Precision Medicine and Health Journal
Online ISSN: 3105-9295 | Print ISSN: 3105-9287
DOI: 10.65459/pmhj.000000001
2025, Vol. 1, Issue 1

Extended Review

OPEN ACCESS

The Environmental-Clinical Nexus: How Agricultural Fungicide Use is Driving the Antifungal Resistance and the Race for Novel Solutions

Sadam Hussain Shaikh M.Phil[1] **Muneer Ahmed Qazi Ph.D**[2]

1 Center for Hematology and Bone Marrow Transplant, Pir Abdul Qadir Shah Jeelani Institute of Medical Sciences Gambat, Khairpur Mir's.
2 Institute of Microbiology, Shah Abdul Latif University, Khairpur Mir's.

Correspondence: Sadam Hussain Shaikh, Center for Hematology and Bone Marrow Transplant, Pir Abdul Qadir Shah Jeelani Institute of Medical Sciences Gambat, Khairpur Mir's.; sadam.shaikh07@gmail

Abstract

Background: Fungal pathogens are an increasing global health threat, especially for immunocompromised individuals. The rise of antifungal resistance, driven by factors such as overuse of agricultural pesticides, challenges effective treatment. In response, the WHO published its first Fungal Priority Pathogens List (FPPL) in 2022, guiding research and public health efforts. **Objectives:** This review synthesizes current knowledge on the WHO priority fungal pathogens, explores factors driving antifungal resistance, and highlights emerging diagnostic and therapeutic strategies, such as marine natural products and nanotechnology, to combat these infections. **Methods:** A narrative literature review was conducted using databases such as PubMed, Scopus, and Web of Science, along with official WHO reports. The search focused on publications from 2008 to 2024 using keywords such as "antifungal resistance," "WHO fungal priority list," "marine natural products," and "nanotechnology antifungals." **Results:** The review presents details on the 19 pathogens listed on the WHO FPPL, categorized into three priority tiers: critical, high, and medium. Emphasis is placed on the top five threats: *Cryptococcus* spp., *Aspergillus* spp., *Candida* spp., *Fusarium* spp., and *Mucorales*. Promising strategies include marine natural products as sources of new compounds, nano-enabled technologies for better drug delivery, and the importance of rapid, accurate diagnostics. **Conclusion:** Fungal pathogens remain a serious threat, worsened by increasing drug resistance. A comprehensive approach combining improved diagnostics, antimicrobial stewardship, and the development of innovative treatments from marine metabolites and nanotechnology is essential for better patient outcomes.

Keywords:
Antifungal resistance, Priority, diagnosis, Marine compounds, Nanotechnology

1. Introduction

Fungal resistance is increasing quickly, and many areas have limited access to high-quality diagnosis and treatment. These factors contribute to the lack of awareness about invasive fungal diseases and increase their threat to global health.[4] Antifungal resistance significantly affects human health. It often results in longer treatment periods, extended hospital stays, and a higher demand for costly, often highly toxic second-line antifungal drugs. Middle- and lower-income nations typically lack access to these medications.[5]

Systemic antifungal drugs currently come in four main forms: azoles, echinocandins, pyrimidines, and polyenes.[6] Several additional types are in development. Antifungals can have several unforeseen side effects, even when they are effective.[7] Drug interactions make using

Received: September 27, 2025 | Revised: November 2, 2025 | Accepted: November 25, 2025 | Published: December 2, 2025

Precision Medicine and Health Journal
Online ISSN: 3105-9295 | Print ISSN: 3105-9287

these medications not only essential but also reliant on knowledge. These interactions also have additional implications for patient safety and prognosis, besides requiring long treatment durations.[8]

Frequent fungal infections have been associated with fatalities and severe illnesses in COVID-19 patients, among other conditions.[9] Fungal infections can vary in severity from superficial to subcutaneous, cutaneous, mucosal, and systemic levels.[10] The human microbiota includes organisms such as *Candida* spp., which can lead to invasive candidiasis infections—potentially deadly infections in immunocompromised individuals, including those with HIV, cancer patients undergoing chemotherapy, and other immunosuppressed people.[11]

Fungal resistance is increasing rapidly, and in many regions, there is limited access to quality diagnosis and treatment.[12] These factors contribute to the lack of awareness about invasive fungal diseases and increase their threat to global health.[13] Antifungal resistance significantly affects human health. It results in longer treatment times, extended hospital stays, and a higher demand for costly, often highly toxic second-line antifungal drugs.[14] Middle- and lower-income countries usually lack such prescriptions.[15]

This review argues that the widespread use of azole fungicides in agriculture is the primary cause of clinical resistance in important pathogens like *Aspergillus fumigatus*, highlighting an urgent need for new treatments that avoid traditional action methods.

2. Methods

This work presents a narrative literature review that synthesizes current knowledge on World Health Organization (WHO) priority fungal pathogens, antifungal resistance, and emerging therapeutic strategies. A comprehensive search of peer-reviewed articles was conducted in PubMed, Scopus, Web of Science, and Google Scholar. Additionally, authoritative reports from the World Health Organization (WHO) and other international health agencies were consulted.

The search strategy used keywords and Boolean operators, including "fungal pathogens," "antifungal resistance," "WHO fungal priority list," "novel antifungals," "marine natural products," and "nanotechnology antifungals." Literature published mainly from 2008 to 2024 was considered, with earlier landmark studies included when historically relevant. Only articles published in English were reviewed.

The sources were selected based on relevance, scientific rigor, and their contribution to understanding fungal pathogenesis, antifungal pharmacology, resistance mechanisms, and innovative therapeutic approaches. Duplicates, non-peer-reviewed commentaries, and conference abstracts lacking sufficient data were excluded.

Since this is a narrative review rather than a systematic one, no formal protocol such as PRISMA was followed. Instead, the focus was on providing a thorough and critical synthesis of the most important findings. These findings are intended to guide future research directions and clinical approaches, supporting global efforts to combat fungal resistance.

3. Results

Due to the rapid and widespread increase in antibiotic resistance, the first list of priority bacteria was published in 2017 to raise awareness of the issue.[16] The initial file of fungus-related priority diseases (FPPL) was released in October 2022.[17] This program has continued using a methodology similar to that for prioritizing bacterial pathogens, which involves a decision analysis method based on several criteria to guide scientific research efforts toward the most important fungal diseases.[18]

The three research priority levels for fungal pathogens are listed on this page: medium, high, and critical.[19] It also provides a comprehensive overview of the challenges involved in diagnosing and treating fungal illnesses, as well as achieving research and development objectives.[20] The priority of nineteen pathogenic organisms has been determined using ten criteria: death, annual incidence, current global distribution, trends over the last decade, patient care, complications and outcomes, fungal resistance, prevention, and availability of data-driven diagnostic and treatment tests.[21]

3.1. Critical fungal pathogens

Table 1 shows that the World Health Organization (WHO) has identified four critical fungal pathogens: *Cryptococcus neoformans*, *Candida auris*, *Aspergillus fumigatus*, and *Candida albicans*. These fungi pose a significant threat to vulnerable populations, including neonates, the elderly, patients with chronic illnesses, and those undergoing therapy. Additionally, individuals with COVID-19, cystic fibrosis, CMV, COPD, transplant recipients, TB patients, and cancer patients are at increased risk. If untreated, the mortality rate is 100% in immunocompromised patients, and even with treatment, it can be as high as 20%. To combat these fungal infections, various antifungal medications are used, such as fluconazole,

2025, Vol. 1, Issue 1
DOI: 10.65459/pmhj.000000001

Table 1: The WHO's fungal pathogens priority list is categorized into Medium, High, and Critical[22–24].

PRIORITY	PATHOGEN	DEATH RATIO + AMR	AT RISK PATIENTS
Medium	*Scedoporium* spp.	50% organ transplant patients + Itraconazole	Cystic fibrosis and organ transplant recipients
	Lomentospora prolificans	46.9% and 87.5% disseminated disease + MDR, pan-resistant	Cystic fibrosis, immunocompetent and immunocompromised people
	Coccidiodes spp.	70% of immunocompromised people + Azoles	COVID-19-infected, pregnant, immunocompromised people
	Pichia kudriaveii	30% + Innately resistant to fluconazole, Echinocandin resistance common	Neonates in ICUs and immunocompromised people
	Cryptococcus gattii	10% + Echinocandins	AIDS/HIV patients
	Talaromyces marneffei	13.30% + N/A	AIDS/HIV patients
	Pneumocystis jirovecii	50% of immunocompromised persons + Polyenes (AmB)	AIDS/HIV and CMV patients
	Paracoccidioides spp.	6.2%–27% + AmB, Ketoconazole, Fluconazole, Itraconazole, Sulfamethoxazole	AIDS/HIV and immunocompromised patients
Hard	*Nakaseomyces glabrata*	54% + Fluconazole, Echinocandins	Renal failure and ICU patients
	Histoplasma spp.	60% AIDS/HIV patients + Azoles	AIDS/HIV patients, TB patients
	Eumycetoma – *Madurella mycetomatis*	Scarce + Prolong treatment needed, which can lead to toxicity and surgery	Barefoot walking populations of tropical and subtropical countries
	Mucorales	80% + Echinocandins	Immunocompromised, COVID-19-infected, and diabetes mellitus patients
	Fusarium spp.	37% disseminated fusariosis, cases + MDR, intrinsically to azoles	Immunocompromised oncology and organ transplant patients Nosocomial patients and oncology patients
	Candida tropicalis	64-86% at 10-30 days + Echinocandins	AIDS/HIV patients and TB patients
	Candida parapsilosis	26% + Echinocandins	AIDS/HIV patients and oncology patients
Critical	*Cryptococcus neoformans*	20%, if untreated 100% + Fluconazole, flucytosine	AIDS/HIV patients and TB patients
	Candida auris	70% + Azoles, lower sensitivity to the Polyene Amphotericin B, MDR, Echinocandins, and Flucytosine	Neonates, the elderly, chronically ill, and patients on therapy
	Aspergillus fumigatus	70% of immunocompromised patients + Triazolesresistance and echincandins	Cystic fibrosis, COVID-19-infected, COPD, CMV, TB, and transplant patients
	Candida albicans	30-40% + Echinocandinsand flucytosine	TB and cancer patients

Precision Medicine and Health Journal
Online ISSN: 3105-9295 | Print ISSN: 3105-9287

flucytosine, polyene amphotericin B, and echinocandins. However, the emergence of resistance to these drugs, such as triazole resistance, necessitates ongoing vigilance and the development of new treatments to manage these life-threatening infections effectively.

3.2. High fungal pathogens

Among the leading fungal pathogens, *Candida parapsilosis*, *Eumycetoma madurella mycematis*, *Nakaseomyces glabrata*, Mucorales, *Histoplasma* spp., *Fusarium* spp., and *Candida tropicalis* pose a significant threat to different populations. Barefoot individuals in tropical and subtropical regions, immunocompromised patients, COVID-19-infected individuals, and those with diabetes mellitus are at higher risk. Additionally, immunocompromised oncology and organ transplant patients, nosocomial patients, and AIDS/HIV patients are vulnerable (see Table 1).

The death rate from these fungal infections is alarmingly high, ranging from 30% to 70%. Effective treatment options include Fluconazole, Echinocandins, and Azoles, but prolonged use can cause toxicity and may require surgery. Notably, Echinocandins are effective against MDR strains that are inherently resistant to azoles. However, invasive infections caused by these fungal pathogens are associated with high mortality rates, emphasizing the urgent need for prompt and effective treatment (see Table 1).

3.3. Medium fungal pathogens

Scedosporium spp., *Lomentospora prolificans*, *Coccidioides* spp., *Pichia kudriavzevii*, *Cryptococcus gattii*, *Talaromyces marneffei*, *Pneumocystis jirovecii*, and *Paracoccidioides* spp. are considered medium-risk but are still notorious for causing significant infections. Vulnerable populations include cystic fibrosis patients, organ transplant recipients, and both immunocompetent and immunocompromised individuals. COVID-19–infected patients, pregnant women and neonates in NICUs, and AIDS/HIV patients are also at risk.

Mortality rates are concerning, ranging from 10% to 87.5% depending on the affected population and disease severity. Antifungal agents used to treat these infections include Itraconazole, Azoles, Echinocandins, and Polyenes. However, resistance is a growing concern, as some strains show innate resistance to Fluconazole, Echinocandins, and Azoles.

Treatment options may also include Amphotericin B (AMP-B), Ketoconazole, Fluconazole, Itraconazole, and Sulfamethoxazole, although efficacy varies depending on the specific fungal pathogen and population (see Table 1).

4. Profiles of Priority Fungal Pathogens

4.1. Cryptococcus species

The two main *Cryptococcus* species, *Cryptococcus neoformans* and *Cryptococcus gattii*, have significantly different priorities.[25] One of the most common opportunistic infections among HIV-positive individuals is cryptococcosis, caused by *Cryptococcus neoformans*. In 2020, there was a concerning increase in cryptococcal meningitis cases (152,000), with 112,000 deaths linked to cryptococcosis.[26]

Additionally, about 48,000 cases of cryptococcal meningitis occur annually in individuals without health issues or among those with immunological deficiencies unrelated to HIV, totaling 26,693 cases.[27] Although pathogenicity levels vary, six distinct strains of the *C. gattii* complex have been identified across nearly every continent, including Asia and Europe.[28] While the mortality rate for *C. gattii* (10–43%) is lower than that of *C. neoformans*, *C. gattii* is more often associated with neurological disorders and inflammatory intestinal reconstitution syndrome in both HIV-positive individuals (20–61%) and HIV-negative individuals (8–50%).[29] Given all these factors, we believe that *C. gattii* should at least be classified as a high-priority pathogen.[30]

4.2. Aspergillus species

The *Aspergillus* genus includes several hundred species known to potentially cause harm and be linked to serious disorders.[31] The term Aspergillosis refers to a range of diseases caused by *Aspergillus* species, which vary depending on the host's immune system, from non-invasive allergy symptoms to invasive chronic pneumonia.[32] *Aspergillus* conidia are found throughout the environment.[33] Whether an infection spreads locally or systemically depends on the patient's immune status and whether exposure occurred through injection or inhalation.[34] Due to the introduction of numerous biological agents targeting the immune system and the rise in viral infections such as Coronavirus, the risk factors for this infection fluctuate regularly.[35]

Although significant advances have been made in diagnosing and managing Aspergillosis, severe fungal infections remain difficult to treat.[36] The mortality rate remains high, particularly in individuals with compromised immune systems.[37] Concerns about resistant antifungal agents continue to complicate Aspergillosis management, and limitations in current mycological diagnostic procedures often delay prompt diagnosis.[38] Focusing on in-

2025, Vol. 1, Issue 1
DOI: 10.65459/pmhj.000000001

Table 2: Antifungal Drug Profile, Target and Resistance Mechanisms[92–95].

S.No.	Antifungal drug	Cellular target and mechanism	Resistance mechanism/genes
1	Azoles (e.g., *Fluconazole*, *Itraconazole*)	Lanosterol 14α-demethylase, to inhibit ergosterol synthesis	Heteroresistance (aneuploidy of regions containing ERG11 and drug efflux genes TAC1 or AFR1) Point mutations in ERG11 Increased expression of ERG11 Increased azole efflux through pumps: MDR1, PDR1, CDR1, CDR2, and AZR1
2	Allylamines (e.g., Terbinafine)	Squalene epoxidase, to inhibit ergosterol synthesis	Point mutations in ERG1
3	Polyenes (e.g., Amphotericin B)	Binds ergosterol and induces pore formation in the cell membrane	Mutation in ERG2, ERG3, ERG6, 7, 8, isomerase
4	Echinocandins	1,3-β-D-glucan synthase, to inhibit the glucans required for the cell wall	Mutations in FKS1 and FKS2 encoding subunits of 1,3-β-D-glucan synthase

vasive pulmonary Aspergillosis, this review provides an overview of risk factors and the clinical spectrum of Aspergillosis, along with recent developments in diagnosis, treatment, and antifungal resistance.[39]

4.3. Candida

The term "opportunistic infection" is often used to describe invasive Candidiasis, a systemic fungal infection caused by the *Candida* genus.[40] The groups most at risk for *Candida* infection are those with serious illnesses or immunosuppressive conditions, such as solid organ or blood cancers, bone marrow transplants, recent abdominal surgery, as well as individuals receiving parenteral nutrition and central venous grafting.[41]

The invasive diagnostic method for *Candida* relies on growth cultures, which are commonly used to identify the infection.[42] Additionally, tissue biopsies are employed alongside cultures to diagnose deep-seated *Candida*.[43] This meta-analysis only included studies that utilized cultures of positive blood cells to evaluate biofilm development and other relevant aspects of *Candida* pathogenicity.[44]

Because of the well-developed ability of biofilms, *Candida* species produce biofilms very early, which provides them with resistance to various stresses, including antifungal medications and immune defenses.[45] It is widely recognized that *Candida* biofilms weaken the host's innate immunity, although the mechanisms behind the biofilm-host relationship remain unclear.[46] Therefore, our main aim was to examine the connection between biofilms and mortality in *Candida* spp.-related diseases, which poses a significant public health risk.[47]

4.4. Fusarium

Fusarium consists of various long, hyaline filamentous fungi that can adapt to any habitable environment, making them highly opportunistic. The disease in humans begins when an individual inhales *Fusarium* conidia or makes contact with materials contaminated with the fungus. Additionally, when conditions are suitable, the conidia develop and form filaments that invade the surrounding tissue.[48]

Few studies describe the predisposing factors as well as the clinical and physical characteristics of patients with *Fusarium*. The immune status of the individual influences the clinical presentation of fusariosis.[49]

Invasive infections include sinusitis, pneumonia, deep skin infections, and widespread infections. These are primarily marked by a fever that does not respond to antimicrobial treatments. Risk factors for invasive fusariosis include neutropenia, deficiencies in cellular immunity, chemotherapy for leukemia, and blood cell transplantation. Conversely, immunocompetent individuals are more likely to develop superficial infections, such as cataracts and onychomycosis.[50]

4.5. Mucorales

Mucorales infections involve a fungal infection that affects immunocompromised individuals. This infection is becoming more common and is linked to low survival rates. A group of illnesses called "Mucorales disease" is caused by fungi from the Mucorales order.[51] It is a fungal infection impacting those with weakened immune systems. This infection is spreading increasingly, again associated with very low survival rates.

Precision Medicine and Health Journal
Online ISSN: 3105-9295 | Print ISSN: 3105-9287

Mucormycosis is a granulomatous, opportunistic, and often contagious disease caused by fungi from the class Mucoromycota, a subgroup of Mucoromycotina.[52] It can result from conditions like diabetes mellitus with ketoacidosis, various metabolic acidoses, corticosteroid use, organ or tissue transplants, neutropenia, trauma, surgery, and deferoxamine therapy in dialysis patients.[53]

Although some forms are sporadic, the most common mucormycosis infections are in the skin, brain, gastrointestinal system, paranasal sinuses, and lungs, especially in medical cases.[54]

4.6. Antifungal resistance in the age of pesticides

The impact of pesticides on increasing antifungal resistance is a major concern. Pesticide use, such as overuse of fungicides like chlorothalonil and azoxystrobin, can lead to the development of resistant fungal strains, including *Aspergillus* and *Fusarium*.[55] These resistant strains can then undergo genetic changes, enabling them to evade antifungal drugs such as itraconazole and voriconazole.[56] Additionally, pesticide residues in the environment can spread resistance, harming beneficial fungi like *Trichoderma* and *Beauveria*, which are essential for soil health, and disrupting the balance of fungal communities.[57]

This can lead to the development of resistance to various chemicals, including pyrethroids and neonicotinoids, which are used to control insect pests, as well as the spread of resistance genes among fungal populations.[58] Fungicides like azoxystrobin and pyraclostrobin have led to the emergence of resistant fungi, including *Septoria* and *Cercospora*. The consequences will be severe, risking the effectiveness of antifungals and threatening global food security and human health as fungal infections become more difficult to treat.[59] To decrease reliance on chemical pesticides and reduce pesticide-driven antifungal resistance, integrated pest management strategies that promote responsible pesticide use along with alternative methods such as crop rotation, biological control, and cultural practices should be adopted.[60] Implementing sustainable farming techniques will ensure a safer future for food production and human health. Additionally, the use of biofungicides like *Bacillus subtilis* and *Trichoderma harzianum*, which are effective against fungal diseases, can help minimize the development of antifungal resistance.[61]

4.7. Solutions to Overcome Challenges

Breaking fungal resistance requires a multi-faceted approach. First, marine natural products offer a promising source of new antifungal candidates, with unique structures and mechanisms of action.[62] Additionally, nano-enabled antifungal agents can improve drug delivery and effectiveness. Proper and early diagnosis is essential, using advanced techniques like PCR and mass spectrometry to quickly identify fungal infections. Novel antifungal drugs in clinical trials, such as ibrexafungerp and olorofim, show promising results.[63] Furthermore, repurposing existing drugs and combining therapies can lead to better outcomes. Implementing antimicrobial stewardship programs and developing fungal-specific biomarkers will also help combat fungal infections. Moreover, exploring fungal genomics and epigenomics can uncover new targets. Public awareness campaigns and reducing environmental fungicide use will help prevent resistance development. By integrating these strategies, we can effectively fight fungal resistance and improve patient outcomes.[64] Doing so allows us to stay ahead of evolving fungal pathogens and protect vulnerable populations. With the power of marine natural products, nano-enabled agents, and new drugs, we can break the cycle of resistance and offer hope to those affected by fungal infections.[65]

4.8. Antifungal Agents

Four different types of antifungal agents are now used in systemic treatment by veterinarians and physicians. These groups target different areas of the fungal cell.[66] The primary component of the fungal cell membrane, ergosterol, interacts with the first polymer, Amphotericin B, a polyene. Amphotericin B is highly effective against *A. fumigatus* and *A. flavus* fusariosis, as well as other forms of *Candida*.[67] Next, the lanosterol demethylation stage of the ergosterol synthesis pathway is inhibited by first- and second-generation Triazoles. Triazoles typically have a fungistatic effect on fungi; however, some *Aspergillus* species may be susceptible to a fungicidal impact. The synthesis of β-glucan is blocked by echinocandins.[68]

Echinocandins exhibit fungicidal and fungistatic effects against *Aspergillus* species and *Candida*, respectively. Lastly, the pyrimidine analogue flucytosine (5-FC) interacts with the fungal nucleus to affect protein and DNA synthesis.[69]

4.9. Azoles

For decades, azoles have been used to treat fungal infections, making them one of the most commonly used classes of antifungals.[74] Conversely, researchers have explored new techniques and procedures to develop antifungal therapies with improved safety and tolerability profiles, reduced drug interactions, lower toxicity and resistance, and enhanced effectiveness against fungi.[75] Additionally, a new strategy involves adding azole molecules to naturally occurring bioactive products, which could lead to

2025, Vol. 1, Issue 1
DOI: 10.65459/pmhj.000000001

the development of components with potent antifungal activity, especially against resistant fungi.[76] Preclinical research requires further testing, such as toxicological analyses, sensitivity assessments to other substances and their mechanisms of action, and in vivo studies to evaluate their effects. Furthermore, it is crucial to conduct studies with resistant species to determine the effectiveness of these supplements in treating specific types of fungi that are not responsive to existing antifungal medications (See Table 2).[77]

4.10. Polyenes

One of the most powerful groups in fighting fungal infections is polyenes. They form inside the molecular channels that contain lipids and chemical compounds found in cell membranes.[78] They have lactone molecules in their structure. Although they have strong antifungal properties, none of these polymers are effective against all fungi. The six antifungal polymers used are Trichomycin, Methyl Partricin, Candicidin, Natamycin, Amphotericin B (Amb), and Nystatin.[79] Of these six polyenes, only three are commonly used in antifungal treatment: Nystatin for mucous membrane infections (oral or vulvovaginal candidiasis), Amb for invasive intracerebral infections, and Natamycin for eye infections.[80] The initial mechanism of action was reported as forming openings by binding to sterols in the cell membrane (See Table 2).[81]

4.11. Echinocandins

A class of antifungal drugs drastically changed the treatment of invasive fungal diseases.[82] Their unique mechanism involves blocking the production of β-glucan, an essential part of the fungal cell wall, which leads to the lysis and death of fungal cells.[83] By targeting the fungal cell wall, a vital component for fungal survival, this approach has a clear advantage over other antifungal classes. The primary causes of invasive fungal infections—*Aspergillus* and *Candida*—are mainly targeted by echinocandins. The three main echinocandins used clinically are caspofungin, micafungin, and anidulafungin.[84] They are highly effective against various fungal infections and have favorable safety profiles. These drugs are often combined with other antifungals to improve therapy outcomes, especially in patients with weakened immune systems.[85] Echinocandin therapy has greatly improved patient outcomes, lowering mortality rates and increasing survival among those with severe fungal infections.[86] Additionally, their role in antifungal management has helped reduce resistance development. Overall, echinocandins are a vital treatment option for invasive fungal infections, and ongoing use and research will be key in fighting these serious diseases (See Table 2).[87]

4.12. Allylamines

Allylamines are a type of antifungal medication that work by inhibiting the squalene epoxidase enzyme, which is necessary for the fusion of fungal cell membranes.[88] This enzyme suppression affects the production of ergosterol, a crucial component of fungal cell membranes, which in turn triggers a chain of biological events that ultimately lead to the demise of the fungal cells. A range of fungal species, including *Aspergillus*, *Candida*, and dermatophytes, have been successfully treated with allylamine esters terbinafine and naftifine.[89] This family of medications has demonstrated significant efficacy in treating superficial infections, such as Tinea pedis and onychomycosis, as well as invasive fungal infections in patients with weakened immune systems. It has been shown that allylamines have a favorable pharmacokinetic profile, excellent oral bioavailability, and tissue penetration.[90] Additionally, they work in concert with other antifungal agents. Furthermore, several biochemical and molecular investigations have elucidated their mechanism of action, highlighting their critical role in antifungal treatment (See Table 2).[91]

4.13. Proper and Early Diagnosis of Fungal Pathogens

Early detection of IFD, including the precise identification of the responsible gene and, when possible, the antibiotic resistance, is essential for proper patient management and better outcomes.[97] Although culture and microscopy remain the gold standard for diagnosing IFD, their sensitivity and specificity are limited, as these methods take up to two weeks and depend on specimens containing fungi. Some fungi have developed antifungal resistance to environmental and clinical use, and it is possible to exclude cryptozoal species that have inherent resistance.[98]

To directly identify fungal species in clinical specimens and detect medication resistance more rapidly, more sensitive and targeted diagnostic techniques are needed for IFD. This article describes the characteristics of the fungi, including their resistance profiles, as well as the latest molecular diagnostic methods for directly detecting fungi in clinical specimens. Additionally, new techniques like ADN barcoding and NGS sequencing are discussed.[99] The study explains these techniques within their clinical contexts, offers an integrated view of their use in a diagnostic lab, and concludes with the potential for broader application of molecular tests as their use is expected to expand.[100]

Precision Medicine and Health Journal
Online ISSN: 3105-9295 | Print ISSN: 3105-9287

Due to increasing proficiency with PCR tests for the direct identification of fungi in clinical specimens, as demonstrated by clinical validation studies, these test types are becoming standard in clinical laboratories.[101] Likewise, standardization of *Aspergillus* PCR has been used as a biomarker for IA in clinical trials and allows for reliable inter-laboratory comparisons. Molecular techniques that directly detect *Candida* spp. from blood cultures or whole blood have a high likelihood of providing information about infection risk when combined with other fungal biomarkers.[102] Similar to molecular tests that enable the simultaneous identification of infections and their key resistance markers, it is anticipated that other general or specific assays will also gain importance in routine diagnostics as they become more common.[103] In summary, it seems that reaching a "one single point of sale" for fungal biomarkers is getting closer in the coming years, thanks to the use of high-quality genetic barcodes, NGS technologies, and metagenomic approaches.[104]

4.14. Marine Natural Products as New Antifungal Agents

In addition to bacteria and fungi, sponges are considered the primary and most common sources of secondary compounds with antifungal properties in marine systems.[105] The presence of these substances is beneficial in treating certain fungal infections.[106] Due to their unique characteristics, such as great diversity, low toxicity, high effectiveness with few side effects, and a wide range of antifungal activity, these naturally occurring substances have attracted significant interest. They are now more likely to be regarded as essential components for exploring other novel substances.[107] Sea cucumbers are also thought to be a rich source of bioactive substances and secondary products.

Marine bacteria are a particularly prolific source of such compounds. For instance, *Bacillus licheniformis* produces Ledoglucomide C, a glycolipid effective against a broad spectrum of fungi including *Aspergillus niger* and *Candida albicans*. Similarly, lipopeptides such as Gageopeptides A–D from *Bacillus subtilis* and macrolides like Neomaclafungins A–I from *Actinoalloteichus* NPS702 demonstrate potent activity against pathogens such as *Rhizoctonia solani* and *Trichophyton mentagrophytes*, respectively. Marine-derived fungi also contribute significantly to this chemical diversity. These include peptides like Sclerotide B from *Aspergillus sclerotiorum*, which is active against *C. albicans*, and alkaloids such as Didymellamide A from *Stagonosporopsis cucurbitacearum*, which shows efficacy against both *C. albicans* and *Cryptococcus neoformans*.

Sponges are an especially important source, underscoring their value in marine drug discovery. The sponge *Theonella swinhoei* is a source of multiple peptides, including Theonellamide G and Theopapuamides A, B, and C, all of which are active against *C. albicans*. Another noteworthy example is Jasplakinolide, a peptide from *Jaspis johnstoni*, which exhibits a spectrum of activity against several *Candida* species. Other marine organisms also provide unique chemical scaffolds. The triterpene glycoside Variegatuside D from the sea cucumber *Stichopus variegates* and the xylene-containing compound Caulerprenylol B from the alga *Caulerpa racemosa* further illustrate the chemical diversity and broad antifungal potential of metabolites derived from marine ecosystems. This collection of compounds, spanning various chemical classes from peptides and macrolides to alkaloids and glycolipids, highlights the immense potential of marine natural products to provide lead structures for the development of the next generation of antifungal therapeutics.[108–111]

4.15. Nano-enabled Antifungal Agents

Nanotechnology offers a practical approach to improve the effectiveness and decrease the toxicity of antifungal treatments. Nanoformulation can enhance the solubility, stability, and bioavailability of antifungal medications.[112] Antifungal drugs can be delivered specifically to fungal cells or tissues through targeted delivery methods. Controlled release systems can maintain effective medication levels. Nanoparticles can improve penetration across biological barriers. Combination therapy can deliver multiple antifungal drugs simultaneously or along with immunotherapy.[113] Nano-enabled antifungal medicines are revolutionizing the treatment of fungal infections. Polyenes, such as liposomal Amphotericin B and liposomal Nystatin, improve efficacy while reducing toxicity.

Azoles, such as nanostructured Itraconazole and nanoparticle-based Voriconazole, demonstrate improved bioavailability and targeted delivery. Echinocandins, including liposomes loaded with micafungin and polymeric nanoparticles loaded with caspofungin, show increased antifungal effectiveness. Pyrimidines, like nanostructured lipid carriers loaded with flucytosine and nanocrystals loaded with terbinafine, have higher solubility and bioavailability.[114] Allylamines, such as terbinafine-loaded and amorolfine-loaded nanocrystals, exhibit enhanced antifungal activity.[115] Additionally, silver-based antifungals, including silver nanoparticles, display antifungal properties. These nano-enabled antifungal agents offer promise for improved treatment outcomes and reduced toxicity, providing new hope in the fight against fungal diseases.[116,117] In preclini-

2025, Vol. 1, Issue 1
DOI: 10.65459/pmhj.000000001

cal trials, nanotechnology-based antifungal medications have demonstrated potential for clinical use. The future of antifungal therapy hinges on the development of nanotechnology-driven antifungal drugs.[118]

4.16. Novel Antifungal Agents Under Clinical Trials

Although significant progress has been made over the past few decades in preventing, detecting, and treating IFDs,[119] they still pose a considerable risk to animals with weakened immune systems. It is crucial to quickly identify new therapies with high antifungal activity and low toxicity, as well as find ways to enhance host response and reduce immune system inhibitors.[120] We are examining medications still in development, including three compounds from new classes of antifungals that target the fungal cell wall and nucleic acid metabolism: Fosmanogepix, Olorofim, and Ibrexafungerp. Ibrexafungerp offers a specific benefit as oral treatment for fungi like *C. glabrata* and *C. auris*, which are resistant to Echinocandins.[122] Among the various antifungal classes currently used, such as PC945, CAmB, Oteseconazole, and Rezafungin, there are improved pharmacokinetic and pharmacodynamic features, leading to better safety and tolerance profiles.[123,124] Rezafungin, especially with daily dosing, may facilitate providing restroom care to patients requiring echinocandin for treatment or prevention.[125,126]

The translation of myco-nanotechnology from preclinical studies to clinical application is actively underway, with several nano-formulations of antifungal agents currently being evaluated in human trials. These trials are investigating a range of nanocarriers to enhance drug delivery, improve efficacy, and reduce toxicity for various fungal infections.

Several studies are focused on topical applications for superficial mycoses. Two separate Phase II clinical trials are assessing the efficacy of nanoemulsion gels for treating *Tinea versicolor*, with one trial using itraconazole and the other using voriconazole. Another formulation, a transfersome designed to enhance skin penetration, is being used to deliver terbinafine (Td067) in a Phase III trial for onychomycosis.

Lipid-based nanoparticles are also being investigated for the treatment of mucosal infections. Matinas Biopharma is sponsoring two Phase II trials using a cochleate lipid-crystal nanoparticle formulation to deliver the potent polyene amphotericin B. One trial is targeting vulvovaginal candidiasis, while the other is focused on mucocutaneous candidiasis.

Furthermore, metal-based nanoparticles are emerging as another important area of clinical research. A silver nanoparticle gel is under investigation for the treatment of mycosis. In trials that are currently recruiting participants, titanium dioxide nanoparticles are being evaluated for candidiasis, and a separate silver nanoparticle formulation is being studied for its potential in treating invasive aspergillosis. These ongoing clinical evaluations highlight the significant potential of nanotechnology-based strategies to provide novel and more effective treatments for a broad spectrum of fungal diseases.[127–130]

5. Conclusions

Fungal pathogens pose a growing and serious threat to global health, causing severe and often deadly infections, especially in immunocompromised populations. The World Health Organization (WHO) has highlighted this problem by identifying priority fungal pathogens, including Candida, Aspergillus, and Cryptococcus species, which result in high mortality rates and substantial economic costs worldwide.

This review offers a detailed analysis of the main fungal threats. It describes how the effectiveness of current antifungal drug classes—such as Azoles, Amphotericin B, and Echinocandins—is heavily reduced by the increasing problem of antifungal resistance. A key factor fueling this issue is the widespread use of agricultural pesticides, which creates environmental selective pressure that encourages the development of drug-resistant fungal infections in clinical settings.

To address this emerging threat, a comprehensive approach is crucial. Breaking the cycle of resistance requires a commitment to innovation across multiple fronts. Promising strategies include exploring marine natural products, which offer a rich source of new bioactive compounds with unique antifungal mechanisms. Additionally, nano-enabled antifungal agents offer a powerful means to enhance drug delivery, increase bioavailability, and improve the effectiveness of both new and existing treatments. The importance of accurate and early diagnosis cannot be overstated, as it is vital for better patient outcomes and guiding proper treatment.

Staying ahead of evolving fungal pathogens requires a continuous and coordinated effort. By exploring new drug sources, utilizing advanced technologies such as nanotechnology, and employing rapid and precise diagnostics, the global health community can develop more effective strategies to combat drug-resistant fungal infections, protect vulnerable populations, and improve patient outcomes.

Precision Medicine and Health Journal
Online ISSN: 3105-9295 | Print ISSN: 3105-9287

6. List of abbreviations

COPD	Chronic obstructive pulmonary disease
IVF	Invasive fungal disease
HIV	Human immunodeficiency viruses
WHO	World Health Organization
FPPL	Fungal Priority Pathogens List
AMR	Antifungal/Antimicrobial Resistance
IFD	Invasive Fungal Disease
PCR	Polymerase Chain Reaction
NGS	Next-Generation Sequencing

7. Authorship

All authors are accountable for this work, meet ICMJE authorship criteria, and have approved the final version for publication.

8. Authors' Contributions:

Both authors contributed equally to this work. Both were involved in conceptualization, literature search, drafting, and critical revision of the manuscript. Both authors have read and approved the final version for publication.

9. Conflicts of interest

None

10. Funding

None

11. Consent for publication

Not Applicable

12. AI Use Disclosure

ChatGPT assisted with portions of the writing to improve language clarity. The authors reviewed and edited the content and are responsible for the final manuscript.

Cite as: Shaikh SH, Qazi MA. The environmental–clinical nexus: how agricultural fungicide use is driving the antifungal resistance crisis and the race for novel solutions. Precision Med Health J. 2025;1(1):1–15.

ORCID
Sadam Hussain Shaikh https://orcid.org/0009-0006-7708-5040

References

1. Olatunji, A.O., Olaboye, J.A., Maha, C.C., Kolawole, T.O. and Abdul, S., 2024. Environmental microbiology and public health: Advanced strategies for mitigating waterborne and airborne pathogens to prevent disease. *International Medical Science Research Journal*, 4(7), pp.756-770.
2. Vermund, S.H., Scott, M.E., and Humphries, D.L., 2021. Public Health and Clinical Implications of Nutrition-Infection Interactions. *Nutrition and Infectious Diseases: Shifting the Clinical Paradigm*, pp.459-481.
3. Gudiol, C., Albasanz-Puig, A., Cuervo, G. and Carratalà, J., 2021. Understanding and managing sepsis in patients with cancer in the era of antimicrobial resistance. *Frontiers in Medicine*, 8, p.636547.
4. Ball, B., Langille, M. and Geddes-McAlister, J., 2020. Fun (gi) omics: Advanced and diverse technologies to explore emerging fungal pathogens and define mechanisms of antifungal resistance. *MBio*, 11(5), pp.10-1128.
5. Mancuso, G., Midiri, A., Gerace, E. and Biondo, C., 2021. Bacterial antibiotic resistance: the most critical pathogens. *Pathogens*, 10(10), p.1310.
6. Nnadi, N.E. and Carter, D.A., 2021. Climate change and the emergence of fungal pathogens. *PLoS Pathogens*, 17(4), p.e1009503.
7. Godeau, C., 2022. Evaluation of the impact of the dissemination of triazole fungicides in agriculture on *Aspergillus fumigatus* and proposal of solutions (Doctoral dissertation, Université Bourgogne Franche-Comté).
8. Srivastava, S.R. and Dubey, S., 2020. Knowledge-based systems in medical applications. In *Computational Intelligence and its Applications in Healthcare* (pp. 189-215). Academic Press.
9. Bhatt, K., Agolli, A., Patel, M.H., Garimella, R., Devi, M., Garcia, E., Amin, H., Domingue, C., Del Castillo, R.G. and Sanchez-Gonzalez, M., 2021. High mortality co-infections of COVID-19 patients: mucormycosis and other fungal infections. *Discoveries*, 9(1).
10. Kaushik, N., Pujalte, G.G. and Reese, S.T., 2015. Superficial fungal infections. *Primary Care: Clinics in Office Practice*, 42(4), pp.501-516.
11. Hameed, S., Hans, S., Monasky, R., Thangamani, S. and Fatima, Z., 2021. Understanding human microbiota offers novel and promising therapeutic options against *Candida* infections. *Pathogens*, 10(2), p.183.
12. Pham, D., Sivalingam, V., Tang, H.M., Montgomery, J.M., Chen, S.C.A. and Halliday, C.L., 2024. Molecular Diagnostics for Invasive Fungal Diseases: Current and Future Approaches. *Journal of Fungi*, 10(7), p.447.
13. Bisen, A.C., Sanap, S.N., Agrawal, S., Biswas, A., Mishra, A., Verma, S.K., Singh, V. and Bhatta, R.S., 2024. Etiopathology, Epidemiology, Diagnosis, and Treatment of Fungal Keratitis. *ACS Infectious Diseases*.

2025, Vol. 1, Issue 1
DOI: 10.65459/pmhj.000000001

14. Alara, J.A. and Alara, O.R., 2024. An Overview of the Global Alarming Increase of Multiple Drug Resistant: A Major Challenge in Clinical Diagnosis. *Infectious Disorders-Drug Targets (Formerly Current Drug Targets-Infectious Disorders)*, 24(3), pp.26-42.
15. Lim, M. and Shu, Y., 2022. The Future is Fungi: How Fungi Can Feed Us, Heal Us, Free Us and Save Our World. Thames & Hudson Australia.
16. Harsha, M.V., Venkatachalam, S., Pooja, M. and Paranjothy, M., 2017. Emerging fungal pathogens: A major threat to human life. *Int J Pharm Sci*, 8(5), p.1923.
17. Denning, D.W. and Hope, W.W., 2010. Therapy for fungal diseases: opportunities and priorities. *Trends in Microbiology*, 18(5), pp.195-204.
18. Rodrigues, M.L. and Nosanchuk, J.D., 2023. Recognition of fungal priority pathogens: What next?. *PLoS Neglected Tropical Diseases*, 17(3), p.e0011136.
19. Geddes-McAlister, J. and Shapiro, R.S., 2019. New pathogens, new tricks: emerging, drug-resistant fungal pathogens and future prospects for antifungal therapeutics. *Annals of the New York Academy of Sciences*, 1435(1), pp.57-78.
20. Hoenigl, M., Arastehfar, A., Arendrup, M.C., Brüggemann, R., Carvalho, A., Chiller, T., Chen, S., Egger, M., Feys, S., Gangneux, J.P. and Gold, J.A., 2024. Novel antifungals and treatment approaches to tackle resistance and improve outcomes of invasive fungal disease. *Clinical Microbiology Reviews*, pp.e00074-23.
21. Fang, W., Wu, J., Cheng, M., Zhu, X., Du, M., Chen, C., Liao, W., Zhi, K. and Pan, W., 2023. Diagnosis of invasive fungal infections: challenges and recent developments. *Journal of Biomedical Science*, 30(1), p.42.
22. Parums, D.V., 2022. The World Health Organization (WHO) fungal priority pathogens list in response to emerging fungal pathogens during the COVID-19 pandemic. *Medical Science Monitor: International Medical Journal of Experimental and Clinical Research*, 28, pp.e939088-1.
23. Osborn, J., Roberts, T., Guillen, E., Bernal, O., Roddy, P., Ongarello, S., Sprecher, A., Page, A.L., Ribeiro, I., Piriou, E. and Tamrat, A., 2020. Prioritising pathogens for the management of severe febrile patients to improve clinical care in low-and middle-income countries. *BMC Infectious Diseases*, 20, pp.1-11.
24. Garvey, M. and Rowan, N.J., 2023. Pathogenic drug resistant fungi: a review of mitigation strategies. *International Journal of Molecular Sciences*, 24(2), p.1584.
25. Dao, A., Kim, H.Y., Garnham, K., Kidd, S., Sati, H., Perfect, J., Sorrell, T.C., Harrison, T., Rickerts, V., Gigante, V. and Alastruey-Izquierdo, A., 2024. Cryptococcosis—a systematic review to inform the World Health Organization Fungal Priority Pathogens List. *Medical Mycology*, 62(6).
26. Zhao, Y., Ye, L., Zhao, F., Zhang, L., Lu, Z., Chu, T., Wang, S., Liu, Z., Sun, Y., Chen, M. and Liao, G., 2023. Cryptococcus neoformans, a global threat to human health. *Infectious Diseases of Poverty*, 12(02), pp.1-18.
27. Tugume, L., Ssebambulidde, K., Kasibante, J., Ellis, J., Wake, R.M., Gakuru, J., Lawrence, D.S., Abassi, M., Rajasingham, R., Meya, D.B. and Boulware, D.R., 2023. Cryptococcal meningitis. *Nature Reviews Disease Primers*, 9(1), p.62.
28. Kenosi, K., Mosimanegape, J., Daniel, L. and Ishmael, K., 2023. Recent Advances in the Ecoepidemiology, Virulence and Diagnosis of Cryptococcus neoformans and Cryptococcus gattii Species Complexes. *The Open Microbiology Journal*, 17(1).
29. Casalini, G., Giacomelli, A. and Antinori, S., 2024. The WHO fungal priority pathogens list: a crucial reappraisal to review the prioritisation. *The Lancet Microbe*.
30. Fisher, M.C. and Denning, D.W., 2023. The WHO fungal priority pathogens list as a game-changer. *Nature Reviews Microbiology*, 21(4), pp.211-212.
31. Perrone, G. and Gallo, A., 2017. Aspergillus species and their associated mycotoxins. In *Mycotoxigenic Fungi: Methods and Protocols*, pp.33-49.
32. Guarro, J., Xavier, M.O. and Severo, L.C., 2010. Differences and similarities amongst pathogenic Aspergillus species. In *Aspergillosis: From Diagnosis to Prevention*, pp.7-32.
33. O'Gorman, C.M., 2011. Airborne Aspergillus fumigatus conidia: a risk factor for aspergillosis. *Fungal Biology Reviews*, 25(3), pp.151-157.
34. De Linares, C., Navarro, D., Puigdemunt, R. and Belmonte, J., 2023. Aspergillus conidia and allergens in outdoor environment: a health hazard?. *Journal of Fungi*, 9(6), p.624.
35. Zhou, Y., Zhang, Z., Tian, J. and Xiong, S., 2020. Risk factors associated with disease progression in a cohort of patients infected with the 2019 novel coronavirus. *Annals of Palliative Medicine*, 9(2), pp.42836-42436.
36. Douglas, A.P., Smibert, O.C., Bajel, A., Halliday, C.L., Lavee, O., McMullan, B., Yong, M.K., van Hal, S.J., Chen, S.C.A., Australasian Antifungal Guidelines Steering Committee and Slavin, M.A., 2021. Consensus guidelines for the diagnosis and management of invasive aspergillosis, 2021. *Internal Medicine Journal*, 51, pp.143-176.
37. Raoult, D., Zumla, A., Locatelli, F., Ippolito, G. and Kroemer, G., 2020. Coronavirus infections: Epidemiological, clinical and immunological features and hypotheses. *Cell Stress*, 4(4), p.66.
38. Zhang, S.X., Babady, N.E., Hanson, K.E., Harrington, A.T., Larkin, P.M., Leal Jr, S.M., Luethy, P.M., Martin, I.W., Pancholi, P., Procop, G.W. and Riedel, S., 2021. Recognition of diagnostic gaps for laboratory diagnosis of fungal diseases: expert opinion from the Fungal Diagnostics Laboratories Consortium (FDLC). *Journal of Clinical Microbiology*, 59(7), pp.10-1128.
39. Das, R., Kotra, K., Singh, P., Loh, B., Leptihn, S. and Bajpai, U., 2022. Alternative treatment strategies for secondary bacterial and fungal infections associ-

Precision Medicine and Health Journal
Online ISSN: 3105-9295 | Print ISSN: 3105-9287

ated with COVID-19. *Infectious Diseases and Therapy*, pp.1-25.

40. Snelders, E., Melchers, W.J.G. and Verweij, P.E., 2012. General introduction and outline of this thesis. *Azole Resistance in Aspergillus fumigatus: Collateral Damage of Fungicide Use*, 6, p.9.
41. Vazquez, J.A., Miceli, M.H. and Alangaden, G., 2013. Invasive fungal infections in transplant recipients. *Therapeutic Advances in Infectious Disease*, 1(3), pp.85-105.
42. Ahmad, S. and Khan, Z., 2012. Invasive candidiasis: a review of nonculture-based laboratory diagnostic methods. *Indian Journal of Medical Microbiology*, 30(3), pp.264-269.
43. Nguyen, M.H., Wissel, M.C., Shields, R.K., Salomoni, M.A., Hao, B., Press, E.G., Shields, R.M., Cheng, S., Mitsani, D., Vadnerkar, A. and Silveira, F.P., 2012. Performance of Candida real-time polymerase chain reaction, β-D-glucan assay, and blood cultures in the diagnosis of invasive candidiasis. *Clinical Infectious Diseases*, 54(9), pp.1240-1248.
44. Roberts, C.L., Algert, C.S., Rickard, K.L. and Morris, J.M., 2015. Treatment of vaginal candidiasis for the prevention of preterm birth: a systematic review and meta-analysis. *Systematic Reviews*, 4, pp.1-9.
45. Nasution, A.I., 2013. Virulence factor and pathogenicity of Candida albicans in oral candidiasis. *World Journal of Dentistry*, 4(4), pp.267-271.
46. Cuéllar-Cruz, M., López-Romero, E., Villagómez-Castro, J.C. and Ruiz-Baca, E., 2012. Candida species: new insights into biofilm formation. *Future Microbiology*, 7(6), pp.755-771.
47. Chandra, J. and Mukherjee, P.K., 2015. Candida biofilms: development, architecture, and resistance. In *Microbial Biofilms*, pp.115-134.
48. Alves, P.G.V., de Paula Menezes, R., Silva, N.B.S., de Oliveira Faria, G., de Souza Bessa, M.A., de Araújo, L.B., Aguiar, P.A.D.F., Penatti, M.P.A., dos Santos Pedroso, R. and de Brito Röder, D.V.D., 2024. Virulence factors, antifungal susceptibility and molecular profile in Candida species isolated from the hands of health professionals before and after cleaning with 70% ethyl alcohol-based gel. *Journal of Medical Mycology*, 34(2), p.101482.
49. Zhang, S.X., O'Donnell, K. and Sutton, D.A., 2015. Fusarium and other opportunistic hyaline fungi. In *Manual of Clinical Microbiology*, pp.2057-2086.
50. Cortés-López, P.N., Guzmán-Montijo, E., Fuentes-Venado, C.E., Arenas, R., Bonifaz, A., Pinto-Almazán, R. and Martínez-Herrera, E., 2024. Cutaneous Fusarium disease and leukaemias: A systematic review. *Mycoses*, 67(7), p.e13759.
51. Nucci, M. and Anaissie, E., 2023. Invasive fusariosis. *Clinical Microbiology Reviews*, 36(4), pp.e00159-22.
52. Prakash, S. and Kumar, A., 2023. Mucormycosis threats: a systemic review. *Journal of Basic Microbiology*, 63(2), pp.119-127.
53. Mahalaxmi, I., Jayaramayya, K., Venkatesan, D., Subramaniam, M.D., Renu, K., Vijayakumar, P., Narayanasamy, A., Gopalakrishnan, A.V., Kumar, N.S., Sivaprakash, P. and Rao, K.R.S., 2021. Mucormycosis: An opportunistic pathogen during COVID-19. *Environmental Research*, 201, p.111643.
54. Kasvala, D., Monpara, P., Patel, P. and Upadhyay, U., 2021. A review of mucormycosis. *World Journal of Pharmaceutical Research*, 13.
55. Reid, G., Lynch III, J.P., Fishbein, M.C. and Clark, N.M., 2020, February. Mucormycosis. In *Seminars in Respiratory and Critical Care Medicine* (Vol. 41, No. 01, pp. 099-114). Thieme Medical Publishers.
56. Bastos, R.W., Rossato, L., Goldman, G.H. and Santos, D.A., 2021. Fungicide effects on human fungal pathogens: cross-resistance to medical drugs and beyond. *PLoS Pathogens*, 17(12), p.e1010073.
57. Lee, Y., Puumala, E., Robbins, N. and Cowen, L.E., 2020. Antifungal drug resistance: molecular mechanisms in Candida albicans and beyond. *Chemical Reviews*, 121(6), pp.3390-3411.
58. Adetunji, C.O. and Varma, A., 2020. Biotechnological application of Trichoderma: A powerful fungal isolate with diverse potentials for the attainment of food safety, management of pest and diseases, healthy planet, and sustainable agriculture. In *Trichoderma: Agricultural Applications and Beyond*, pp.257-285.
59. Tsalidis, G.A., 2022. Human health and ecosystem quality benefits with life cycle assessment due to fungicides elimination in agriculture. *Sustainability*, 14(2), p.846.
60. Kaur, L., 2023. Fungicide Resistance in the Early and Late Leaf Spot Pathogens of Peanut and Their Management (Master's thesis).
61. Francis, C.A. and Clegg, M.D., 2020. Crop rotations in sustainable production systems. In *Sustainable Agricultural Systems*, pp.107-122. CRC Press.
62. Meher, J., Rajput, R.S., Bajpai, R., Teli, B. and Sarma, B.K., 2020. Trichoderma: A globally dominant commercial biofungicide. In *Trichoderma: Agricultural applications and beyond*, pp.195-208.
63. Sen, A., Oswalia, J., Yadav, S., Vachher, M. and Nigam, A., 2024. Current Research in Biotechnology. *Current Research in Biotechnology*, 7, p.100205.
64. Hoenigl, M., Sprute, R., Egger, M., Arastehfar, A., Cornely, O.A., Krause, R., Lass-Flörl, C., Prattes, J., Spec, A., Thompson, G.R. and Wiederhold, N., 2021. The antifungal pipeline: fosmanogepix, ibrexafungerp, olorofim, opelconazole, and rezafungin. *Drugs*, 81, pp.1703-1729.
65. Armstrong-James, D., 2021. Future directions for clinical respiratory fungal research. *Mycopathologia*, 186(5), pp.685-696.
66. Hyde, K.D., Al-Hatmi, A.M., Andersen, B., Boekhout, T., Buzina, W., Dawson, T.L., Eastwood, D.C., Jones, E.G., de Hoog, S., Kang, Y. and Longcore, J.E., 2018. The world's ten most feared fungi. *Fungal Diversity*, 93, pp.161-194.
67. Roberts, D.M. and Gilger, B.C., 2024. Current therapy and advancements in the treatment of equine fungal

2025, Vol. 1, Issue 1
DOI: 10.65459/pmhj.000000001

keratitis. *Journal of the American Veterinary Medical Association*, 1(aop), pp.1-9.

68. Pfaller, M.A., Castanheira, M., Messer, S.A., Moet, G.J. and Jones, R.N., 2011. Echinocandin and triazole antifungal susceptibility profiles for Candida spp., Cryptococcus neoformans, and Aspergillus fumigatus: application of new CLSI clinical breakpoints and epidemiologic cutoff values to characterize resistance in the SENTRY Antimicrobial Surveillance Program (2009). *Diagnostic Microbiology and Infectious Disease*, 69(1), pp.45-50.
69. Kumari, H., Prakash, S., Minakshi and Kumar, A., 2024. Strategies for Enhancing the Production of Echinocandin. In *Fungi Bioactive Metabolites: Integration of Pharmaceutical Applications*, pp.633-647. Singapore: Springer Nature Singapore.
70. Vishwakarma, M., Haider, T. and Soni, V., 2023. Update on fungal lipid biosynthesis inhibitors as antifungal agents. *Microbiological Research*, p.127517.
71. Pfaller, M.A., Carvalhaes, C.G. and Castanheira, M., 2023. Susceptibility patterns of amphotericin B, itraconazole, posaconazole, voriconazole and caspofungin for isolates causing invasive mould infections from the SENTRY Antifungal Surveillance Program (2018–2021) and application of single-site epidemiological cutoff values to evaluate amphotericin B activity. *Mycoses*, 66(10), pp.854-868.
72. Yenişehirli, G., Alıcı, A. and Yenişehirli, A., 2023. Antifungal drug susceptibility profiles and molecular mechanisms of azole resistance in Candida blood stream isolates. *Indian Journal of Medical Microbiology*, 45, p.100389.
73. Alcazar-Fuoli, L. and Mellado, E., 2014. Current status of antifungal resistance and its impact on clinical practice. *British Journal of Haematology*, 166(4), pp.471-484.
74. Sanglard, D., 2002. Resistance of human fungal pathogens to antifungal drugs. *Current Opinion in Microbiology*, 5(4), pp.379-385.
75. Kanafani, Z.A. and Perfect, J.R., 2008. Resistance to antifungal agents: mechanisms and clinical impact. *Clinical Infectious Diseases*, 46(1), pp.120-128.
76. Rabaan, A.A., Sulaiman, T., Al-Ahmed, S.H., Buhaliqah, Z.A., Buhaliqah, A.A., AlYuosof, B., Alfaresi, M., Al Fares, M.A., Alwarthan, S., Alkathlan, M.S. and Almaghrabi, R.S., 2023. Potential strategies to control the risk of antifungal resistance in humans: A comprehensive review. *Antibiotics*, 12(3), p.608.
77. Hoenigl, M., Sprute, R., Egger, M., Arastehfar, A., Cornely, O.A., Krause, R., Lass-Flörl, C., Prattes, J., Spec, A., Thompson III, G.R. and Wiederhold, N., 2021. The antifungal pipeline: fosmanogepix, ibrexafungerp, olorofim, opelconazole, and rezafungin. *Drugs*, 81(15), pp.1703-1729.
78. Carmo, A., Rocha, M., Pereirinha, P., Tomé, R. and Costa, E., 2023. Antifungals: from pharmacokinetics to clinical practice. *Antibiotics*, 12(5), p.884.
79. Sousa, F., Nascimento, C., Ferreira, D., Reis, S. and Costa, P., 2023. Reviving the interest in the versatile drug nystatin: A multitude of strategies to increase its potential as an effective and safe antifungal agent. *Advanced Drug Delivery Reviews*, 199, p.114969.
80. Taori, T., Wadher, B., Maheshwari, S., Mohod, S. and Dangore, S., 2024. Pharmacological management of oral lesion. *International Arab Journal of Dentistry (IAJD)*, 15(1), pp.184-198.
81. Sant, D.G., Tupe, S.G., Ramana, C.V. and Deshpande, M.V., 2016. Fungal cell membrane—promising drug target for antifungal therapy. *Journal of Applied Microbiology*, 121(6), pp.1498-1510.
82. Chen, S.C.A., Slavin, M.A. and Sorrell, T.C., 2011. Echinocandin antifungal drugs in fungal infections: a comparison. *Drugs*, 71, pp.11-41.
83. Szymański, M., Chmielewska, S., Czyżewska, U., Malinowska, M. and Tylicki, A., 2022. Echinocandins–structure, mechanism of action and use in antifungal therapy. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 37(1), pp.876-894.
84. Mroczyńska, M. and Brillowska-Dąbrowska, A., 2020. Review on current status of echinocandins use. *Antibiotics*, 9(5), p.227.
85. Murphy, S.E. and Bicanic, T., 2021. Drug resistance and novel therapeutic approaches in invasive candidiasis. *Frontiers in Cellular and Infection Microbiology*, 11, p.759408.
86. Roy, M., Karhana, S., Shamsuzzaman, M. and Khan, M.A., 2023. Recent drug development and treatments for fungal infections. *Brazilian Journal of Microbiology*, 54(3), pp.1695-1716.
87. Logan, A., Wolfe, A. and Williamson, J.C., 2022. Antifungal resistance and the role of new therapeutic agents. *Current Infectious Disease Reports*, 24(9), pp.105-116.
88. Hammoudi Halat, D., Younes, S., Mourad, N. and Rahal, M., 2022. Allylamines, benzylamines, and fungal cell permeability: a review of mechanistic effects and usefulness against fungal pathogens. *Membranes*, 12(12), p.1171.
89. Raj, G.M., 2021. Antifungal Drugs. In *Introduction to Basics of Pharmacology and Toxicology: Volume 2: Essentials of Systemic Pharmacology: From Principles to Practice*, pp.905-926.
90. Odds, F.C., 2003. Antifungal agents: their diversity and increasing sophistication. *Mycologist*, 17(2), pp.51-55.
91. Hay, R.J., 2023. Antifungal drugs. In *European handbook of dermatological treatments* (pp.1543-1554). Cham: Springer International Publishing.
92. Denning, D.W., 2022. Antifungal drug resistance: an update. *European Journal of Hospital Pharmacy*, 29(2), pp.109-112.
93. Mota Fernandes, C., Dasilva, D., Haranahalli, K., McCarthy, J.B., Mallamo, J., Ojima, I. and Del Poeta, M., 2021. The future of antifungal drug therapy: novel compounds and targets. *Antimicrobial Agents and Chemotherapy*, 65(2), pp.10-1128.

Precision Medicine and Health Journal
Online ISSN: 3105-9295 | Print ISSN: 3105-9287

94. Perfect, J.R. and Ghannoum, M., 2020. Emerging issues in antifungal resistance. *Infectious Disease Clinics*, 34(4), pp.921-943.

95. Pemán, J., Cantón, E. and Espinel-Ingroff, A., 2009. Antifungal drug resistance mechanisms. *Expert Review of Anti-infective Therapy*, 7(4), pp.453-460.

96. Perfect, J.R., 2013. Fungal diagnosis: how do we do it and can we do better?. *Current Medical Research and Opinion*, 29(sup4), pp.3-11.

97. Mendonca, A., Santos, H., Franco-Duarte, R. and Sampaio, P., 2022. Fungal infections diagnosis–past, present and future. *Research in Microbiology*, 173(3), p.103915.

98. Sedik, S., Wolfgruber, S., Hoenigl, M. and Kriegl, L., 2024. Diagnosing fungal infections in clinical practice: a narrative review. *Expert Review of Anti-infective Therapy*, (just-accepted).

99. Terrero-Salcedo, D. and Powers-Fletcher, M.V., 2020. Updates in laboratory diagnostics for invasive fungal infections. *Journal of Clinical Microbiology*, 58(6), pp.10-1128.

100. Ray, M., Ray, A., Dash, S., Mishra, A., Achary, K.G., Nayak, S. and Singh, S., 2017. Fungal disease detection in plants: Traditional assays, novel diagnostic techniques and biosensors. *Biosensors and Bioelectronics*, 87, pp.708-723.

101. Zeller, I., Schabereiter-Gurtner, C., Mihalits, V., Selitsch, B., Barousch, W., Hirschl, A.M., Makristathis, A. and Willinger, B., 2017. Detection of fungal pathogens by a new broad range real-time PCR assay targeting the fungal ITS2 region. *Journal of Medical Microbiology*, 66(10), pp.1383-1392.

102. Willinger, B., Kienzl, D. and Kurzai, O., 2013. Diagnostics of Fungal Infections. In *Human Fungal Pathogens* (pp.229-259). Berlin, Heidelberg: Springer Berlin Heidelberg.

103. Caceres, D.H., Chiller, T. and Lindsley, M.D., 2020. Immunodiagnostic assays for the investigation of fungal outbreaks. *Mycopathologia*, 185(5), pp.867-880.

104. Rodrigues, M.L. and Nosanchuk, J.D., 2023. Recognition of fungal priority pathogens: What next?. *PLoS Neglected Tropical Diseases*, 17(3), p.e0011136.

105. Thomas, T.R.A., Kavlekar, D.P. and LokaBharathi, P.A., 2010. Marine drugs from sponge-microbe association—A review. *Marine Drugs*, 8(4), pp.1417-1468.

106. Saxena, S., Chhibber, M. and Singh, I.P., 2019. Fungal bioactive compounds in pharmaceutical research and development. *Current Bioactive Compounds*, 15(2), pp.211-231.

107. Xu, C., Zhang, R. and Wen, Z., 2018. Bioactive compounds and biological functions of sea cucumbers as potential functional foods. *Journal of Functional Foods*, 49, pp.73-84.

108. Molinski, T.F., 2004. Antifungal compounds from marine organisms. *Current Medicinal Chemistry-Anti-Infective Agents*, 3(3), pp.197-220.

109. Thawabteh, A.M., Swaileh, Z., Ammar, M., Jaghama, W., Yousef, M., Karaman, R., A. Bufo, S. and Scrano, L., 2023. Antifungal and antibacterial activities of isolated marine compounds. *Toxins*, 15(2), p.93.

110. El-Hossary, E.M., Cheng, C., Hamed, M.M., Hamed, A.N.E.S., Ohlsen, K., Hentschel, U. and Abdelmohsen, U.R., 2017. Antifungal potential of marine natural products. *European Journal of Medicinal Chemistry*, 126, pp.631-651.

111. Abad, M.J., Bedoya, L.M. and Bermejo, A.P., 2011. Marine compounds and their antimicrobial activities. *Science Against Microbial Pathogens: Communicating Current Research and Technological Advances*, 51, pp.1293-1306.

112. Soliman, G.M., 2017. Nanoparticles as safe and effective delivery systems of antifungal agents: Achievements and challenges. *International Journal of Pharmaceutics*, 523(1), pp.15-32.

113. Wu, S., Song, R., Liu, T. and Li, C., 2023. Antifungal therapy: Novel drug delivery strategies driven by new targets. *Advanced Drug Delivery Reviews*, 199, p.114967.

114. de Almeida Campos, L., Fin, M.T., Santos, K.S., de Lima Gualque, M.W., Freire Cabral, A.K.L., Khalil, N.M., Fusco-Almeida, A.M., Mainardes, R.M. and Mendes-Giannini, M.J.S., 2023. Nanotechnology-based approaches for voriconazole delivery applied to invasive fungal infections. *Pharmaceutics*, 15(1), p.266.

115. Waghule, T., Sankar, S., Rapalli, V.K., Gorantla, S., Dubey, S.K., Chellappan, D.K., Dua, K. and Singhvi, G., 2020. Emerging role of nanocarriers based topical delivery of anti-fungal agents in combating growing fungal infections. *Dermatologic Therapy*, 33(6), p.e13905.

116. Matras, E., Gorczyca, A., Przemieniecki, S.W. and Oćwieja, M., 2022. Surface properties-dependent antifungal activity of silver nanoparticles. *Scientific Reports*, 12(1), p.18046.

117. Żarowska, B., Koźlecki, T., Piegza, M., Jaros-Koźlecka, K. and Robak, M., 2019. New look on antifungal activity of silver nanoparticles (AgNPs). *Polish Journal of Microbiology*, 68(4), pp.515-525.

118. Sousa, F., Ferreira, D., Reis, S. and Costa, P., 2020. Current insights on antifungal therapy: Novel nanotechnology approaches for drug delivery systems and new drugs from natural sources. *Pharmaceuticals*, 13(9), p.248.

119. Hariharan, G. and Prasannath, K., 2021. Recent advances in molecular diagnostics of fungal plant pathogens: a mini review. *Frontiers in Cellular and Infection Microbiology*, 10, p.600234.

120. Jacobs, S.E., Zagaliotis, P. and Walsh, T.J., 2021. Novel antifungal agents in clinical trials [version 1; peer].

121. Espinel-Ingroff, A., 2009. Novel antifungal agents, targets or therapeutic strategies for the treatment of invasive fungal diseases: a review of the literature (2005-2009). *Revista Iberoamericana de Micologia*, 26(1), pp.15-22.

2025, Vol. 1, Issue 1
DOI: 10.65459/pmhj.000000001

122. Hoenigl, M., Arastehfar, A., Arendrup, M.C., Brüggemann, R., Carvalho, A., Chiller, T., Chen, S., Egger, M., Feys, S., Gangneux, J.P. and Gold, J.A., 2024. Novel antifungals and treatment approaches to tackle resistance and improve outcomes of invasive fungal disease. *Clinical Microbiology Reviews*, pp.e00074-23.
123. Zhu, P., Li, Y., Guo, T., Liu, S., Tancer, R.J., Hu, C., Zhao, C., Xue, C. and Liao, G., 2023. New antifungal strategies: drug combination and co-delivery. *Advanced Drug Delivery Reviews*, 198, p.114874.
124. Boyer, J., Hoenigl, M. and Kriegl, L., 2024. Therapeutic drug monitoring of antifungal therapies: do we really need it and what are the best practices?. *Expert Review of Clinical Pharmacology*, 17(4), pp.309-321.
125. August, B.A. and Kale-Pradhan, P.B., 2024. Management of invasive candidiasis: A focus on rezafungin, ibrexafungerp, and fosmanogepix. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*.
126. Chaudhari, V., Vairagade, V., Thakkar, A., Shende, H. and Vora, A., 2024. Nanotechnology-based fungal detection and treatment: current status and future perspective. *Naunyn-Schmiedeberg's Archives of Pharmacology*, 397(1), pp.77-97.
127. Abd-Elsalam, K.A., 2023. Fungal nanotechnology for improving farm productivity and sustainability: A note.
128. Kuddus, M., Ahmad, I.Z. and Hussain, C.M. eds., 2023. *Myconanotechnology and Application of Nanoparticles in Biology: Fundamental Concepts, Mechanism and Industrial Applications*. Elsevier.
129. Jacobs, S.E., Zagaliotis, P. and Walsh, T.J., 2021. Novel antifungal agents in clinical trials. *F1000Research*, 10.
130. Neoh, C.F., Jeong, W., Kong, D.C. and Slavin, M.A., 2023. The antifungal pipeline for invasive fungal diseases: what does the future hold?. *Expert Review of Anti-infective Therapy*, 21(6), pp.577-594.