance-associated mutations

Genomic studies have pinpointed key mutations responsible for antifungal resistance:

Azole resistance: Mutations in the ERG11 gene (e.g., Y132F, K143R) reduce azole binding affinity.[13]

Echinocandin resistance: Point mutations in the FKS1 gene hotspot regions (e.g., S639F) confer resistance to echinocandins.[10]

Efflux pump overexpression: ABC transporters (CDR1, CDR2) and MFS transporters (MDR1) contribute to multidrug resistance.[22]

In addition, mutations in transcription factors regulating drug efflux and stress response genes, such as TAC1B, have been associated with increased resistance.[10]

Genomic plasticity and adaptation

C. auris exhibits genomic features conducive to rapid adaptation, including high rates of chromosomal rearrangements, copy number variations, and potential for aneuploidy. These mechanisms facilitate environmental survival, antifungal resistance development, and persistence in hospital environments.[20]

Molecular epidemiology and outbreak investigation

WGS has become an essential tool for outbreak investigations and surveillance. Sequencing data help trace transmission pathways, identify clade-specific traits, and monitor the emergence of resistance mutations. Molecular typing methods, including amplified fragment length polymorphism (AFLP) and short tandem repeat (STR) analysis, complement WGS by providing rapid genotypic differentiation of isolates.[21]

Implications for public health

Understanding the genomic landscape of *C. auris* informs infection control policies, guides antifungal stewardship, and facilitates the development of targeted diagnostics and therapeutics. Continued global genomic surveillance is crucial for tracking the evolution and spread of this pathogen.[7]

INFECTION CONTROL AND PREVENTION STRATEGIES

Given the high transmissibility, environmental resilience, and multidrug resistance of *C. auris*, stringent infection control measures are critical to prevent nosocomial outbreaks and limit transmission.[4,8]

Standard and contact precautions

Patients identified with *C. auris* infection or colonization should be placed under contact precautions. This includes the use of gowns and gloves by healthcare personnel and, where possible, patient isolation or COHORT-ing. Strict adherence to hand hygiene with alcohol-based hand rubs or soap and water is essential.[4]

Environmental decontamination

C. auris can survive on surfaces for weeks, and standard cleaning agents may be ineffective. Disinfectants with proven efficacy-such as those containing chlorine, hydrogen peroxide, or quaternary ammonium compounds with sporicidal activity-should be used. Frequent cleaning of high-touch surfaces, medical equipment, and patient rooms is mandatory.[8,23]

Screening and surveillance

Active surveillance is essential, especially in intensive care units and long-term care facilities. Screening of close contacts and patients with prolonged hospitalization, mechanical ventilation, or prior broad-spectrum antibiotic use is recommended. Swabs from the axilla, groin, and the other skin sites can detect asymptomatic colonization.[4,24]

Outbreak response

In the event of an outbreak, rapid identification of cases, environmental sampling, COHORTING of affected patients, and reinforcement of infection control protocols are vital. WGS can assist in tracing transmission pathways and identifying clonal outbreaks.[2,25]

Antifungal stewardship

Antifungal stewardship programs help minimize the unnecessary use of antifungals, reducing the selection

pressure for resistance development. These programs should promote evidence-based prescribing, dose optimization, and susceptibility testing.[9]

Education and training

Regular education sessions for healthcare personnel on *C. auris* transmission, infection control practices, and antimicrobial resistance are essential to ensure compliance and vigilance.[8]

By implementing these comprehensive strategies, healthcare facilities can reduce the incidence of *C. auris* transmission and improve patient outcomes.

FUTURE DIRECTIONS AND RESEARCH PRIORITIES

Despite significant advances in understanding *C. auris*, major gaps remain in diagnostics, therapeutics, epidemiology, and our understanding of the pathogen's biology. Addressing these gaps is critical for controlling the spread of this emerging threat.[4,8]

Development of rapid and accurate diagnostics

Timely identification of *C. auris* is key to effective treatment and infection control. Continued development and validation of affordable, rapid diagnostic tools-especially in resource-limited settings-are a priority.[26] Molecular assays, point-of-care tests, and enhanced MALDI-TOF MS databases are promising directions.[3]

Novel therapeutic agents

Current treatment options are limited by high resistance rates. Research into new antifungal classes, improved formulations of existing drugs, and combination therapies must continue.

Promising candidates like ibrexafungerp, fosmanogepix, and rezafungin require further clinical evaluation for efficacy and safety against multidrug-resistant *C. auris*.[15,27]

Understanding resistance mechanisms

Greater insight into the molecular mechanisms of antifungal resistance-including the roles of efflux pumps, stress response pathways, and biofilm-associated resistance-can inform drug development and resistance surveillance.[10,11]

Vaccine and immunotherapy development

Preventive strategies, including vaccines and immunotherapies targeting virulence factors or enhancing host immune responses, are underexplored but could offer valuable adjuncts to antifungal treatment, especially for high-risk patients.[28,29]

Genomic surveillance and molecular epidemiology

Expansion of global genomic surveillance will allow for better tracking of transmission patterns, clade evolution, and emergence of novel resistance mutations. Integrating WGS into routine surveillance can improve outbreak response and inform infection control practices.[2,25]

Public health preparedness

Healthcare systems must be equipped to manage *C. auris* outbreaks, including staff training, resource allocation, and the development of comprehensive response protocols. International collaboration and data sharing are essential to combat the global spread of *C. auris*.[8,9]

By addressing these research priorities, the medical and scientific community can develop innovative solutions to mitigate the threat posed by *C. auris* and improve patient care outcomes.

CONCLUSION

C. auris represents a critical global health concern due to its rapid spread, high resistance to antifungal therapies, and persistence in healthcare environments. This review synthesized current insights into its resistance mechanisms, virulence traits, diagnostic hurdles, and emerging treatment options. Our findings underscore the urgent need for improved diagnostic tools, robust infection control practices, and continued development of novel antifungal agents. This work contributes to the growing knowledge base required to manage and mitigate the threat of multidrug-resistant C. auris infections worldwide.

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