

The escalating crisis of antifungal resistance: Clinical, molecular and public health perspectives

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Abstract

Antifungal resistance (AFR) has become a pressing global health threat, particularly among immunocompromised populations, leading to rising morbidity, mortality, and healthcare costs. This review explores the multifactorial drivers of AFR, including clinical overuse, agricultural fungicide application, and environmental selection pressures. Major resistant pathogens such as *Candida auris* and *Aspergillus fumigatus* exemplify the growing clinical challenge. Mechanistic insights highlight genetic mutations, efflux pump overexpression, biofilm formation, and alterations in sterol biosynthesis as key contributors to resistance. The limited antifungal pipeline, coupled with toxicity and therapeutic gaps in existing agents, further exacerbates treatment limitations. Emerging strategies—novel therapeutics like ibrexafungerp and olorofim, nanotechnology-based delivery, immunotherapies, and rapid diagnostics—show promise in combating resistance. A One Health approach, global surveillance, and robust antifungal stewardship are essential to mitigate this escalating crisis. Coordinated interdisciplinary action is critical to safeguard public health and ensure effective management of resistant fungal infections.

Keywords: Antifungal; Resistance; Mortality; Morbidity; Mutations; Toxicity

1. Introduction

Antifungal resistance (AFR) has emerged as a significant global health concern (1)(2)(3)(4)(5), particularly affecting immunocompromised individuals such as cancer patients, organ transplant recipients, and people living with HIV/AIDS (1)(2)(6). The increasing use of antifungal agents and a growing at-risk population have contributed to the rise of resistant fungal pathogens, especially *Candida* and *Aspergillus* species (7)(8). Resistant infections are associated with elevated morbidity, mortality, prolonged hospital stays, and increased healthcare costs (7)(8)(9).

This review aims to provide a comprehensive analysis of AFR by assessing global prevalence and resistance patterns, identifying major risk factors such as antifungal overuse in clinical and agricultural settings, and elucidating molecular mechanisms of resistance including target site mutations, efflux pump overexpression, and biofilm formation (2)(9)(10). It also examines clinical consequences and therapeutic limitations.

The article underscores the urgent need for improved diagnostic tools, antifungal stewardship programs, and novel antifungal therapies (2)(9)(10). It highlights gaps in surveillance and calls for harmonized global data collection and interdisciplinary collaboration (11)(12)(13). By critically reviewing current literature, the article aims to support

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healthcare professionals, researchers, and policymakers in addressing AFR and guiding future strategies for effective management and control.

2. Global Impact of Antifungal Resistance

Fungal infections represent a significant yet often overlooked global health burden, causing an estimated 1.5 to 1.7 million deaths annually and affecting over 1 billion individuals worldwide (14,15). Among these, over 150 million cases are classified as severe or life-threatening, with incidence rates continuing to rise due to evolving medical and societal factors (15). Fungal infections frequently complicate conditions such as asthma, HIV/AIDS, cancer, organ transplantation, and corticosteroid therapy, making timely diagnosis and treatment critical (14). However, limited diagnostic access and delays in antifungal therapy contribute substantially to morbidity, mortality, and complications such as blindness (14). Despite fungal-related deaths rivaling tuberculosis and exceeding those from malaria, fungal diseases remain under-prioritized in global health agendas (15).

Long-term antifungal use, especially among immunocompromised patients, has accelerated the emergence of drug-resistant fungal strains like *Candida auris* and multidrug-resistant *Aspergillus fumigatus*, significantly complicating treatment and reducing survival (15). Current global estimates show a growing burden of conditions such as chronic pulmonary aspergillosis (3 million), cryptococcal meningitis (223,100), invasive candidiasis (700,000), fungal asthma, and keratitis (14), reinforcing the urgent need for improved diagnostic tools, surveillance systems, and broader antifungal access.

The socioeconomic impact of antifungal resistance is severe, with increasing mortality, longer hospital stays, and higher healthcare costs. Effective antifungal stewardship, clinical awareness, and enhanced diagnostic capacities are crucial to mitigate this escalating crisis (15).

2.1. WHO Priority Pathogens and Emerging Threats

In response to the rising threat of antifungal resistance, the WHO released a fungal priority pathogen list, categorizing 19 fungi into critical, high, and medium priority groups based on global burden and resistance profiles (24).

2.1.1. Critical Priority Pathogens include

- *Cryptococcus neoformans*: Causes ~194,000 annual cases of cryptococcal meningitis, with ~147,000 deaths, predominantly among HIV patients (18,29,21).
- *Candida albicans*: The leading cause of candidemia, resulting in ~995,000 deaths annually due to biofilm-associated drug resistance (25,18).
- *Aspergillus fumigatus*: Causes ~1.83 million annual cases, particularly pulmonary aspergillosis, with 340,000 deaths and rising azole resistance (19,18).
- *Candida auris*: A multidrug-resistant yeast linked to nosocomial outbreaks in over 50 countries, with mortality reaching up to 72% (30,22,16).

2.1.2. High Priority Pathogens

- *Candida glabrata*, *C. parapsilosis*, and *C. tropicalis*: Major causes of invasive candidiasis, often resistant to multiple drugs (17,26).
- *Fusarium* and *Histoplasma species*: Cause invasive disease in immunocompromised patients, particularly in tropical regions (31,32,23).
- *Mucorales*: Cause aggressive mucormycosis with mortality up to 80% (28).
- *Eumycetoma*: Caused by fungi such as *Madurella spp.*, often leading to amputation and chronic morbidity in poor populations (31,28).

2.1.3. Medium Priority Pathogens

- *Candida krusei*: Associated with mucosal and bloodstream infections, especially in critical care settings (17).
- *Coccidioides species*: Soil-borne fungi causing systemic infections, with greater risk in immunocompromised patients and high-risk regions (28).
- *Cryptococcus gattii*: Causes meningitis in immunocompetent individuals, predominantly in tropical climates (28).
- *Lomentospora prolificans* and *Scedosporium species*: Cause severe infections with high mortality rates, especially in cancer and transplant patients (28).

- *Paracoccidioides species*: Endemic to South America, causes systemic infection through inhalation or skin contact (28).
- *Pneumocystis jirovecii*: A common opportunistic pathogen in AIDS patients, spread via respiratory droplets (33,27).
- *Talaromyces marneffeii*: Endemic in Southeast Asia, causes severe systemic infections in immunocompromised individuals (24).

2.1.4. Economic Impact: Escalating Healthcare Costs and Resource Burden

Limitations in antifungal therapeutics and diagnostics significantly burden healthcare systems and individuals. Prolonged hospital stays, intensive monitoring, and intravenous therapies for invasive fungal infections drive up direct medical costs (34). Toxicities and drug interactions further require supportive care, while the reliance on costly second- or third-line agents increases expenses (34). Diagnostic delays lead to inappropriate treatments and longer admissions. In LMICs, referral to tertiary centers and high out-of-pocket spending compound the burden (34). Additionally, the lack of pediatric formulations complicates care. WHO emphasizes investing in antifungal drug development, diagnostics, and workforce training as an economic necessity (34).

Clinical resistance occurs when patients fail to respond to standard antifungal therapy despite appropriate dosing. This resistance arises from host factors—such as immune status—and microbial factors (35). Fungistatic drugs rely on the immune system to clear infection; immunocompromised patients are therefore more vulnerable to treatment failure (36). Medical devices like catheters and prosthetic valves facilitate pathogen attachment and biofilm formation, further protecting microbes from antifungal agents (37)(38)(39). Effective therapy requires adequate drug concentration at infection sites, but drug penetration is often insufficient, enabling microbes to persist and form reservoirs that contribute to recurrent infections. This environment selects for resistant strains, including primary (intrinsically resistant) and secondary (acquired resistance after drug exposure). The molecular mechanisms are often shared between these groups (35).

2.1.5. Mechanisms of Antifungal Resistance

Resistance is categorized as intrinsic (primary), genetically encoded and independent of drug exposure, or acquired (secondary), resulting from exposure to antifungals or their analogues (40). Resistance to one drug often extends to its entire class, limiting treatment options. The rise in invasive fungal infections partly stems from increasing resistance and the scarcity of new antifungals. Although fungal resistance elements like plasmids are rare, extensive antifungal use globally, especially in high-income countries, has increased resistance risk (41). Long-term treatment complicates disease management and promotes non-adherence, increasing resistance risk. Fungi adapt rapidly via mutation and environmental pressure, often raising minimum inhibitory concentrations (MICs) during therapy. *Candida* species pose a major threat; *Candida auris* has emerged globally with 30-50% fluconazole resistance and some echinocandin resistance (42)(43)(44). Mutations in *ERG11* and *TAC1B* genes relate to azole resistance, while *FKS* gene mutations cause echinocandin resistance (34).

2.1.6. *ERG11* Mutations and Azole Resistance

Mutations in *ERG11*, encoding lanosterol 14 α -demethylase—the azole target—reduce drug binding, leading to resistance. Flowers et al. (2015) identified 26 unique amino acid substitutions in 63 fluconazole-resistant isolates; mutations like Y132F, K143R, and G464S markedly increased azole MICs. Combined mutations, such as Y132F+K143R, had synergistic effects. Most mutations cluster near the enzyme's active or heme-binding sites, altering azole interaction. Some mutations, like E266D, were neutral. This detailed mapping aids resistance monitoring (45).

2.1.7. Genes Driving Resistance in *Candida albicans*

Resistance involves overexpression of efflux pump genes—*CDR1*, *CDR2* (ABC transporters), and *MDR1* (MFS transporter)—which pump azoles out of cells, lowering intracellular drug levels. Mutations in *ERG11* and *ERG3* alter enzyme structure and membrane sterol composition, diminishing drug susceptibility. These genetic adaptations create complex resistance mechanisms requiring continuous surveillance and novel therapies (46).

2.1.8. Efflux Pump Overexpression

Efflux pump overexpression is a major resistance mechanism in *C. albicans*, particularly against azoles (47)(48)(49). Key pumps include *Cdr1*, *Cdr2* (ABC family), and *Mdr1* (MFS family). Their upregulation reduces intracellular azole concentrations. Regulatory factors like *Mrr1p* and *Upc2p* control efflux gene expression, with azole exposure inducing

rapid increases in ERG11 transcripts, facilitating tolerance. Mutations in ERG11 further reduce drug binding, e.g., F72S, F145I, G227D, enhancing resistance (47)(48)(49).

2.1.9. Biofilm Formation

Candida albicans biofilms form protective extracellular matrices that impede antifungal penetration and efficacy (50)(51)(52)(53)(54). Biofilms develop through adhesion, proliferation, and maturation stages. Cells within biofilms exhibit tolerance to antifungals at concentrations far above planktonic MICs. This tolerance arises from physical barriers, altered metabolism, persister cells, and specific resistance gene expression. Biofilms thus complicate treatment and foster persistent infections, demanding therapies that disrupt biofilm integrity and target resistant subpopulations (50)(51)(52)(53)(54).

2.1.10. Alterations in Membrane Sterol Composition

Mutations affecting sterol biosynthesis genes like ERG3 alter membrane sterol profiles, enabling azole and polyene resistance (50)(51)(52)(53)(54). ERG3 mutations lead to accumulation of alternative sterols that maintain membrane function despite drug action. Deletion of TLO genes also influences ergosterol synthesis and mitochondrial function, increasing fluconazole tolerance. These sterol changes reduce antifungal binding and efficacy, underscoring the need for strategies targeting compensatory pathways (50)(51)(52)(53)(54).

2.1.11. Impact of Antifungal Agents on Lipid Biosynthesis and Membranes

Antifungals disrupt lipid biosynthesis and membrane integrity, essential for fungal viability. Georgopapadakou et al. (1987) showed imidazole's inhibit sterol biosynthesis, causing ergosterol depletion and accumulation of toxic intermediates, compromising membrane fluidity and permeability. Polyenes bind ergosterol, forming membrane pores leading to ion leakage and cell death. Changes in membrane lipid composition influence drug susceptibility and resistance development, highlighting membrane-targeting as a key therapeutic avenue (55).

3. Limited Arsenal of Antifungal Drugs and Their Modes of Action

The therapeutic landscape for antifungal agents remains critically underdeveloped. According to the WHO report on antifungal drugs, only four new antifungal medicines have been approved in the past decade in major markets like the US, EU, and China, a rate of innovation that is insufficient given the rising incidence and severity of fungal infections worldwide (66).

Currently, only nine antifungal drugs targeting the most threatening fungal pathogens on the WHO's Fungal Priority Pathogens List (FPPL) are in clinical development. Of these, merely three have advanced to Phase 3 clinical trials—the final stage before approval—indicating few new drugs will reach the market in the near future. Additionally, 22 candidates remain in preclinical development. Considering the high attrition rates in early phases and the cost and risk of antifungal drug development, this pipeline is inadequate for sustainable therapeutic progress (66).

Current antifungal treatments also present several limitations, including severe adverse effects, frequent drug-drug interactions, narrow dosing options, and often prolonged treatment durations requiring hospitalization. Some drugs necessitate continuous therapeutic drug monitoring, burdening healthcare systems further. There is an urgent need for new antifungals that are safer, more effective, and have broader activity against diverse fungal pathogens (66).

Children are especially vulnerable due to a lack of pediatric clinical trials and appropriate formulations, exposing critical gaps in antifungal drug development. Moreover, many healthcare providers lack sufficient training and awareness about fungal infections and antifungal resistance, impeding timely diagnosis and management (66).

The WHO stresses the importance of global surveillance, incentives for drug development, research into novel fungal targets, and therapies enhancing host immunity. Yet, therapeutic advances must be matched by improved diagnostics. Although tests for fungal-priority pathogens exist, they often require advanced labs and trained personnel, limiting accessibility in low- and middle-income countries (LMICs). Current diagnostic tools are restricted in pathogen range, accuracy, and speed, often unsuitable for resource-limited settings (66).

3.1. Toxicity of Existing Antifungal Agents: Nephrotoxicity and Hypokalemia with Amphotericin B

Amphotericin B deoxycholate (AMB), despite being a highly effective broad-spectrum antifungal, is associated with significant toxicity, particularly nephrotoxicity and hypokalemia. These side effects limit its use, especially in resource-poor settings where safer lipid-based formulations are unavailable.

A recent study on AMBD-induced nephrotoxicity found no significant demographic, clinical, or treatment-related predictors, implying that renal toxicity may occur unpredictably and reinforcing the need for routine renal monitoring in all patients receiving AMBD (67).

Another study analyzing hypokalemia during AMBD treatment reported that 33.3% of patients developed hypokalemia, with female gender and younger age showing significant correlations ($p = 0.013$ and $p = 0.041$). Female gender emerged as an independent risk factor ($p = 0.01$). While concurrent colistin administration and higher cumulative AMBD doses were associated with hypokalemia, these were not independent predictors after multivariable adjustment (68).

Clinically, electrolyte and renal function monitoring is critical during AMBD therapy. Hypokalemia can worsen nephrotoxicity and clinical outcomes, especially when combined with other nephrotoxic drugs (68). The narrow therapeutic index, potential for serious toxicity, and lack of reliable predictors underscore the urgent need for safer antifungals and strategies to reduce AMBD-related adverse effects (67,68).

3.2. Multidrug-Resistant *Candida auris*: Challenges and Treatment Implications

The emergence of *Candida auris* as a multidrug-resistant fungal pathogen poses a serious global health challenge. Resistant to azoles, echinocandins, and polyenes, *C. auris* complicates treatment and requires innovative therapeutic strategies. Hospital outbreaks lead to prolonged stays, higher costs, and elevated mortality among critically ill patients (70).

Control efforts are hampered by *C. auris*' ability to persist on surfaces and resist common disinfectants. Misidentification in clinical labs delays diagnosis and treatment initiation. Advanced diagnostics such as PCR assays and MALDI-TOF mass spectrometry are crucial for accurate identification and timely intervention (71,72).

Research into resistance mechanisms, including genetic adaptations, highlights the urgent need for new antifungal agents and optimized treatment protocols (70,73). Healthcare systems emphasize strict infection control measures—rigorous hygiene and patient isolation—to curb spread. Global surveillance and investments in drug development are vital to address this pathogen's public health threat. Collaboration among healthcare providers, microbiologists, and researchers is essential to improve outcomes (73,74).

4. Emerging Strategies and Innovations

4.1. Environmental and Agricultural Factors Promoting Antifungal Resistance

The rise of antifungal resistance is increasingly driven by environmental and agricultural practices, notably the widespread use of azole fungicides in crop protection. These practices exert selective pressure favoring resistant fungal strains, posing significant public health challenges (75)(76).

Azole fungicides extensively used in agriculture have been linked to azole-resistant *Aspergillus fumigatus* strains. Mutations in the *cyp51A* gene identified in isolates from agricultural environments confer resistance to medical azoles. These resistant strains can spread environmentally and infect humans, particularly immunocompromised patients, leading to difficult-to-treat infections (75)(76).

Persistent environmental exposure to sub-lethal azole concentrations promotes resistance mechanisms such as efflux pump overexpression and drug target alterations, undermining both agricultural and clinical antifungal efficacy (75)(76).

The interconnectedness of human, animal, and environmental health necessitates a One Health approach to combat antifungal resistance. Resistant strains originating in agriculture can transmit to humans and animals, underscoring the need for integrated surveillance and management strategies (75)(76).

Mitigation requires stewardship programs for prudent fungicide use, enhanced environmental resistance surveillance, and collaboration between agricultural and healthcare sectors to preserve antifungal effectiveness and protect public health (75)(76).

4.2. Emerging Antifungal Therapeutics

The challenge of antifungal resistance has spurred development of novel agents with unique mechanisms. Among these, ibrexafungerp and olorofim are promising candidates (75)(76)(77)(78)(79)(80).

Ibrexafungerp, a triterpenoid glucan synthase inhibitor, targets β -(1,3)-D-glucan synthase critical for fungal cell wall synthesis. Unlike echinocandins, it is orally bioavailable and effective against a broad range of *Candida* species, including azole- and echinocandin-resistant strains and multidrug-resistant *Candida auris*. Its favorable safety profile supports clinical utility (75)(76)(77)(78)(79)(80).

Olorofim belongs to the orotomide class, inhibiting dihydroorotate dehydrogenase (DHODH) in pyrimidine biosynthesis—a mechanism distinct from existing antifungals, reducing cross-resistance risk. It shows potent activity against *Aspergillus* spp., including azole-resistant strains, with oral bioavailability and promising pharmacokinetics for invasive fungal infection treatment (75)(76)(77)(78)(79).

Other investigational strategies include agents targeting fungal virulence factors like biofilm formation and hyphal growth, mitochondrial function, and cell wall integrity. Efforts to develop antifungal vaccines and immunotherapies aim to enhance host defenses. These innovations collectively promise to expand antifungal options and improve outcomes (78)(79).

4.3. Nanotechnology for Antifungal Drug Delivery

Nanotechnology offers a novel approach to overcoming resistance by improving drug solubility, stability, and targeted delivery, thus bypassing resistance mechanisms such as efflux pumps, poor membrane penetration, and biofilm barriers. Nanocarriers—liposomes, solid lipid nanoparticles (SLNs), polymeric nanoparticles, and dendrimers—have enhanced pharmacokinetics and bioavailability of agents like amphotericin B and voriconazole (80)(81)(82).

Nanoformulations enable sustained drug release, concentrating antifungals at infection sites while reducing systemic toxicity. SLNs and liposomes enhance penetration into biofilms, which are resistant to standard therapies. Polymeric nanoparticles improve fungal cell drug accumulation by circumventing efflux transporters, crucial in azole resistance (80)(81)(82).

Encapsulation also protects drugs from enzymatic degradation and enhances penetration across biological barriers such as skin and mucosa. Voriconazole-loaded nanoparticles have demonstrated superior efficacy in pulmonary and ocular delivery models (80)(81)(82).

Overall, nanotechnology-based delivery systems provide a multifaceted approach to combat resistance, offering better drug retention, biofilm disruption, dose reduction, and toxicity minimization—a vital advancement in antifungal therapy (80)(81)(82).

4.4. Immunotherapy and Monoclonal Antibodies

Immunotherapies and monoclonal antibodies (mAbs) have emerged as adjuncts to traditional antifungals, aiming to enhance host immunity, neutralize fungal virulence factors, or inhibit fungal growth, thereby overcoming drug resistance (83)(84)(85)(86).

mAbs targeting fungal antigens like heat shock protein 90 (Hsp90) and β -glucans have shown protective effects against *Candida* and *Aspergillus* in experimental models by reducing fungal burden and improving survival. mAbs can also neutralize toxins, block adhesion, and modulate immune signaling (83)(84)(85)(86).

Cytokine therapies (e.g., interferon- γ , GM-CSF) boost innate immunity in immunocompromised patients, demonstrating benefits in invasive fungal infections. Immune checkpoint inhibitors targeting PD-1/PD-L1 pathways are under exploration to restore T-cell function (83)(84)(85)(86).

Advanced approaches include dendritic cell vaccines and CAR-T cells engineered to target fungal antigens, though these remain early-stage. Chimeric mAbs like Mycograb, an anti-Hsp90 fragment, show synergy with amphotericin B against *Candida albicans*, though further clinical validation is needed (83)(84)(85)(86).

Challenges such as cost, immunogenicity, toxicity, and limited clinical data restrict widespread use. Nonetheless, progress in molecular targeting and fungal antigen discovery continues to drive this field forward (83)(84)(85)(86).

4.5. Rapid Diagnostic Tools for Resistance Detection

The rise of antifungal resistance necessitates rapid, accurate diagnostics to guide treatment. Traditional culture methods are slow and inadequate for resistance detection. Point-of-care (POC) tests and genomic sequencing technologies offer transformative solutions (87)(88)(89)(90).

POC diagnostics—lateral flow assays, biosensors, microfluidics—enable real-time identification of pathogens and resistance markers without complex labs, improving detection of *Candida* and *Aspergillus* with high sensitivity and specificity (87)(88)(89)(90).

Genomic tools like whole genome sequencing (WGS) and next-generation sequencing (NGS) comprehensively profile resistance genes (e.g., *ERG11*, *FKS1*, efflux pump mutations), revealing both known and novel mechanisms (87)(88)(89)(90).

Emerging CRISPR-based diagnostics and portable sequencing devices promise ultra-rapid resistance detection with minimal infrastructure, ideal for low-resource settings and outbreak response (87)(88)(89)(90).

Integration of advanced POC and genomic diagnostics is revolutionizing antifungal resistance management, enabling early intervention, surveillance, and informed stewardship amid escalating multidrug resistance (87)(88)(89)(90).

5. The Role of Antifungal Stewardship

Antifungal resistance poses a critical global health threat, driven largely by misuse and overuse of antifungal agents in clinical and agricultural settings (91, 92, 93). Pathogens like *Candida auris* and *Aspergillus fumigatus* demonstrate rising resistance, causing treatment failures and increased mortality (91, 93). Antifungal stewardship (AFS) programs aim to promote rational antifungal use, improve patient outcomes, and preserve existing therapies (92, 93).

5.1. Key Stewardship Strategies

5.1.1. Optimized Dosing Regimens

Tailoring therapy via therapeutic drug monitoring (TDM) ensures antifungals such as voriconazole and posaconazole maintain therapeutic levels while reducing toxicity. TDM improves outcomes and safety, with pharmacist-led interventions proving effective in optimizing prescriptions and minimizing unnecessary antifungal use (91, 92).

5.1.2. Reduced Agricultural Use of Antifungals

Extensive azole use in agriculture contributes to environmental emergence of resistant *A. fumigatus*. Regulatory policies limiting fungicide use, such as those in the Netherlands, have led to measurable declines in resistant fungal strains (93).

5.1.3. Education and Awareness Programs

Educating healthcare professionals and the public on appropriate antifungal use, early diagnosis, and guideline adherence is vital. Pharmacist-led educational initiatives in countries like Pakistan have improved prescribing practices and decreased adverse drug reactions (92, 94).

5.1.4. Improved Diagnostic Infrastructure

Strengthening diagnostic capacity enables early detection and management of fungal infections. For instance, India's Indian Council of Medical Research (ICMR) has established a network of advanced mycology centers to address diagnostic limitations and rising resistance (94).

5.2. Regional Success Stories

- **United States:** The Mycoses Study Group Education and Research Consortium developed AFS core recommendations emphasizing diagnostics, TDM, and multidisciplinary collaboration (92).
- **United Kingdom:** The NHS incorporated antifungal stewardship within broader antimicrobial stewardship, focusing on reducing unnecessary prescriptions (94).
- **Netherlands:** Effective regulation of azole use in agriculture mitigated resistance emergence.
- **India:** ICMR-MycoNet improved access to fungal diagnostics, facilitating timely intervention (93).

- **Pakistan:** Pharmacist-led programs reduced inappropriate antifungal prescriptions and adverse outcomes (92).

6. Future Perspectives

The expanding threat of antifungal resistance calls for coordinated global action involving governments, healthcare providers, and researchers. Strengthening international collaboration through integrated resistance surveillance is paramount. The WHO's GLASS initiative has established a framework, but wider adoption, fungal resistance inclusion, and integration into national health systems are critical. Enhanced surveillance requires reference laboratories, standardized testing, and accessible genomic databases to enable early detection and resistance mapping (97)(98)(99).

Increased funding for antifungal research and development is equally urgent. The antifungal pipeline remains limited due to high RANDD costs and low market incentives, with few new drug classes emerging. Incentive models—combining push funding for early-stage research and pull mechanisms like market entry rewards—are needed to stimulate innovation. Recent investments, such as those supporting colorific development, demonstrate the impact of financial backing on expanding treatment options (97)(98)(99).

Incorporating antifungal resistance monitoring within public health frameworks is vital for timely response. This includes laboratory support, professional education, and data-sharing platforms to track regional and global resistance trends. Exploring alternative treatment paradigms, such as combining traditional medicine with modern antifungals, may offer complementary mechanisms, though this remains underexplored. Immunotherapeutic strategies—including vaccines, monoclonal antibodies, and immune adjuvants—show promise as adjuncts, especially for immunocompromised patients (97)(98)(99).

Overall, effectively managing the antifungal resistance crisis requires a comprehensive, forward-looking approach: global cooperation, strategic funding, robust surveillance, and openness to innovative and integrative therapies. Such a united, multi-pronged effort is essential to ensure sustainable progress against resistant fungal infections (97)(98)(99).

7. Conclusion

Antifungal resistance represents an emerging global crisis that threatens effective management of life-threatening fungal infections. The rise of multidrug-resistant pathogens such as *Candida auris* and *Aspergillus fumigatus* underscores the urgent need for coordinated public health, clinical, and research responses. Mechanistic insights reveal that resistance stems from genetic mutations, efflux pump overexpression, and biofilm formation, all of which compromise current antifungal therapies. Limited drug availability, diagnostic delays, and toxicity issues further exacerbate clinical challenges. Addressing this crisis demands an integrated One Health approach that encompasses antifungal stewardship, environmental regulation of fungicide use, and investment in novel therapeutics and rapid diagnostics. Strengthened global surveillance, interdisciplinary collaboration, and sustained innovation are imperative to preserve the efficacy of existing antifungals and ensure preparedness against future fungal threats.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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