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Antifungal Resistance in Invasive Candida and Aspergillus Species: Molecular Mechanisms, Global Epidemiology, and the Emerging Therapeutic Pipeline

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Abstract: Invasive fungal infections, predominantly caused by *Candida* and *Aspergillus* species, represent a major global mortality burden that is increasingly threatened by escalating resistance to primary antifungal classes such as azoles, echinocandins, and polyenes. This convergent crisis is clearly exemplified by the simultaneous global rise of multidrug-resistant *Candida auris* and the emergence of pan-azole-resistant *Aspergillus fumigatus* driven by environmental agricultural fungicide use. To bridge the gap between isolated resistance mechanisms and broader epidemiological trends, this review synthesises contemporary data across four core themes: molecular resistance pathways (including *CYP51A*, *FKS*, and *ERG11* mutations, alongside efflux and biofilm-associated resistance), the clade-structured transmission dynamics of *C. auris*, the environmental selection of azole-resistant *A. fumigatus*, and the therapeutic pipeline of novel agents like olorofim, ibrexafungerp, fosmanogepix, and rezafungin. Ultimately, the manuscript argues that fungal resistance must be managed as a complex "One Health" systems phenomenon spanning hospitals, farms, and the environment, requiring harmonised global surveillance, robust stewardship, and a reconceptualisation of invasive mycoses as a central priority within the global antimicrobial resistance agenda.

Keywords: *Invasive fungal infections; Candida auris; Aspergillus fumigatus; antifungal resistance; CYP51A mutations; echinocandin resistance; novel antifungals*.

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Introduction

Invasive fungal infections kill approximately 1.5 million people annually, a mortality burden comparable to tuberculosis, yet receive a fraction of the research investment. The emergence of pan-azole-resistant Aspergillus fumigatus, spreading from agricultural fungicide use through environmental routes, and the global dissemination of *Candida auris*, resistant to three of four antifungal drug classes at first isolation, represents a convergence of resistance threats that the infectious disease community is only beginning to fully appreciate (Burks et al., 2021; Chowdhary et al., 2017; Denning, 2024).

Over the past decade, estimates of the global incidence and mortality of severe fungal disease have roughly doubled as improved surveillance, diagnostics, and modelling have revealed the scale of previously under-recognised infections (Denning, 2024; Ikuta et al., 2024). Recent analyses suggest that around 6.5 million invasive fungal infections occur annually, with approximately 3.8 million deaths, of which nearly two-thirds are directly attributable to the mycosis rather than underlying comorbidities (Denning, 2024; Ikuta et al., 2024). Candida bloodstream infections and invasive candidiasis, together with invasive and chronic pulmonary aspergillosis, account for a substantial fraction of this burden, particularly among patients with haematological malignancies, solid organ or stem cell transplants, intensive-care admissions, and advanced HIV or chronic lung disease (Burks et al., 2021; Pappas et al., 2018).

Historically, antifungal resistance was perceived as a relatively contained problem, dominated by fluconazole resistance in Candida albicans and Candida glabrata, sporadic azole resistance in Aspergillus fumigatus, and occasional amphotericin B resistance in non-albicans Candida or Mucorales (Pappas et al., 2018; Rivero-Menéndez et al., 2019). Azole resistance in A. fumigatus was initially associated with long-term triazole therapy in chronic pulmonary aspergillosis, whereas echinocandin resistance emerged in the context of prolonged treatment for candidemia, often in patients with deep-seated foci and high fungal burdens (Rivero-Menéndez et al., 2019; Chen et al., 2024). What these earlier patterns shared was their linkage to individual patient-level selection under therapeutic drug pressure.

The discovery of environmentally selected, pan-azole-resistant A. fumigatus harboring promoter tandem repeat plus coding mutations in the CYP51A gene, such as TR34/L98H and TR46/Y121F/T289A, disrupted this framing by demonstrating that non-clinical triazole fungicide use could generate resistant strains that then cause invasive disease in azole-naïve patients (Burks et al., 2021; Hsu et al., 2022; Verweij et al., 2016). In parallel, the near-simultaneous emergence of four major clades of C. auris on multiple continents, each with high rates of resistance to azoles and, in some clades, to amphotericin B and echinocandins, highlighted that invasive candidiasis could also be driven by globally disseminated resistant clones adapted to the

health-care environment (Chow et al., 2020; Lockhart et al., 2017; Hayes, 2024).

These developments have prompted a conceptual shift from viewing antifungal resistance as a series of isolated case reports to recognising a complex, multi-scale phenomenon in which molecular mechanisms, ecological niches, health-care practices, and agricultural policies interact. The World Health Organization's fungal priority pathogens list explicitly places C. auris, A. fumigatus, C. albicans, and N. glabrata in the "critical" tier, reflecting both their current public health impact and their capacity for resistance evolution (WHO, 2022; Casalini et al., 2024; Zou et al., 2023). At the same time, antifungal drug development, long constrained by issues of toxicity, narrow therapeutic windows, and limited targets, is finally yielding first-in-class agents with novel mechanisms, including dihydroorotate dehydrogenase (DHODH) inhibition, Gwt1 inhibition, and triterpenoid glucan synthase inhibition (Gamal et al., 2021; Jallow & Govender, 2021; Maertens et al., 2025; Pappas et al., 2023).

Existing reviews tend to focus either on molecular mechanisms of resistance in individual genera, on the clinical management of specific syndromes such as invasive aspergillosis, or on the clinical development of new antifungals, but rarely integrate these strands (Burks et al., 2021; Gamal et al., 2021; Rivero-Menéndez et al., 2019; Verweij et al., 2016). The pattern that emerges from this fragmented literature is that critical cross-cutting questions such as how environmental azole resistance shapes empirical therapy algorithms, or how the resistance potential of new drugs should influence their stewardship, remain under-theorised and empirically underexplored. A holistic synthesis that links molecular resistance biology to population-level epidemiology and to the strategic deployment of the emerging pipeline is therefore overdue.

The purpose of this narrative review is to synthesize current evidence on antifungal resistance in invasive Candida and Aspergillus infections across four intersecting dimensions: (1) core molecular resistance mechanisms, with emphasis on CYP51A-mediated azole resistance in Aspergillus, FKS-mediated echinocandin resistance and ERG11 mutations in Candida, and efflux pump and biofilm-associated multidrug resistance; (2) the global clade structure, transmission dynamics, and resistance phenotypes of C. auris; (3) environmental selection and dispersion of azole-resistant A. fumigatus driven by agricultural fungicide use; and (4) the pharmacology, spectrum, and resistance potential of next-generation agents, including olorofim, ibrexafungerp, fosmanogepix, and rezafungin.

The manuscript is organised as follows. The next section develops a conceptual framework, defining key constructs and articulating why invasive mycology, resistance mechanisms, and antifungal development should be analysed together rather than in isolation. Subsequent thematic sections examine molecular resistance mechanisms (Theme 1), the unique epidemiology of C. auris (Theme 2), environmental azole resistance in A. fumigatus (Theme 3), and the novel antifungal pipeline (Theme 4). These are followed by a critical synthesis that integrates findings across themes, a discussion of research, clinical, policy, and theoretical implications, a brief reflection on limitations of this review, and a concluding section that argues for a re-positioning of invasive mycoses within the broader antimicrobial resistance agenda.

Conceptual Framework

Key Constructs and Boundaries

This review focuses on invasive disease caused by Candida and Aspergillus species, defined as infection of normally sterile sites (for Candida, bloodstream or deep tissues; for Aspergillus, invasion beyond the bronchial mucosa into lung parenchyma or other organs) (Pappas et al., 2018; Patterson et al., 2016). Superficial candidiasis, allergic bronchopulmonary aspergillosis, and colonisation are not considered except where they serve as precursors to invasive disease or reservoirs for resistance selection. The discussion is restricted to resistance mechanisms with clear clinical relevance, those that alter minimum inhibitory concentrations (MICs) in ways that are associated with treatment failure or require regimen modification (CLSI, 2017; Rivero-Menéndez et al., 2019).

Four constructs are central. First, *molecular resistance mechanisms* refer to defined genetic or regulatory changes such as point mutations, promoter tandem repeats, gene overexpression, or biofilm-associated phenotypes that reduce susceptibility to one or more antifungal classes. Second, *invasive mycology* denotes the clinical and pathobiological study of deep-seated fungal infections in high-risk hosts. Third, *global epidemiology* here encompasses clade distributions, geographic spread, transmission dynamics, and resistance prevalence across regions and patient populations. Fourth, the *novel antifungal pipeline* comprises agents in late preclinical or clinical development with new targets or structural classes, with particular emphasis on DHODH inhibitors (olorofim), triterpenoid glucan synthase inhibitors (ibrexafungerp), Gwt1 inhibitors (fosmanogepix), and long-acting echinocandins (rezafungin) (Gamal et al., 2021; Jallow & Govender, 2021; Maertens et al., 2025; Pappas et al., 2023).

Conceptual clarity also requires distinguishing intrinsic resistance, innate reduced susceptibility in wild-type isolates of certain species, from acquired resistance that arises through de novo mutation or horizontal transmission under drug pressure (ISHAM, 2025; Rivero-Menéndez et al., 2019). Candida krusei and several non-fumigatus Aspergillus species illustrate intrinsic azole or echinocandin resistance, whereas C. auris and azole-resistant A. fumigatus represent acquired resistance amplified by clonal expansion (Burks et al., 2021; Chowdhary et al., 2017; Verweij et al., 2016). Conceptually, invasive disease in a high-risk host can thus result either from an intrinsically resistant species encountering empirical therapy to which it is poorly susceptible, or from acquired resistance in previously susceptible species.

Theoretical Underpinnings of the Intersecting Fields

At a mechanistic level, most clinically relevant antifungals target a limited set of processes: ergosterol biosynthesis (azoles, polyenes), β-1,3-D-glucan synthesis (echinocandins, triterpenoid glucan synthase inhibitors), nucleic acid synthesis (flucytosine), or, for newer agents, pyrimidine biosynthesis (DHODH inhibitors) and glycosylphosphatidylinositol (GPI) anchor biosynthesis (Gwt1 inhibitors) (Cowen et al., 2014; Gamal et al., 2021; Pappas et al., 2018). From an evolutionary perspective, resistance reflects the interplay between selective pressure (drug exposure in humans, animals, and the environment), mutation supply and genetic background, and the fitness costs or benefits of resistance mutations in different niches (Cowen et al., 2014; Chen et al., 2020).

Invasive mycology brings host factors into this equation. Profound neutropenia, allogeneic stem cell transplantation, and high-dose corticosteroid or biologic immunosuppression creates ecological opportunities for opportunistic moulds and yeasts that would otherwise be cleared or contained (Patterson et al., 2016; Pappas et al., 2018). In these settings, high organism burdens, deep-seated foci, and prolonged therapy create ideal conditions for within-host selection of resistance, particularly for fungistatic azoles and echinocandins used as monotherapy (Rivero-Menéndez et al., 2019; Chen et al., 2024). At the same time, intensive-care and long-term acute-care environments provide opportunities for onward transmission of resistant clones, as seen for *C. auris* (Chow et al., 2020; Hayes, 2024).

Global epidemiology provides the population-level context in which these processes unfold. The recognition of multiple C. auris clades emerging nearly simultaneously across continents, as well as the convergent emergence of TR34/L98H and TR46/Y121F/T289A in A. fumigatus in disparate geographic regions, exemplifies parallel evolution under shared selection regimes rather than simple linear spread from a single source (Burks et al., 2021; Chowdhary et al., 2017; Chow et al., 2020). International trade in agricultural commodities, cross-border health-care referral networks, climate change, and urbanisation all modulate the spatial and temporal dynamics of resistant fungi, in ways that are only beginning to be systematically mapped (Burks et al., 2021; Casalini et al., 2024; Zou et al., 2023).

Rationale for Synthesising These Fields

The conceptual rationale for treating molecular resistance mechanisms, invasive disease epidemiology, and the antifungal pipeline as a single analytical object is threefold. First, molecular mechanisms strongly shape clinical outcomes and stewardship decisions but cannot be interpreted without epidemiological context. For example, the risk-benefit calculus of azole monotherapy versus combination therapy in invasive aspergillosis depends on local prevalence of CYP51A-mediated resistance and the relative fitness of resistant strains (Burks et al., 2021; Patterson et al., 2016; Verweij et al., 2016). Second, the value and vulnerability of new antifungals depend on the resistance landscape into which they are introduced. Agents that circumvent existing mechanisms may still select for novel or collateral pathways if deployed without stewardship informed by molecular epidemiology (Gamal et al., 2021; Maertens et al., 2025; Pappas et al., 2023).

Third, policy and surveillance frameworks, as codified in the WHO fungal priority pathogens list and emerging ISHAM-led resistance networks, increasingly emphasise a One Health perspective that links environmental, agricultural, and clinical drivers (ISHAM, 2025; WHO, 2022; Zou et al., 2023). To be decision-useful for these agendas, scientific syntheses must therefore traverse disciplinary silos. This review argues that understanding antifungal resistance in invasive Candida and Aspergillus infections requires an explicitly integrative conceptual lens, in which gene-level changes are embedded in pathogen populations, health-care systems, and global drug and fungicide markets.

Table 1 summarises key constructs and distinctions used throughout the manuscript, providing a scaffold for the thematic analyses that follow.

Table 1
Antifungal resistance mechanisms, clinical entities, and conceptual distinctions

Table 1.

Key definitions and conceptual distinctions in invasive candidiasis and aspergillosis

Concept/term	Definition	Illustrative examples
Invasive candidiasis	Bloodstream or deep-seated infection by Candida spp. with clinical signs of sepsis or organ invasion	Candidemia in ICU patient with central venous catheter; hepatosplenic candidiasis in leukaemia
Invasive aspergillosis	Angioinvasive infection by Aspergillus spp., usually in lungs or sinuses, in immunocompromised host	Pulmonary invasive aspergillosis in allogeneic HSCT recipient
Intrinsic resistance	Innate reduced susceptibility present in wild-type isolates of a species	C. krusei to fluconazole; A. terreus to amphotericin B
Acquired resistance	Resistance arising via mutation, recombination, or horizontal spread under drug pressure	FKS1 mutations in C. glabrata after prolonged echinocandin therapy
Target-site mutation	Amino acid substitution in drug target reducing binding affinity	CYP51A TR34/L98H in A. fumigatus; ERG11 Y132F in Candida
Efflux-mediated resistance	Upregulation of transporters exporting drug from fungal cell	Overexpression of CDR1/CDR2 in azole-resistant C. albicans
Biofilm-associated resistance	Reduced susceptibility due to biofilm architecture, matrix, and altered physiology	C. auris biofilms on indwelling devices resistant to azoles and amphotericin B
One Health antifungal resistance	Integrated perspective linking human, animal, and environmental drivers of resistance	Azole fungicide use selecting TR34/L98H A. fumigatus that infects humans.

Note. HSCT = haematopoietic stem cell transplantation. Definitions synthesized from Burks et al. (2021), Casalini et al. (2024), Pappas et al. (2018), and Rivero-Menéndez et al. (2019).

Theme 1: Molecular Resistance Mechanisms

CYP51A-Mediated Azole Resistance in Aspergillus fumigatus

To contextualise these genetic changes, **Figure 1** outlines the primary cellular targets of current and emerging antifungals alongside their respective molecular resistance mechanisms. A

consistent observation across molecular studies is that the bulk of clinically significant triazole resistance in A. fumigatus is mediated by mutations in CYP51A, encoding the azole target 14-α-sterol demethylase, often coupled with promoter alterations that increase gene expression (Burks et al., 2021; Chen et al., 2020; Hsu et al., 2022; Verweij et al., 2016). Point mutations at residues such as G54, G138, M220, and G448 reduce azole binding and are frequently seen in isolates from patients with chronic pulmonary aspergillosis exposed to long-term itraconazole or voriconazole therapy (Chen et al., 2020; Hsu et al., 2022). In contrast, environmental resistance is dominated by tandem repeat–associated alleles, notably TR34/L98H and TR46/Y121F/T289A, in which a promoter repeat enhances CYP51A expression while the coding change further diminishes drug affinity (Burks et al., 2021; Hsu et al., 2022; Verweij et al., 2016).

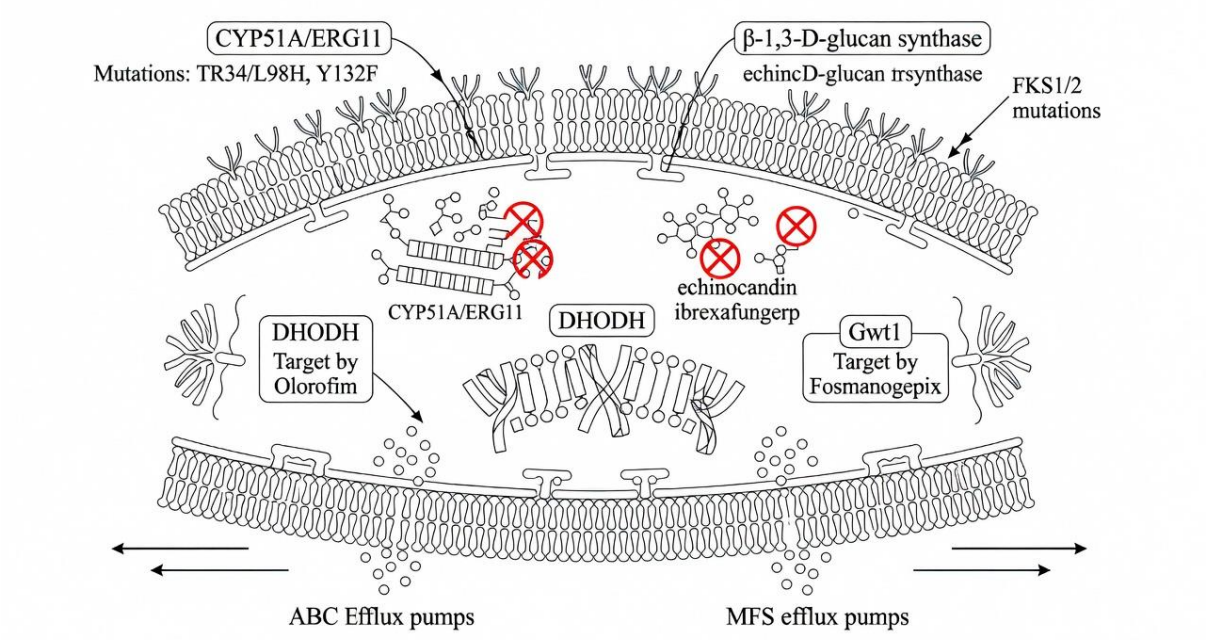

Figure 1: Schematic representation of a fungal cell highlighting primary antifungal targets and corresponding molecular resistance mechanisms. Azoles inhibit CYP51A/ERG11, with resistance heavily mediated by key genetic mutations such as TR34/L98H and Y132F. Echinocandins and the triterpenoid ibrexafungerp target beta-1,3-D-glucan synthase, where FKS1/2 point mutations can significantly reduce drug susceptibility. Emerging agents olorofim and fosmanogepix engage entirely novel cellular targets—DHODH and Gwt1, respectively—allowing them to bypass these traditional resistance pathways. Additionally, the upregulation of ABC and MFS efflux pumps contributes to multidrug resistance by actively exporting therapeutic agents out of the intracellular space.

Global epidemiological syntheses suggest that TR34/L98H is now widely distributed across Europe, Asia, and parts of Africa and the Americas, with environmental surveys frequently detecting it in agricultural soils, compost, and air samples near intensive azole fungicide use (Burks et al., 2021; Sen et al., 2024; Verweij et al., 2016). TR46/Y121F/T289A, while less prevalent overall, has been linked to high-level voriconazole resistance and has emerged in multiple countries, indicating repeated selection rather than single-origin spread (Burks et al., 2021; Verweij et al., 2016). More recently, complex alleles incorporating additional substitutions (e.g., TR34/R65K/L98H, TR34/L98H/V242I/S297T/F495I, or novel G54 and M220 variants) have been reported, underscoring the dynamic nature of CYP51A evolution under combined agricultural and clinical azole pressure (Burks et al., 2021; Chen et al., 2020; Sen et al., 2024).

Functionally, these mutations variably affect susceptibility to different triazoles. TR34/L98H typically confers high-level resistance to itraconazole and reduced susceptibility to voriconazole and posaconazole, whereas TR46/Y121F/T289A is often associated with high voriconazole MICs and variable effects on other azoles (Burks et al., 2021; Chen et al., 2020). The clinical implication is that in settings with substantial environmental resistance, voriconazole monotherapy for invasive aspergillosis may be unreliable unless local resistance rates are low and susceptibility testing is routinely performed (Patterson et al., 2016; Verweij et al., 2016).

A critical observation from in vitro evolution and protein modelling studies is that CYP51A mutations often incur modest fitness costs, which can be mitigated by compensatory changes or by the ecological advantages conferred in azole-contaminated environments (Chen et al., 2020; Sen et al., 2024). This pattern helps explain the persistence and spread of resistant clones despite the absence of continuous drug exposure in individual human hosts. It also suggests that interventions confined to clinical stewardship, without addressing environmental fungicide use, may be insufficient to reverse established resistance.

FKS Gene Mutations and Echinocandin Resistance in Candida

Echinocandins inhibit β-1,3-D-glucan synthase, whose catalytic subunits are encoded by FKS genes (primarily FKS1 and FKS2 in Candida). Echinocandin resistance across Candida species typically arises via amino acid substitutions in conserved “hot spot” regions of these genes, resulting in elevated MICs and reduced in vivo efficacy (Rivero-Menéndez et al., 2019; Chen et al., 2024; Zajac et al., 2025). In C. glabrata, which displays higher baseline MICs and a greater propensity for resistance than C.

albicans, mutations in FKS2 hot spot 1 (e.g., S663P, F659del) are the most common, although FKS1 mutations also occur and may be associated with distinct phenotypic profiles (Memon et al., 2023; Rivero-Menéndez et al., 2019; Zajac et al., 2025).

Clinical series of serial C. glabrata isolates from patients on prolonged echinocandin therapy consistently demonstrate stepwise acquisition of FKS mutations coupled with rising MICs and breakthrough candidemia or persistent deep-seated infection (Rivero-Menéndez et al., 2019; Chen et al., 2024). Recent genomic work further reveals that structural variation and hotspot gene conversion events between FKS1 and FKS2 can contribute to high-level resistance and complex MIC patterns (Zajac et al., 2025). The pattern that emerges is that chronic deep-seated candidiasis in heavily treated hosts provides a fertile ground for mosaic FKS genotypes, some of which can disseminate within hospitals.

Echinocandin resistance has also been described in C. auris, where FKS1 mutations such as S639P are associated with elevated MICs and reduced responsiveness in animal models and clinical series (Chow et al., 2020; Lockhart et al., 2017; Zajac et al., 2025). Notably, however, the baseline MIC distribution and clinical breakpoints for C. auris remain under refinement, complicating interpretation. This reinforces the need for standardised susceptibility testing and genotype–phenotype correlation studies specifically in this species.

ERG11 Mutations, Efflux Pumps, and Multidrug Resistance in Candida and Aspergillus

In Candida species, azole resistance is frequently multifactorial, involving target-site mutations in ERG11 (encoding 14-α-sterol demethylase), upregulation of efflux pumps from the ATP-binding cassette (ABC) and major facilitator superfamily (MFS), and changes in sterol biosynthesis pathways (Cowen et al., 2014; Jallow & Govender, 2021; Rivero-Menéndez et al., 2019). ERG11 mutations such as Y132F and K143R are widely reported in C. albicans, C. tropicalis, and C. auris and are associated with reduced fluconazole susceptibility (Chow et al., 2020; Jallow & Govender, 2021; Lockhart et al., 2017). In C. auris, copy number variation of ERG11, in combination with point mutations, appears to enhance azole resistance in specific clades (Chow et al., 2020; Lockhart et al., 2017).

Efflux pump overexpression, mediated by transcription factors such as TAC1 and MRR1, often acts synergistically with ERG11 alterations to produce high-level azole resistance (Cowen et al., 2014; Jallow & Govender, 2021). In C. auris, overexpression of CDR1, MDR1, and related transporters has been documented and linked to multidrug resistance and biofilm-associated persistence on surfaces and devices (Gamal et al., 2021; Jallow & Govender, 2021). A plausible mechanistic interpretation is that efflux and target-site mutation co-evolve under drug pressure, with efflux providing a first line of defence and ERG11 changes consolidating resistance.

In Aspergillus, azole resistance beyond CYP51A involves less well-characterised mechanisms, including overexpression of CYP51A or CYP51B, upregulation of ABC and MFS transporters, and alterations in membrane composition (Burks et al., 2021; Sen et al., 2024). Recent work in black aspergilli suggests that azole resistance can be driven primarily by efflux overexpression (e.g., mdr1, mfs genes) even in the absence of substantial structural CYP51A changes (Sen et al., 2024). Although extrapolation to A. fumigatus must be cautious, this evidence underscores that focusing exclusively on CYP51A may underestimate resistance complexity.

Biofilms, Stress Responses, and Tolerance Phenotypes

Beyond discrete mutations, biofilm formation and stress response pathways contribute importantly to reduced antifungal susceptibility. Candida biofilms on intravascular catheters and other devices exhibit marked tolerance to azoles and amphotericin B, mediated by altered metabolic states, extracellular matrix, and heterogeneous cell populations, including persister cells (Cowen et al., 2014; Jallow & Govender, 2021). C. auris, in particular, forms robust biofilms on skin and abiotic surfaces, with substantial reductions in azole and amphotericin B susceptibility compared with planktonic cells (Gamal et al., 2021; Jallow & Govender, 2021).

In Aspergillus, biofilm-like growth in chronic pulmonary cavities and on airway surfaces may similarly modulate drug penetration and stress responses, although direct clinical correlations remain limited (Burks et al., 2021). Stress response regulators, such as Hsp90 and calcineurin, buffer cells against antifungal-induced damage and can promote tolerance that precedes stable resistance (Cowen et al., 2014). Accumulating evidence suggests that inhibiting these pathways, for example with calcineurin inhibitors, could potentiate existing antifungals, but toxicity and drug–drug interactions remain limiting.

From a conceptual standpoint, these tolerance phenomena blur the binary category of susceptible versus resistant and emphasise that time-dependent killing dynamics, host immunity, and anatomical site must be integrated into resistance assessment. This becomes particularly salient when evaluating new agents whose MICs may not fully predict clinical behaviour in biofilm-rich or immunologically specialised compartments.

Theme 2: *Candida auris*: Global Clades, Transmission, and Multidrug Resistance

Clade Structure and Global Distribution

Candida auris has emerged as a paradigmatic example of an invasive fungal pathogen with global clade structure, high multidrug resistance, and strong adaptation to the health-care environment. As mapped in **Figure 2**, whole-genome sequencing studies have delineated at least five major clades: South Asian (Clade I), East Asian (Clade II), African (Clade III), South American (Clade IV), and a putative Iranian clade (sometimes termed Clade V) (Chow et al., 2020; Lockhart et al., 2017; mBio C. auris Consortium, 2020). These clades are genetically distinct, with tens of thousands of single nucleotide polymorphisms (SNPs) separating them, but relatively low diversity within clades, consistent with clonal expansion after emergence (Chow et al., 2020; Lockhart et al., 2017).

Retrospective case compilations and national surveillance reports indicate that Clade I is the most widely distributed and frequently associated with large nosocomial outbreaks, having been identified in South Asia, the Middle East, Europe, and North America (Chow et al., 2020; Hayes, 2024). Clade III predominates in parts of Africa and has also been exported to other continents, whereas Clade IV has been prominent in South America and more recently in North America (Chow et al., 2020; Hayes, 2024). Clade II, originally described from East Asian ear infections, appears less

frequently associated with invasive disease but exhibits notable resistance phenotypes (Chow et al., 2020; Hayes, 2024). Iran has reported genetically distinct isolates consistent with a fifth clade, implying that C. auris emergence is not a simple single-origin event (Chowdhary et al., 2017).

Genomic epidemiology studies further show that within-clade diversity accumulates primarily through point mutations and small structural variants, with limited recombination, reflecting the predominance of clonal, nosocomial transmission (Chow et al., 2020; Hayes, 2024). The pattern that emerges is of near-simultaneous regional emergences followed by rapid spread within and between health-care networks, amplified by interfacility transfers and gaps in infection prevention.

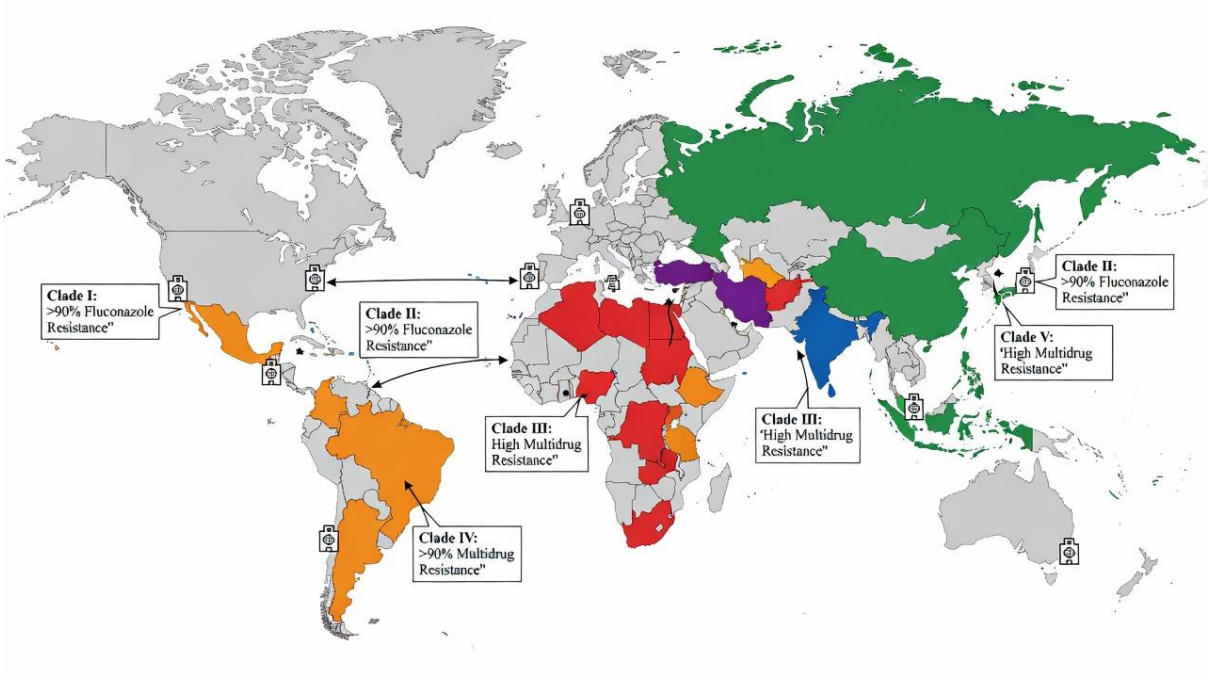

Figure 2:Global geographic distribution and primary resistance phenotypes of the five major Candida auris clades. The map outlines the presumed origins and predominant spread of the South Asian (Clade I), East Asian (Clade II), African (Clade III), South American (Clade IV), and putative Iranian (Clade V) clades. Clades I, III, and IV are most frequently associated with high fluconazole and multidrug resistance, driving severe nosocomial outbreaks and sustained transmission chains within global healthcare networks.

Hospital Transmission Dynamics and Outbreak Patterns

Unlike most other Candida species, which mainly colonise the gastrointestinal tract, C. auris preferentially colonises skin and the external auditory canal, facilitating environmental contamination and transmission via contact (Chow et al., 2020; Hayes, 2024). Outbreak investigations consistently document heavy contamination of bed rails, bedside tables, monitoring equipment, and reusable medical devices, with viable organisms persisting for weeks despite routine cleaning (Chow et al., 2020; Hayes, 2024). Misidentification by conventional biochemical or phenotypic methods, which may label C. auris as C. haemulonii or other uncommon yeasts, has also delayed recognition and control in many settings (Chowdhary et al., 2017; Hayes, 2024).

Risk factors for colonisation and infection include extended ICU stays, central venous catheters, broad-spectrum antibacterial exposure, prior antifungal therapy, mechanical ventilation, and severe underlying comorbidities (Hayes, 2024; Pappas et al., 2018). Once introduced into a high-acuity unit, C. auris can establish sustained transmission chains, with attack rates and colonisation prevalence influenced by infection prevention resources, patient turnover, and screening strategies (Hayes, 2024; Tsay et al., 2017). Whole-genome sequencing has been used to differentiate between multiple introductions and local amplification, revealing complex patterns in regions where multiple clades co-circulate (Chow et al., 2020; Hayes, 2024).

From a control perspective, C. auris behaves more like a multidrug-resistant bacterial pathogen than like traditional Candida species, necessitating active surveillance cultures, contact precautions, environmental decontamination with agents active against fungi (e.g., chlorine-based or hydrogen peroxide systems), and, in some cases, cohorting of patients and staff (Hayes, 2024; Tsay et al., 2017). Outbreak containment failures often trace back to delayed organism identification, inconsistent screening of contacts, limitations in environmental services, and underestimation of the organism's environmental hardiness.

Intrinsic and Acquired Multidrug Resistance

Phenotypically, C. auris is notable for high rates of resistance to azoles and amphotericin B and for emerging echinocandin resistance, with substantial geographic and clade-specific variation (Chow et al., 2020; Jallow & Govender, 2021; Lockhart et al., 2017). Many Clade I and IV isolates exhibit fluconazole MICs far above clinical breakpoints, often associated with ERG11 mutations such as Y132F or K143R and, in some cases, ERG11 copy number increases (Chow et al., 2020; Lockhart et al., 2017). Amphotericin B resistance, although variably defined, is reported in a significant minority of isolates, particularly in certain clades (Chow et al., 2020; Lockhart et al., 2017). Echinocandin resistance remains less common but is clinically consequential when FKS1 hot spot mutations emerge under therapy (Chow et al., 2020; Zajac et al., 2025).

Mechanistically, ERG11 mutations and overexpression underpin much of the azole resistance, while overexpression of ABC transporters (e.g., CDR1) and MFS pumps further reduces intracellular drug accumulation (Gamal et al., 2021; Jallow & Govender, 2021). FKS1 mutations, particularly S639P, have been correlated with elevated echinocandin MICs and breakthrough infections in both animal models and clinical series (Chow et al., 2020; Zajac et al., 2025). Biofilm formation and stress response activation add further layers of tolerance that may not be captured by planktonic MIC testing (Gamal et al., 2021; Jallow & Govender, 2021).

Mortality associated with C. auris candidemia remains high, with crude rates often exceeding 30–40%, although attribution to resistance per se is difficult because of confounding by host factors and care intensity (Hayes, 2024; Pappas et al., 2018). Nonetheless, the frequent need to resort to echinocandins sometimes in combination or with higher exposure targets limits therapeutic flexibility, especially in resource-limited settings where echinocandins may be unavailable or unaffordable.

Table 2 synthesises key features of the major C. auris clades, including geographic distribution, predominant resistance patterns, and typical outbreak settings.

Table 2

Candida auris clade-specific epidemiology and resistance patterns

Table 2

Candida auris clades: geographic distribution, resistance phenotypes, and outbreak characteristics

Clade	Presumed origin/primary regions	Typical resistance profile	Common outbreak settings
I (South Asian)	South Asia; Middle East; Europe; North America	High fluconazole resistance; variable amphotericin B; emerging echinocandin resistance	Tertiary ICUs, long-term acute-care hospitals, step-down units
II (East Asian)	East Asia (Japan, South Korea)	Variable azole resistance; some isolates less multidrug-resistant; often ear isolates	Otology clinics, medical wards, occasional ICU clusters
III (African)	Southern and Eastern Africa; export to other regions	High azole resistance; moderate amphotericin B resistance; sporadic echinocandin resistance	ICUs and high-dependency units, often in public hospitals
IV (South American)	South America; North America	High fluconazole resistance; variable amphotericin B and echinocandin susceptibility	Surgical ICUs, oncology units, long-term care facilities
Putative V (Iranian)	Iran	Limited data; often fluconazole-resistant, amphotericin B variable	Mixed hospital wards, including otolaryngology
Mixed-clade regions	Multiple continents with overlapping clades	Heterogeneous; local dominance of Clade I or IV common	Regions with high international patient transfer and referral networks

Note. Clade allocation and resistance profiles synthesised from Chow et al. (2020), Lockhart et al. (2017), Hayes (2024), and national surveillance reports. Resistance profiles are approximate and may change as surveillance expands.

Theme 3: Environmental Azole Resistance in Aspergillus fumigatus

Agricultural Fungicide Use and Selective Pressure

A striking feature of azole resistance in A. fumigatus is the clear ecological link to intensive azole fungicide use in agriculture and horticulture. Triazole fungicides used to protect cereals, fruits, ornamentals, and other crops share structural similarity with medical triazoles and target the same CYP51 enzymes, creating a shared selective landscape across environmental and clinical niches (Burks et al., 2021; Verweij et al., 2016). Environmental surveys in Europe, Asia, and Latin America consistently report higher prevalence of TR34/L98H and TR46/Y121F/T289A in soils and compost from sites with extensive fungicide applications than in untreated or minimally treated areas (Burks et al., 2021; Sen et al., 2024; Verweij et al., 2016).

The conceptual model that emerges, illustrated in **Figure 3**, is one of environmental amplification: azole-contaminated plant waste, compost, and soil serve as breeding grounds in which large, genetically diverse A. fumigatus populations are exposed to sustained sublethal azole concentrations, favouring the emergence and expansion of resistant genotypes (Burks et al., 2021; Chen et al., 2020; Sen et al., 2024). Air currents then disseminate conidia regionally and globally, leading to inhalation exposure in humans, including those with no prior azole therapy. Clinical isolates from azole-naïve patients frequently carry environmental TR alleles identical or closely related to environmental strains from the same region, supporting this model (Burks et al., 2021; Verweij et al., 2016).

From a One Health standpoint, this scenario parallels the emergence of extended-spectrum β-lactamase-producing Enterobacterales in livestock and the environment following extensive cephalosporin use: agricultural practices reshape the resistance landscape in ways that undermine human therapeutics. However, regulatory and surveillance frameworks for fungicide use remain less developed than for antibacterial agents, and harmonised environmental monitoring of azole residues and resistant A. fumigatus is still in its infancy.

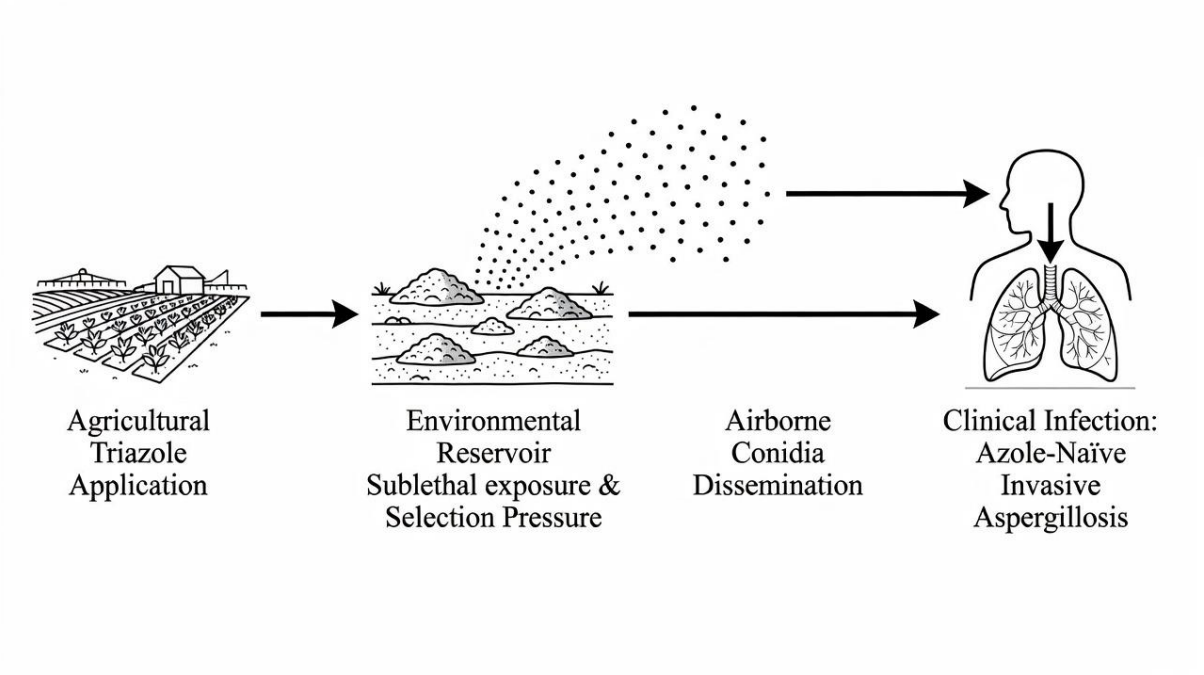

Figure 3:The environmental "One Health" transmission cycle of azole-resistant Aspergillus fumigatus. Intensive application of agricultural triazole fungicides creates a shared selective pressure in environmental reservoirs, such as compost and agricultural soils, driving the emergence and amplification of resistant genotypes like TR34/L98H. Airborne dissemination of these resistant conidia leads to direct inhalation exposures, causing severe, drug-resistant invasive aspergillosis in human hosts who are often completely naïve to prior medical azole therapy.

Global Spread and Hotspots of Azole-Resistant Aspergillus fumigatus

Aggregated data from environmental and clinical surveys suggest that environmental azole-resistant A. fumigatus has been documented on all inhabited continents, with especially high prevalence in parts of Western Europe, South Asia, and East Asia (Burks et al., 2021; Hsu et al., 2022; Verweij et al., 2016). Countries such as the Netherlands, the United Kingdom, India, and China have reported TR34/L98H or TR46/Y121F/T289A in 5–30% of environmental or clinical isolates, although estimates vary widely across sites and over time (Burks et al., 2021; Hsu et al., 2022). Hotspots often coincide with regions of intensive flower bulb, vegetable, or cereal production with frequent azole spraying and with composting operations that generate large volumes of spore-rich dust (Burks et al., 2021; Sen et al., 2024).

Clinical data indicate that infection with azole-resistant A. fumigatus is associated with higher mortality in invasive aspergillosis, particularly when azole monotherapy is used empirically without knowledge of local resistance rates (Patterson et al., 2016; Verweij et al., 2016). Although some centres have implemented routine susceptibility testing or molecular detection of TR alleles in high-risk patients, coverage remains patchy, and many resistant infections likely go unrecognised. Moreover, surveillance methodologies differ in sampling, breakpoints, and molecular targets, complicating cross-country comparisons (Burks et al., 2021; Hsu et al., 2022).

A critical gap is the limited integration of environmental and clinical surveillance data. Many agricultural regions with extensive azole use lack mycological monitoring capacity, and hospital-based laboratories seldom have resources to sequence resistant isolates or link them to environmental sources. Recent initiatives led by ISHAM and European consortia aim to harmonise protocols and create shared databases, but these efforts are still nascent (ISHAM, 2025; Verweij et al., 2016). Without such integration, the full scope of environmentally mediated resistance selection will remain underestimated, and policy responses will be slow.

Environmental Surveillance and Policy Responses

Emerging environmental surveillance programs illustrate both the potential and the challenges of monitoring azole-resistant A. fumigatus. Studies that systematically sample soils, compost, and air in proximity to agricultural sites, industrial composting facilities, and urban centres have identified discrete hotspots where resistant A. fumigatus constitutes a substantial fraction of isolates, often with dominant TR alleles (Burks et al., 2021; Sen et al., 2024). These data have prompted calls for targeted risk-mitigation strategies, such as limiting the use of certain triazoles, rotating fungicide classes, or modifying composting practices to reduce spore release (Burks et al., 2021; Verweij et al., 2016).

Regulatory responses, however, have been uneven. While some European agencies have issued guidance on balancing agricultural productivity with antifungal stewardship, many countries lack explicit frameworks for considering the human health consequences of fungicide licensing decisions (Burks et al., 2021; Casalini et al., 2024). In low- and middle-income settings, informal pesticide markets and limited enforcement further complicate control efforts. The evidence to date suggests that incremental, voluntary changes at farm level are unlikely to suffice without coordinated policy measures informed by integrated surveillance.

These considerations have direct implications for therapeutic decision-making. In regions with documented environmental resistance, guidelines increasingly recommend considering lipid amphotericin B formulations or combination therapy with an echinocandin for severe invasive aspergillosis, particularly in azole-naïve patients at high risk for resistant A.

fumigatus (Patterson et al., 2016; Verweij et al., 2016). As the next section explores, the emergence of agents such as olorofim that bypass the ergosterol pathway entirely could, if used judiciously, provide alternative options in these settings.

Theme 4: The Novel Antifungal Pipeline: Mechanisms, Spectra, and Resistance Potential

Olorofim: DHODH Inhibition outside the Ergosterol Pathway

Olorofim (F901318) inaugurates the orotomide class and targets fungal dihydroorotate dehydrogenase (DHODH), a key enzyme in de novo pyrimidine biosynthesis, thereby disrupting nucleic acid synthesis and cell proliferation (Gamal et al., 2021; Maertens et al., 2025; Wiederhold, 2020). Olorofim exhibits potent in vitro activity against Aspergillus spp., including many azole-resistant A. fumigatus isolates, and against several difficult-to-treat moulds such as Lomentospora prolificans and Scedosporium species, while showing limited activity against most yeasts, including Candida (Gamal et al., 2021; Maertens et al., 2025).

Phase 2b clinical data in patients with invasive mould infections who had limited treatment options suggest that olorofim achieves encouraging response rates, with day-42 all-cause mortality in the range of 15–20% in a population with substantial baseline mortality risk (Maertens et al., 2025; Wiederhold, 2020). Preliminary analyses indicate activity against infections refractory to or intolerant of existing agents, including invasive aspergillosis due to azole-resistant strains (Maertens et al., 2025). The drug's oral bioavailability and favourable pharmacokinetics offer practical advantages for step-down therapy and outpatient management.

Resistance potential remains an open question. Laboratory studies have identified DHODH mutations that reduce olorofim susceptibility, and there is concern that monotherapy in high-burden disease could select such variants (Gamal et al., 2021). However, the distinct target and lack of cross-resistance to ergosterol-pathway agents provide a valuable option in settings dominated by CYP51A-mediated resistance. The evidence to date suggests that integrating olorofim into combination regimens and stewardship frameworks that limit prolonged monotherapy in high-inoculum disease may be prudent.

Ibrexafungerp: Oral Triterpenoid Glucan Synthase Inhibition

Ibrexafungerp is a first-in-class triterpenoid antifungal that inhibits β-1,3-D-glucan synthase through a binding site partially overlapping but not identical to that of echinocandins (Gamal et al., 2021; Jallow & Govender, 2021; Walley et al., 2025). It combines fungicidal activity against Candida with oral bioavailability, high tissue penetration, and activity at low pH, making it attractive for both mucosal and invasive indications.

In vitro, ibrexafungerp demonstrates broad activity against Candida species, including many azole-resistant and echinocandin-resistant isolates, as well as potent activity against C. auris (Gamal et al., 2021; Jallow & Govender, 2021). Clinical development has so far focused on vulvovaginal candidiasis and recurrent disease, where phase 2 and 3 trials have shown superior or non-inferior cure rates compared with fluconazole, with acceptable safety (Jallow & Govender, 2021; Nyirjesy et al., 2021). Early data in invasive candidiasis, including cases due to resistant Candida, suggest promising efficacy, though patient numbers remain small (Gamal et al., 2021).

Mechanistically, ibrexafungerp binds to the Fks complex at a different site than echinocandins, and some echinocandin-resistant FKS mutations do not fully abrogate its activity (Gamal et al., 2021). Nonetheless, in vitro resistance can be selected via FKS mutations, and cross-resistance with echinocandins has been described for certain alleles, indicating that indiscriminate use could eventually erode its utility (Gamal et al., 2021; Walley et al., 2025). The pattern that emerges is that ibrexafungerp offers a near-term opportunity to expand options against resistant Candida, including C. auris, provided that its use is guided by susceptibility testing and stewardship.

Fosmanogepix: Targeting Gwt1 and the GPI Anchor Pathway

Fosmanogepix is an oral and intravenous prodrug of manogepix, which inhibits Gwt1, an inositol acyltransferase essential for early steps in glycosylphosphatidylinositol (GPI) anchor biosynthesis (Pappas et al., 2023; Vazquez et al., 2023). Inhibition of Gwt1 disrupts the anchoring of mannoproteins to the fungal cell wall, resulting in impaired adherence, biofilm formation, germ tube development, and ultimately cell death (Pappas et al., 2023; Kapoor et al., 2019). Crucially, the mammalian ortholog PIG-W has low homology, conferring a therapeutic window.

Fosmanogepix exhibits potent in vitro activity against a broad range of yeasts and moulds, including Candida spp., C. auris, aspergilli, and some rare moulds, with MICs often substantially lower than those of comparators (Pappas et al., 2023; Vazquez et al., 2023; Kapoor et al., 2019). Phase 2 clinical trials in candidemia and invasive candidiasis report treatment success rates around 80% with favourable safety and pharmacokinetics, including in patients with renal impairment (Pappas et al., 2023; Bulpa et al., 2020). A dedicated study in C. auris candidemia demonstrates high microbiological and clinical response rates, reinforcing the drug's potential in multidrug-resistant settings (Vazquez et al., 2023).

Resistance development in vitro appears infrequent but not absent. Mutations in GWT1 can confer reduced susceptibility, yet their fitness costs and clinical prevalence remain under active investigation (Kapoor et al., 2019). Of particular interest is the agent's activity against biofilms and its potential synergy or additivity with echinocandins or polyenes in recalcitrant infections. The available data support cautious optimism that fosmanogepix, if appropriately stewarded, could substantially expand the therapeutic armamentarium against resistant Candida, including C. auris.

Rezafungin: Long-Acting Echinocandin

Rezafungin is a structurally modified echinocandin designed for enhanced stability and prolonged half-life, allowing once-weekly intravenous administration (Thompson et al., 2023; Locke et al., 2024). Its mechanism of action mirrors that of other echinocandins: non-competitive inhibition of β-1,3-D-glucan synthase, but its pharmacokinetic properties enable high front-loaded exposures and sustained levels above the MIC, which may be advantageous in both treatment and prophylaxis (Thompson et al., 2023; Locke et al., 2024).

The phase 3 ReSTORE trial demonstrated that rezafungin was non-inferior to daily caspofungin for treatment of candidemia and invasive candidiasis, with similar global cure rates, mycological eradication, and all-cause mortality (Thompson et al., 2023; Locke et al., 2024). Sub-analyses in immunocompromised patients suggest comparable efficacy and safety, supporting its use

in high-risk populations (Sandison et al., 2023). In vitro, rezafungin retains activity against most Candida species, including some isolates with elevated MICs to older echinocandins, though cross-resistance mediated by FKS mutations remains a concern (Locke et al., 2024).

From a resistance standpoint, the key question is whether once-weekly dosing alters the selection dynamics for FKS mutations. The high initial exposures may suppress mutant amplification, but prolonged low-level tails could theoretically favour tolerant subpopulations. Empirical data addressing this are limited, and careful post-marketing surveillance will be required. Nevertheless, rezafungin's simplified dosing and prophylactic potential in settings such as stem cell transplantation make it an important addition to the pipeline, especially where adherence and line access are challenges.

Table 3 summarises the mechanisms, spectra, and key clinical data for these four agents, highlighting how they might be positioned relative to existing drug classes.

Table 3

Key features of selected novel antifungal agents

Table 3

Mechanisms, spectra, and resistance considerations for key emerging antifungals

Agent	Target/mechanism	Primary spectrum	Key clinical data	Resistance considerations
Olorofim	Inhibits fungal DHODH (pyrimidine biosynthesis)	Aspergillus spp. (incl. azole-resistant); select rare moulds	Phase 2b single-arm trial in invasive mould disease with limited options shows ~40–45% response, 15–20% day-42 mortality	DHODH mutations selected in vitro; no cross-resistance with azoles or echinocandins; stewardship and combination strategies under evaluation
Ibrexafungerp	Triterpenoid inhibitor of β-1,3-D-glucan synthase (distinct binding site from echinocandins)	Candida spp., including azole- and some echinocandin-resistant strains; C. auris	Phase 3 trials in vulvovaginal candidiasis show high cure rates; early data in invasive candidiasis and C. auris promising.	FKS mutations can confer reduced susceptibility; partial cross-resistance with echinocandins possible; careful use advised
Fosmanogepix	Prodrug of manogepix; inhibits Gwt1 in GPI anchor biosynthesis	Broad yeast and mould spectrum, incl. Candida, C. auris, Aspergillus spp.	Phase 2 trials in candidemia/invasive candidiasis report ~80% success and good safety; dedicated C. auris trial shows high response	GWT1 mutations can reduce susceptibility; low spontaneous mutation frequency; activity against biofilms may limit selection
Rezafungin	Long-acting echinocandin; inhibits β-1,3-D-glucan synthase	Candida spp., including many resistant to other classes; prophylaxis against Candida, Aspergillus, Pneumocystis spp.	Phase 3 ReSTORE trial shows non-inferiority to caspofungin; approval for candidemia and invasive candidiasis	Shares FKS-mediated resistance pathways with older echinocandins; pharmacokinetics may influence selection dynamics; requires surveillance

Note. Data synthesized from Bulpa et al. (2020), Gamal et al. (2021), Jallow & Govender (2021), Locke et al. (2024), Maertens et al. (2025), Pappas et al. (2023), Thompson et al. (2023), Vazquez et al. (2023), and Kapoor et al. (2019).

Critical Synthesis and Analysis

Across these themes, several convergent patterns emerge. At the molecular level, both Candida and Aspergillus predominantly acquire resistance by modifying a limited set of targets—CYP51A and ERG11 for azoles, FKS1/2 for echinocandins—supplemented by efflux pump upregulation, biofilm-associated tolerance, and stress responses (Burks et al., 2021; Cowen et al., 2014; Rivero-Menéndez et al., 2019). From an evolutionary standpoint, this reflects the constrained target space of current antifungals. It also implies that new drugs engaging distinct pathways, such as DHODH or Gwt1, have a genuine opportunity to reset the resistance landscape, at least temporarily.

At the population level, the expansion of C. auris and environmental azole-resistant A. fumigatus demonstrates that resistance can be driven by clonal dissemination and environmental selection rather than solely by individual-level therapy. What these phenomena collectively demonstrate is that antifungal resistance has escaped the traditional hospital-centric framing and now occupies a continuum spanning farms, compost heaps, community air, and intensive-care units (Burks et al., 2021; Casalini et al., 2024; ISHAM, 2025; WHO, 2022). In such a system, stewardship limited to adjusting hospital formularies is unlikely to suffice.

Methodologically, much of the existing evidence derives from case series, retrospective observational studies, and in vitro work. Randomised trials that stratify by resistance mechanism are rare, and few prospective cohorts systematically integrate genotyping, detailed exposure histories (including agricultural and environmental exposure), and long-term clinical outcomes (Burks et al., 2021; Rivero-Menéndez et al., 2019). Surveillance systems are heterogeneous, with variable case definitions, laboratory methods, and reporting completeness, particularly in low- and middle-income countries where invasive fungal disease burden is

high but mycology infrastructure is limited (Denning, 2024; Ikuta et al., 2024; Pappas et al., 2018).

These limitations create several interpretive challenges. First, estimates of resistance prevalence and associated mortality are imprecise and subject to referral and ascertainment bias; centres with the capacity to detect resistance are more likely to report it. Second, mechanistic inferences such as the relative contributions of ERG11 mutation versus efflux in C. auris, or of CYP51A versus efflux in A. fumigatus are often extrapolated from limited isolate collections. Third, data on resistance evolution under exposure to new agents like olorofim and fosmanogepix are preliminary, so predictions about their long-term durability are necessarily tentative (Gamal et al., 2021; Maertens et al., 2025; Pappas et al., 2023).

Nonetheless, the weight of evidence supports several robust conclusions. The first is that resistance in invasive Candida and Aspergillus infections is no longer an exception but an increasingly common clinical reality in many high-risk settings, with direct implications for empirical and targeted therapy (Burks et al., 2021; Pappas et al., 2018; Patterson et al., 2016). The second is that environmental fungicide use is a major driver of azole resistance in A. fumigatus and likely contributes to the broader azole resistance ecosystem, calling for coordinated agricultural and public health policy responses (Burks et al., 2021; Verweij et al., 2016). The third is that C. auris has transformed candidemia from a largely endogenous infection to one where exogenous clonal spread and multidrug resistance play central roles, demanding infection-control paradigms akin to those for multidrug-resistant bacteria (Chow et al., 2020; Hayes, 2024).

The emerging pipeline offers reasons for cautious optimism, but it does not obviate the need for stewardship. If olorofim, ibrexafungerp, fosmanogepix, and rezafungin are deployed without robust surveillance and resistance-aware prescribing, selective pressures analogous to those that produced current resistance crises will likely recur, perhaps in novel guises (Gamal et al., 2021; Maertens et al., 2025; Pappas et al., 2023; Thompson et al., 2023). The evidence therefore warrants a reconceptualisation of antifungal resistance as a dynamic, multi-layered phenomenon in which drug development, stewardship, surveillance, and environmental regulation must be co-designed.

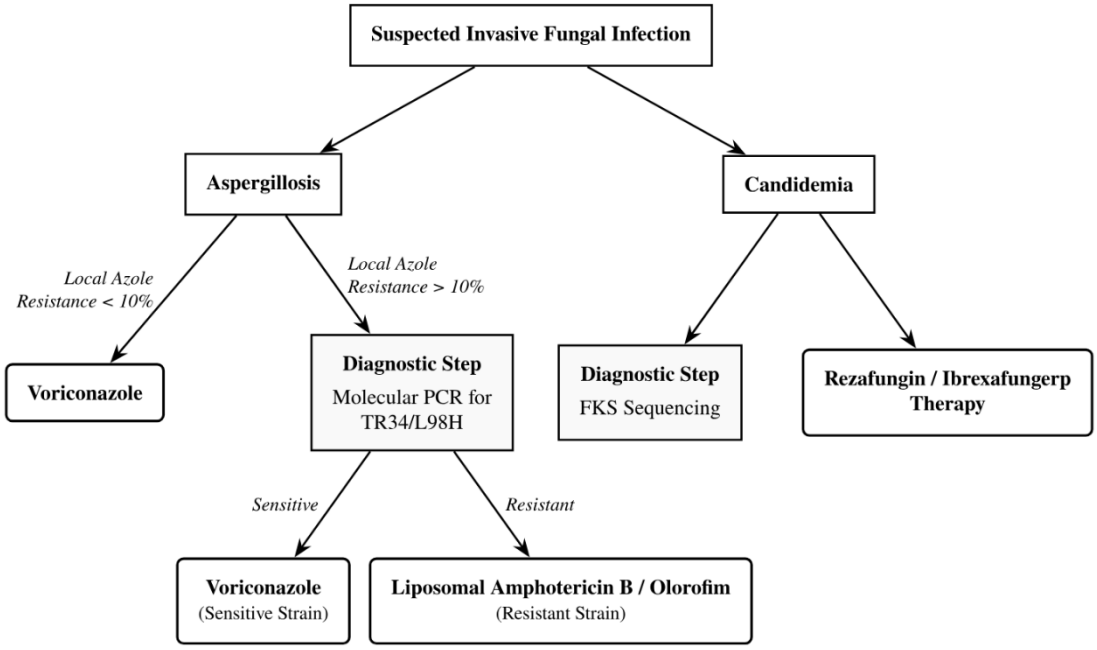

Figure 4:Conceptual diagnostic and therapeutic decision-making algorithm for suspected resistant invasive fungal infections. This clinical flowchart emphasises the necessity of integrating local epidemiological data (e.g., environmental azole resistance thresholds > 10%) and rapid molecular diagnostics (e.g., CYP51A PCR and FKS sequencing) to tailor initial empirical therapy. It highlights the triage pathways for utilising standard frontline agents versus escalating to novel therapeutics, such as olorofim, ibrexafungerp, or rezafungin, in settings with documented multidrug resistance.

Figure 4 and Table 4 integrate these insights into a conceptual treatment algorithm for resistant invasive fungal infections, emphasising the need to align therapeutic choices with local resistance patterns, molecular diagnostics, and available novel agents.

Table 4

Conceptual treatment algorithm for resistant invasive fungal infections

Table 4

Proposed management approach to suspected or confirmed resistant invasive Candida and Aspergillus infections

Clinical scenario	Key diagnostic steps	Preferred initial regimen	Role of novel agents	Stewardship and policy considerations
Suspected invasive aspergillosis in region with low azole resistance	Serum and BAL galactomannan; CT imaging; culture and susceptibility where feasible	Voriconazole or isavuconazole monotherapy	Olorofim as salvage for refractory/proven azole-resistant disease	Maintain azole susceptibility surveillance; avoid unnecessary agricultural azole use
Suspected invasive aspergillosis in region with high environmental azole resistance	As above, plus molecular testing for CYP51A TR alleles when available	Liposomal amphotericin B ± echinocandin; consider azole only if local resistance < 5–10%	Olorofim as targeted therapy for resistant isolates or intolerance to polyenes	Integrate environmental surveillance data into treatment guidelines; engage agricultural regulators
Candidemia with suspected or confirmed *C. auris*	Species ID by MALDI-TOF or molecular assay; susceptibility testing for echinocandins and amphotericin B	Echinocandin (e.g., micafungin, rezafungin) as first line	Ibrexafungerp or fosmanogepix in cases with echinocandin resistance or persistent fungemia; rezafungin for simplified dosing	Implement active surveillance and contact precautions; ensure access to novel agents where resistance is prevalent
Candidemia due to C. glabrata with elevated echinocandin MICs	Species ID, FKS sequencing where possible	Liposomal amphotericin B ± flucytosine or high-dose echinocandin if partial susceptibility	Ibrexafungerp or fosmanogepix as alternatives in documented FKS mutations; consider combination therapy	Limit prolonged echinocandin monotherapy; prioritise susceptibility-guided therapy.
Prophylaxis in allogeneic HSCT with high invasive mould risk	Baseline risk assessment; local epidemiology of azole-resistant moulds	Posaconazole or isavuconazole prophylaxis	Rezafungin prophylaxis in selected high-risk cohorts under trial or protocol; future role for olorofim possible	Align prophylaxis regimens with resistance surveillance; avoid unnecessary broad-spectrum prophylaxis.
Persistent deep-seated candidiasis despite adequate echinocandin therapy	Imaging to identify occult foci; source control; susceptibility and FKS testing	Switch to or add liposomal amphotericin B; consider higher echinocandin exposure	Fosmanogepix or ibrexafungerp as salvage options, ideally within trials	Strengthen source control practices; develop consensus guidelines on combination and salvage regimens

Note. Algorithm is conceptual and must be adapted to local epidemiology, drug availability, and patient-level factors. Based on data and expert opinion synthesised from Burks et al. (2021), Gamal et al. (2021), Maertens et al. (2025), Pappas et al. (2018, 2023), Patterson et al. (2016), Thompson et al. (2023), and Verweij et al. (2016).

Implications

Research Implications

Several priority research questions emerge for the next five years. First, there is a need for prospective, multicenter cohorts that integrate detailed clinical phenotyping, host genomics, pathogen whole-genome sequencing, and longitudinal drug exposure data for both Candida and Aspergillus infections. Such cohorts would enable robust genotype–phenotype correlations, clarify the fitness and transmission dynamics of key resistance mutations, and inform breakpoints and treatment algorithms (Burks et al., 2021; Rivero-Menéndez et al., 2019). Second, controlled clinical trials stratified by resistance mechanisms—for example, comparing olorofim-based regimens versus amphotericin B–based regimens for azole-resistant aspergillosis, or fosmanogepix versus standard of care for C. auris candidemia—are essential to move beyond extrapolation from heterogeneous case series (Gamal et al., 2021; Maertens et al., 2025; Pappas et al., 2023).

Third, mechanistic studies of resistance evolution under exposure to novel agents are urgently needed. In vitro selection experiments and animal models should be complemented by clinical pharmacokinetic/pharmacodynamic analyses to define exposure thresholds that minimise resistance emergence (Gamal et al., 2021; Kapoor et al., 2019). Model systems incorporating biofilms, mixed-species communities, and host immune components will be particularly valuable in moving beyond planktonic MIC paradigms. Fourth, environmental and One Health research should focus on quantifying azole residues in air, soil, and water, mapping resistant A. fumigatus and other moulds across gradients of fungicide use, and modelling the impact of different agricultural policy scenarios on resistance trajectories (Burks et al., 2021; ISHAM, 2025; Verweij et al., 2016).

Finally, methodological standardisation of diagnostic assays, susceptibility testing platforms, resistance definitions, and reporting metrics is essential. International consensus statements, similar to those developed for antibacterial resistance, could harmonise data collection and enable meta-analyses that inform WHO and national priority-setting (Casalini et al., 2024; ISHAM, 2025; WHO, 2022).

Clinical and Policy Implications

Clinically, the evidence compels re-evaluation of empirical and targeted antifungal strategies in high-risk populations. Empirical voriconazole or isavuconazole monotherapy for suspected invasive aspergillosis remains appropriate in regions with low resistance prevalence but may be unsafe in documented hotspots of environmental TR34/TR46 A. fumigatus without concurrent susceptibility testing (Patterson et al., 2016; Verweij et al., 2016). In such settings, guidelines should preferentially recommend lipid amphotericin B–based regimens or early

incorporation of non-azole agents, with rapid diagnostics to tailor therapy.

For candidemia, especially in units with C. auris or high rates of echinocandin resistance in C. glabrata, echinocandins (including rezafungin where available) should remain first-line, but clinicians must be prepared to escalate to novel agents or combination regimens when resistance is detected or suspected (Jallow & Govender, 2021; Locke et al., 2024; Hayes, 2024). Hospital infection-prevention programs need to treat C. auris as a priority pathogen requiring active surveillance cultures, environmental decontamination with fungicidal agents, and interfacility communication about colonisation status (Hayes, 2024; Tsay et al., 2017).

Policy implications extend beyond individual hospitals. WHO's fungal priority pathogens list and associated calls for action emphasise the need to strengthen mycology laboratory capacity, integrate fungal resistance into national action plans on antimicrobial resistance, and invest sustainably in diagnostics, therapeutics, and vaccines (Casalini et al., 2024; WHO, 2022; Zou et al., 2023). Agricultural regulators and ministries must be engaged in discussions about triazole fungicide licensing, stewardship, and alternatives, recognising that decisions taken in crop protection reverberate in intensive-care units years later (Burks et al., 2021; Verweij et al., 2016).

Health-system planners should anticipate the budgetary implications of introducing new antifungals and design formulary and stewardship policies that prioritise use in settings where they provide the greatest marginal benefit, such as documented resistance or high-risk prophylaxis. Global funding mechanisms focused on antimicrobial resistance may need to explicitly include invasive fungal disease to avoid further marginalisation of this domain.

Theoretical and Conceptual Implications

Theoretically, this synthesis challenges several entrenched frameworks. First, it argues against viewing fungal resistance solely through the lens of individual patients and hospitals and instead situates it within a broader eco-evolutionary system. Second, it underscores that "last-line" and "first-line" categorisations for antifungals are fluid: agents like echinocandins and triazoles have moved from rescue to frontline status, and the same may occur with olorofim or fosmanogepix if their safety and efficacy are confirmed.

Third, the review suggests that the classical distinction between intrinsic and acquired resistance is necessary but insufficient. Many clinically relevant scenarios involve species with a baseline reduced susceptibility (e.g., C. glabrata, A. terreus) that subsequently acquire additional resistance mechanisms under therapy, blurring the boundaries between these categories (ISHAM, 2025; Rivero-Menéndez et al., 2019). New conceptual models might instead focus on the continuum of susceptibility within species, integrating MIC distributions, fitness landscapes, and ecological niches.

Finally, the field would benefit from adopting systems-level frameworks commonly used in antibacterial resistance research, such as dynamical models of resistance spread, game-theoretic analyses of stewardship incentives, and network models of pathogen transmission across health-care and environmental interfaces. Applying these tools to invasive mycoses could generate testable predictions and inform more coherent global strategies.

Limitations of This Review

As a narrative review, this work is subject to several limitations. First, it does not employ a formal systematic search or meta-analytic framework, and study selection is inevitably influenced by the author's prior knowledge and interpretation of the literature. Although efforts were made to include recent and representative studies across geographic regions and species, some relevant data, particularly from non-English-language sources or low- and middle-income countries, may have been missed.

Second, the rapidly evolving nature of both resistance epidemiology and the antifungal pipeline means that specific prevalence estimates, clade distributions, or trial results discussed here may be superseded by newer data shortly after publication. This is especially true for agents currently in phase 2 or 3 trials and for emerging resistance mechanisms in C. auris and A. fumigatus. Third, the review necessarily simplifies complex molecular pathways and host–pathogen interactions, emphasising those with strongest evidence for clinical relevance and policy impact.

Fourth, publication bias likely favours the reporting of outbreaks, resistance clusters, and successful novel therapies, whereas negative trials, small outbreaks, or unsuccessful drug candidates may be underrepresented. Finally, the interpretive lens adopted here foregrounds a One Health and systems-level perspective; alternative frameworks might emphasise, for example, host immunology, health economics, or implementation science to different effect. Readers should thus view the synthesis as one integrative interpretation among several possible, rather than as an exhaustive or definitive account.

Conclusion

Antifungal resistance in invasive Candida and Aspergillus infections has transitioned from a sporadic curiosity to a defining challenge of modern mycology. CYP51A-mediated azole resistance in A. fumigatus, FKS-associated echinocandin resistance and ERG11-linked azole resistance in Candida, and efflux- and biofilm-mediated multidrug resistance converge to erode the effectiveness of the limited antifungal classes currently available (Burks et al., 2021; Cowen et al., 2014; Rivero-Menéndez et al., 2019). The global spread of clonal C. auris and environmentally selected azole-resistant A. fumigatus exemplifies how resistance is now shaped as much by agricultural fungicide use and health-system connectivity as by individual prescribing decisions (Burks et al., 2021; Chow et al., 2020; Verweij et al., 2016).

Against this backdrop, the emerging pipeline—olorofim, ibrexafungerp, fosmanogepix, rezafungin, and others—offers genuine hope. These agents expand the mechanistic repertoire beyond the ergosterol pathway, provide options against multidrug-resistant yeasts and moulds, and, in the case of long-acting echinocandins, simplify dosing and prophylaxis (Gamal et al., 2021; Jallow & Govender, 2021; Maertens et al., 2025; Pappas et al., 2023; Thompson et al., 2023). Yet history cautions that any new class, if used without stewardship and surveillance, can select its own resistance.

The central thesis advanced here is that antifungal resistance must be reframed as a systems problem that demands coordinated responses across molecular biology, clinical practice,

agriculture, and global health policy. Concretely, this entails building robust, standardised surveillance for invasive fungal infections and their resistance mechanisms; embedding mechanistic insights into treatment guidelines and stewardship programs; regulating agricultural azole use with explicit attention to human health consequences; and ensuring equitable access to both diagnostics and novel agents worldwide (Burks et al., 2021; Casalini et al., 2024; ISHAM, 2025; WHO, 2022).

A bold but evidence-based forward-looking statement is warranted: if the mycology community, policymakers, and industry can align on a One Health agenda that integrates surveillance, stewardship, and innovation, there is a realistic prospect of stabilising or even reversing current resistance trajectories in invasive Candida and Aspergillus infections over the next decade. If, however, the status quo of fragmented surveillance, unregulated fungicide use, and reactive rather than anticipatory deployment of new drugs persists, antifungal resistance is likely to mirror, and potentially exceed, the trajectory of multidrug-resistant bacterial pathogens in its clinical and economic impact.

Declarations

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