Int. J. Sci. R. Tech., 2025 2(11)
A Multidisciplinary peer-reviewed Journal
www.ijsrtjournal.com [ISSN: 2394-7063]

*Original Article*

# Emerging Multidrug-Resistant Fungal Pathogens: Epidemiology, Mechanisms, and Novel Therapeutic Solutions

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**ABSTRACT**

Fungal pathogens are an emerging and increasingly significant global health concern with escalating rates of severe infections they induce in immunocompromised patients. Though the development of azoles, echinocandins, and polyene antifungal drugs over recent decades has revolutionized treatment options, increasing antifungal resistance is placing medical gains at risk. Highly problematic and alarming Candida Auris, Aspergillus fumigatus, Cryptococcus neoformans pathogens in addition to newly emergent species are invading the world with different prevalence and resistance patterns. Resistance is associated with genetic mutation, overexpression of efflux pumps, biofilm formation, and environmental factors especially due to massive exposure to agricultural fungicides. This carries increased morbidity and mortality, increased costs of healthcare expenditure, and major public health challenges. Current efforts in resistance monitoring and detection still fall short as global surveillance networks struggle under conditions of diagnostic and resource constraints. Such resistance can be prevented by antifungal stewardship as well as stringent infection control practices plus the management of the environment where reservoirs are identified. Present studies focus on new antifungal agents, repositioned drugs, immunomodulators that could serve as alternative therapies, and antifungal vaccines. Future perspectives in this growing threat require robust global surveillance systems accompanied by molecular diagnostics and novel drug discovery initiatives. A unified One-Health strategy and ongoing international cooperation are essential to address the growing danger of antifungal resistance in today's world.

**Keywords:** Antifungal resistance, Multidrug-resistant fungi, Candida auris, Aspergillus fumigatus, Cryptococcus neoformans, Emerging fungal pathogens, One Health approach, Antifungal stewardship, Azole resistance, Echinocandin resistance, Efflux pumps, Biofilm formation, Genetic mutations, Environmental fungicides, Molecular diagnostics, Global surveillance, Antifungal drug discovery, Immunocompromised patients, Invasive fungal infections, Novel antifungal agents, Nanotechnology-based therapeutics, Fungal virulence factors, Public health threat

## INTRODUCTION

Fungi are also dangerous to people and cause considerable worldwide illness and death. However, the gravity of the situation around fungal infections, when compared to bacterial and viral illnesses, seems to have a much lower recognition [1]. Some 625 fungal species have been recorded to infect vertebrates and 200 of those species can infect humans, either as the pathogens of the native microbiome or as more aggressive pathogens [2]. A considerable number of these infected are dead cause of weak immune systems. Annual deaths are considerable as a consequence [3]. Superficial, subcutaneous, and systemic infections are standardly the possible results of the infection [4]. Fungi pathogens, including Aspergillus, Candida, Cryptococcus, and Histoplasma, are also responsible for some of the most serious and invasive diseases [5]. The number of fungal infections and the proportion of patients that are immune compromised and the use of antifungal treatments the fungi are resistant to have all increased [8, 6]. The treatment of fungal infections poses an especially unique challenge because of their interactions with the host immune system. Fungi have developed strategies for immune evasion, as well as the exploitation of host cell death for their own dissemination and within-host spreading infections [3]. Creating antifungal medications poses a challenge because fungi are eukaryotes, and thus, targeting a cell with a eukaryotic structure becomes problematic, as human cells may get affected too [5]. Admittedly,

**Relevant conflicts of interest/financial disclosures**: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

fungal therapeutics and diagnostics have had a much less than adequate attention, but some progress has undoubtedly been made. The fact that there are still no vaccines, however, is a glaring gap. Work towards vaccines for fungal infections, especially in comparison to the work for viral and bacterial infections, is still in the very early phases, although some progress is being made for fungi like Candida and Cryptococcus [1,9]. Fungal pathogens are a rising threat to human health, especially the immunocompromised. Unfortunately, the threat may only be a fraction of what it is if there were enough research to produce effective vaccines. The addition of antifungal resistance and immunology difficulties only strengthen the need for innovation and research in the field [4,6]. Treating fungal infections takes antifungal medicines to save lives so we can see how effective medications are resourceful and well-built treatments are so very essential. The following summaries these advances. The 1950s saw the advent of a gold standard dehydration treatment for the less severe Mycosis and a powerful antifungal, lipid amphotericin. The activity of this antifungal can be accounted to its fungistatic ability to kill and disrupt the fungal cell and kill and fungal cell. Amphotericin is and still a popular choice but its activity is still limited by its fungistatic ability to kill and disrupt the fungal cell and kill and fungal cell. The 1970s saw the emergence of the goal sold standard fluconazole, which, was the first of the subclass of azoles and the first of a new class of antifungals which acted and still acts and functions by inhibiting and disrupting the biosynthetic pathway and mechanisms of its fungal cell membrane and appendage. The fungal cell membrane and appendage is ergosterol, a target and active component of the biosynthesis pathway of fluconazole. ergosterol is a fungal sterol equivalent to Cholesterol which zombify and improves fluconazole activity by provided fungal sterol.

**Echinocandins:** These were introduced in the early 2000s. An example is Compounding, which acts as an inhibitor of β-glucan synthesis component of the fungal cell wall. It has good activity against Candida species and shows low side effects in comparison with other earlier antifungal agents.

**Flucytosine:** It is used in combination therapy as an agent disrupting RNA synthesis of fungi. Its use is limited by resistance that rapidly develops against it when used alone.

**Emergence of Resistance:** One great challenge with antifungals as their use continues to increase is indeed resistance. Pathogens, like Candida Auris, have now developed mechanisms for multidrug resistance against currently existing treatment regimens [15].

**Novel Strategies:** Recent Innovations are a result of attempts geared toward overcoming these resistance challenges. Among the promising strategies include creating nanoparticles since they have better delivery and efficacy characteristics and artificial intelligence-assisted drug discovery [14,16].

**Current and Future Directions:** Research continues to explore new targets and drugs, such as Ibrexafungerp and T-2307, and to leverage technology like AI for discovering and developing new antifungal therapies [14,13]. Great strides not withstanding in antifungal therapy over the decades, continuous research and innovation are badly needed to overcome new emerging resistance challenges and make treatments more effective and safer [11]. There are very compelling reasons for imperative antifungal resistance; it has a very high public health significance and clinical ramifications. Antifungal resistance is an increasing danger because there are ever more fungal infections alongside increasingly more resistant strains of fungi. It increases the complexity of treatment protocols as well as morbidity and mortality rates among immunocompromised patients most particularly. That shows how important dealing with antifungal resistance treatment, which is still limited to only classes available, is becoming more frequent. Such resistance undermines current treatment options thereby indicating that new therapeutic strategies and novel antifungal agents are urgently required [17]. A higher focus on susceptibility testing and antifungal stewardship to better suit the needs of the individual patients is aimed to improve the survival rates and clinical outcomes [18]. Molecular diagnostics has a critical role to play in anti-fungal resistance. These technologies allow fast identification of fungal pathogens and mechanisms of resistance to them, which could result in faster and more effective treatment. This method is especially important in the case of diseases in which inadequate timely treatment may result in serious clinical outcome [19]. It is also important to know the molecular and genetic mechanisms of antifungal resistance. As an example, the discovery of transcriptional regulators and resistance alleles can be used to guide diagnostic and therapeutic measures. This understanding is crucial in designing specific interventions and new drugs that will circumvent available resistance mechanisms [20,21]. Also, the factors of the environment and clinical cause a lot of spreading of antifungal resistance. Antifungal agents used in agriculture can be the force behind resistance which in turn influences human health and this is an issue that is ever more acknowledged as a component of the One Health paradigm. This is a strategy that focuses on human, animal, and environmental health interconnectedness, and advocates holistic approaches to the management of resistance [22]. In addition, more education and application of advanced diagnostic tools in the clinical settings are required to deal with antifungal resistance. Awareness and regular susceptibility testing can contribute to the positive results of the treatment process and give a more realistic image of the resistance pattern and help to make more accurate clinical decisions [23]. The knowledge obtained on resistance and interventions against it will also play a key role in extending the effectiveness of the available drugs and in the effective appearance of new antifungal agents.

## I. Current landscape of fungal pathogens:

Most frequently and most alarming pathogenic fungi which can be found in health care establishments are of a wide variety with Candida spp. and Aspergillus spp. being the most prevalent. These are often pathogens which have a high morbidity rate and mortality rate in hospital settings. The Candida species, especially non- Albicans like Candida krusei and Torulosis (Candida) glabrata have become more widespread, and the rate of infection incidence especially bloodstream infection is increasing [24]. The other drug-resistance pathogen of intense virulence that has emerged in clinical facilities is Candida Auris with severe infections [25]. Aspergillus species have been reported to cause major fungi outbreaks especially in the process of hospital construction and renovation, due to sporulation, leading to pulmonary infections that have a high mortality rate [26]. Mucorales, Fusarium spp., Scedosporium spp., are also problematic pathogens that are hard to diagnose and manage and that lead to a high mortality rate despite treatments with antifungal drugs, as well as the appearance of drug-resistant strains due to the use of antifungal drugs in high-risk patients, and the rise of the number of immunocompromised individuals because of illnesses such as cancer among others and transplant recipients [24,28]. Prevention of the mentioned infections is oriented toward the early introduction of an efficient antifungal treatment and the deployment of the strong infection control strategies, in particular, when a healthcare facility is under redesign [26]. These pathogens are of major danger in healthcare facilities, and there is a need to conduct research and adjust antifungal strategies to the benefit of reducing and preventing these infections [27,28]. New fungal threats are a source of serious threats to the health, ecology, and agriculture across the world. In the past decade, the fungal diseases have increased due to changes in the environment and globalization. Such threats affect many different spheres, such as human well-being, biodiversity of wildlife, and food security [29,30]. The prevalence of fungal diseases in human health has a profound psychosocial aspect as people become infected more than once a billion every year, and at least a million people die each year, exceeding all known human mortality causes, including malaria and breast cancer. The immunocompromised groups especially sickle cell anemic patients are more susceptible to fungal infections that may lead to death. More studies on fungal immunopathology are urgently required to enhance diagnostics and treatment such as personalized medicine, creation of vaccines [34]. New fungal pathogens have been identified as a threat to the biodiversity and the world food security in the field of wildlife and agriculture. In the plants, fungi may result in epidemics, which brings about massive economic and production losses. These pathogens put a strain on food security with about 8,000 species of fasciculating organisms related to plant diseases. There is also a health hazard of ingesting the mycotoxins that are toxic substances produced by certain fungi that result in illness and cancer [33,35]. The increasing risks of fungal infection are compounded by the presence of climatic changes, extreme agricultural activities, and emergence of resistance to the existing antifungal therapies. To resolve these matters a multidisciplinary approach will be required with a collaborative touch where the One Health framework will be applied including the interdependence between human health, animal health and environmental health. This method refers to the significance of a concerted surveillance, prevention and control measures [32,29]. The invention of new technologies, including microneedle tools can also be used in agriculture to help prevent the loss of crops and contribute to the prevention of food poisoning by detecting plant diseases earlier and treating them more effectively. All these technological discoveries, in addition to added control in the use of antifungals are essential in minimizing the effect of fungal infection on food production [30,31]. All in all, multinational collaboration is necessary to ensure that the cause-and-effect factors of fungus disease outbreaks are put into perspective and to fight against the risks of fungal pathogen development and food production with the help of difficulties in their diagnostics, treatment, and regulation [33]. The global distribution and prevalence of emerging fungal threats are both widespread and increasingly recognized as critical issues affecting human health, agriculture, and ecosystems. These threats are not confined to specific regions but are pervasive across all continents, reflecting the extensive distribution of fungi [41]. Fungal pathogens have emerged more prominently due to several factors, including environmental changes, globalization, and anthropogenic activities. These contribute to an increased prevalence of fungal threats across various domains. For instance, approximately 10% of the known fungal species threaten human health directly or indirectly through allergies, food contamination, or mycoses [41]. The incidence of invasive fungal infections, along with the prevalence of fungal allergies, has seen a global uptick, further emphasizing fungi as a substantial health threat [33]. The threat extends to agriculture, where emerging fungal pathogens jeopardize food security by infecting staple and economically important crops. This risk is exacerbated by climate change and intensive agricultural practices, which promote the emergence and spread of resistant fungal pathogens [43,36]. Oomycetes, closely related to fungi, also pose significant threats, causing diseases in both plants and animals, further impacting agriculture and natural ecosystems on a global scale [31]. The distribution of these threats is influenced by various factors, including human demographics, pathogen dispersal, and the global distribution of crops. The presence of fungal pathogens in all ecosystems, from urban to natural environments, further defines their ubiquitous nature and the need for extensive research to understand and mitigate these threats [37,41]. Addressing the global prevalence of fungal threats demands coordinated international research efforts and the development of holistic strategies, incorporating advancements in fungal biology and biosecurity [36]. Through concerted efforts in monitoring, diagnostics, and treatment innovations, it is possible to curtail the impact of these pervasive threats on human and animal health, agriculture, and global ecosystems [33,31].

**Antifungal agents**

Antifungal drugs are crucial in the treatment of fungal infections, and they are categorized into several classes, each with specific mechanisms of action. Here are the primary classes of antifungal drugs:

**Polyenes:** This is one of the oldest classes and includes drugs like Amphotericin B. Polyenes bind to ergosterol, a key component of fungal cell membranes, creating pores that lead to cell death. Despite a broad spectrum of activity, their use is limited by significant toxicity [42]

**Azoles:** This class includes agents such as fluconazole, itraconazole, and isavuconazole. Azoles inhibit the synthesis of ergosterol, thereby disrupting the integrity of the fungal cell membrane. They are commonly used for both superficial and systemic infections and are generally safer than polyenes, although resistance is emerging [43,44].

**Echinocandins:** These include drugs like caspofungin, micafungin, and anidulafungin. Echinocandins inhibit the synthesis of β-glucan, an essential component of the fungal cell wall, leading to cell lysis. They are primarily used for Candida and Aspergillus infections [45,46].

**Nucleoside Analogues:** Flucytosine is a nucleoside analogue that disrupts fungal RNA and protein synthesis. It is often used in combination with other antifungal drugs to enhance effectiveness and prevent resistance development [46]

New antifungal agents and those still under investigation are being developed to address the challenges of drug resistance and to expand the arsenal against resistant strains like Candida auris. These include compounds like rezafungin, ibrexafungerp, and the novel orotomides class, which offer new mechanisms of action and improved pharmacological profiles [47,43]. Overall, while significant progress has been made in antifungal therapy, challenges remain due to the limited number of antifungal classes and the increasing prevalence of drug-resistant fungal strains [48].

## II. Antifungal resistance

Antifungal resistance is a growing concern in medical mycology, posing significant challenges to the treatment of fungal infections. Below, I explore the mechanisms through which antifungal resistance develops, the factors contributing to increased resistance, and notable examples of resistant fungal strains

### Mechanisms of Resistance Development

**Genetic Mutations:** Various mutations within fungal genes can lead to changes in drug target sites, reducing drug affinity. For example, mutations in the ERG11 gene contribute to azole resistance in fungi like *Candida* species by altering the target enzyme, lanosterol 14α-demethylase [51].

**Efflux Pumps:** Overexpression of efflux pumps can actively expel antifungal agents from fungal cells, decreasing intracellular drug concentrations and effectiveness. This mechanism is prevalent in *Candida* species [50].

**Biofilm Formation:** Fungi can form biofilms which act as physical and chemical barriers against drug penetration, contributing to resistance. Biofilms are notably resistant to azoles and echinocandins [52].

**Altered Sterol Composition:** Some fungi can alter their membrane sterol composition to reduce drug binding. This mechanism is significant in resistance to polyenes such as amphotericin B [50].

**Genomic Changes:** Some fungi exhibit genomic plasticity, such as aneuploidy or gene deletion/amplification, which can lead to antifungal resistance. Though not the most common method, gene copy number variation can contribute to resistance [54].

### Factors Contributing to Increased Resistance

The extensive and often unnecessary use of antifungals in agriculture and clinical settings has accelerated selection pressure, leading to increased resistance [49].

**Immunosuppression and Hospitalization:** The rise in the number of immunocompromised patients, due to conditions such as HIV/AIDS or organ transplantation, has led to more frequent and severe fungal infections, challenging treatment efficacy [53].

**Environmental Factors:** Environmental exposure to fungicides in agriculture can promote cross-resistance in clinical settings, particularly with azoles [54].

**Inadequate Dosage and Treatment Duration:** Inappropriate antifungal therapy, including incorrect dosages and insufficient treatment duration, can contribute to resistance development.

### Notable Examples of Resistant Fungal Strains

**Candida auris:** This emerging multidrug-resistant pathogen poses a significant challenge due to its resistance to multiple antifungal classes, including azoles and amphotericin B. *C. auris* is notable for its rapid spread in healthcare settings [54].

**Aspergillus fumigatus:** Resistance to azoles in *A. fumigatus* is increasing, primarily due to environmental exposure to fungicides used in agriculture. This resistance complicates the management of aspergillosis [55].

**Candida vulturna:** Emerging evidence shows azole resistance within this species, partly due to mutations in the ERG11 gene, which are similar to those found in *Candida auris* [51]. Addressing antifungal resistance requires comprehensive strategies, including better diagnostic techniques, novel antifungal agents, and prudent use of existing therapies.

## III. Impacts of antifungal resistance

Antifungal resistance poses a significant threat with wide-ranging impacts on clinical applications, economic considerations, and public health concerns. Antifungal drug resistance complicates the treatment of invasive fungal infections, significantly impacting immunocompromised individuals. These infections contribute to high morbidity and mortality rates among these patients [59]. Effective treatment is challenged by the limited array of antifungal agents available, and the emergence of resistant strains further compounds these challenges [61]. The resistance mechanisms particularly for azoles, polyenes, and echinocandins complicate treatment protocols and can lead to treatment failures [59]. Rapid detection and understanding of resistance mechanisms are crucial for improving patient outcomes [58]. The economic impact of antifungal resistance is significant due to increased healthcare costs associated with prolonged hospital stays, more intensive care, and the need for more expensive or combination therapies. Resistant infections entail substantial financial costs for healthcare systems, as treatment options become limited and more complex [56]. Moreover, the need for advanced diagnostics and the implementation of antifungal susceptibility testing can increase operational costs in healthcare settings [62]. Antifungal resistance is a growing public health challenge, exacerbated by the use of antifungal agents in both clinical and agricultural settings. This has led to the spread of resistant strains like Candida auris and Aspergillus fumigatus, complicating infection control efforts [63]. Implementing a One Health approach is seen as a potential means to address these challenges by coordinating responses across human, animal, and environmental health sectors [57,60]. Education, awareness, improved diagnostics, and stewardship are critical components needed to combat the threat posed by antifungal resistance and to prevent further escalation of its public health impact [63]. Overall, tackling antifungal resistance requires a multidisciplinary approach that incorporates clinical insights, economic analyses, and public health strategies to effectively manage and mitigate its impacts [56]. Detecting antifungal resistance typically involves antifungal susceptibility testing (AFST), which helps ascertain the efficacy of antifungal drugs against specific fungal isolates. This encompasses traditional diagnostic methods like culture-based techniques and newer molecular methods, including whole genome sequencing and PCR [66,64]. Molecular techniques are particularly valuable as they provide rapid and precise identification of resistant strains, enabling more timely interventions. Emerging technologies aimed at detecting resistance include molecular diagnostics platforms that can rapidly detect resistance alleles, particularly for well-known mechanisms such as echinocandin resistance [66,64]. Global surveillance systems like the SENTRY Antifungal Surveillance Program play a crucial role in monitoring antifungal resistance worldwide. These networks collect data from various regions to trace susceptibility patterns of clinical isolates to antifungal agents [66]. The World Health Organization (WHO) has established the GLASS fungi initiative to provide a standardized framework for antifungal resistance monitoring, aiming to enhance awareness and readiness globally Efforts such as the systematic surveillance of Candida species across European surveillance systems highlight regional resistance trends, which are pivotal in forming effective antifungal strategies [68]. Despite these efforts, significant challenges remain in monitoring antifungal resistance. One major difficulty is the inconsistency and variability in resistance data, which often arises due to differences in diagnostic capabilities and methodologies among regions [71]. Furthermore, there is often a lack of coordinated surveillance efforts, which hinders global data sharing and interpretation [67]. Another challenge is the limited number of antifungal agents available, which leaves little room for treatment adjustments and increases the burden of developing resistance [65]. Additionally, in many regions, the infrastructure for performing comprehensive antifungal susceptibility testing is inadequate, leading to underreporting of resistance cases [66]. Enhanced laboratory capacities, improved antifungal stewardship, and better diagnostic capabilities are essential for overcoming these challenges and effectively monitoring antifungal resistance globally [69,70].

## FUTURE PERSPECTIVE

The trend in antifungal resistance is anticipated to continue rising, driven by increased use and potential misuse of antifungal agents. Multidrug resistance in species like *Candida auris* and resistance emergence in *Aspergillus fumigatus* due to environmental exposures are significant concerns [79,80]. Resistance mechanisms are well-understood at the molecular level, suggesting a need for novel therapeutic choices to manage resistant strains better [75]. The continued monitoring and adaptation of treatment strategies are imperative to manage this evolving threat effectively. Recent research highlights promising strategies, such as collateral sensitivity (CS) cycling, where resistance to one drug increases sensitivity to another, potentially preventing resistance development [78]. The development of molecular diagnostic platforms has improved the rapid detection of resistant strains, which is key for early intervention [74]. New antifungal drug targets, including those that address biofilm-associated resistance, and advances in Nano formulations for more effective drug delivery, represent significant steps forward [80,77]. These innovations provide hope for effective treatments against resistant fungal infections and highlight the importance of ongoing research in developing novel antifungals with unique mechanisms of action [79]. Addressing antifungal resistance requires urgent collaborative efforts at multiple levels. Increasing awareness about resistant fungal species, improving diagnostic testing, and implementing robust antifungal stewardship programs are critical measures [81]. It is essential to expand research into understanding resistance mechanisms and developing new antifungal agents and delivery systems [72]. A concerted global effort involving continuous surveillance, research innovation, and improved public health strategies is needed to combat the growing challenge of antifungal resistance [73]. These efforts must include the development of tailored therapies that consider patient-specific factors and local resistance patterns, potentially enhancing treatment efficacy and patient outcomes.

## CONCLUSION

Fungal infections have emerged as a major yet under-recognized component of the global infectious disease burden, particularly among immunocompromised populations. The escalating incidence of antifungal resistance in species such as *Candida auris*, *Aspergillus fumigatus*, and *Trichophyton indotineae* underscores an urgent need for global attention. Resistance mechanisms ranging from efflux pump activation and target enzyme mutations to biofilm formation are increasingly compromising the efficacy of existing antifungal agents, of which only three major classes are clinically available. This growing crisis is driven by multifactorial pressures, including inappropriate antifungal use in medicine, extensive agricultural fungicide application, and changing climatic conditions that enhance fungal adaptability. Addressing these challenges demands a comprehensive One Health framework, integrating clinical, agricultural, and environmental sectors. Strengthening diagnostic infrastructure, establishing global resistance surveillance, and promoting antifungal stewardship programs are key strategies. Simultaneously, innovation in antifungal drug discovery focusing on novel targets and synergistic combinations is critical for future resilience. In conclusion, antifungal resistance represents an emerging frontier in global health that parallels bacterial antimicrobial resistance in urgency and impact. Coordinated action across research, healthcare, and policy domains is imperative to avert a looming therapeutic crisis and safeguard public health.

## REFERENCE

1. Rivera, A., Lodge, J., & Xue, C. (2022). Harnessing the Immune Response to Fungal Pathogens for Vaccine Development. Annual Review of Microbiology, 76(1), 703–726. https://doi.org/10.1146/annurev-micro-041020-111511
2. Kim, J.-Y. (2016). Human fungal pathogens: Why should we learn? Journal of Microbiology, 54(3), 145–148. https://doi.org/10.1007/s12275-016-0647-8
3. Camilli, G., Richardson, J. P., Naglik, J. R., & Blagojevic, M. (2020). Programmed Cell Death: Central Player in Fungal Infections. Trends in Cell Biology, 31(3), 179–196. https://doi.org/10.1016/j.tcb.2020.11.005
4. Brown, G. D., Gow, N. A. R., Denning, D. W., Netea, M. G., Levitz, S. M., & White, T. C. (2012). Hidden Killers: Human Fungal Infections. Science Translational Medicine, 4(165). https://doi.org/10.1126/scitranslmed.3004404
5. Rodrigues, M. L., & Nosanchuk, J. D. (2020). Fungal diseases as neglected pathogens: A wake-up call to public health officials. PLOS Neglected

Tropical Diseases, 14(2), e0007964. https://doi.org/10.1371/journal.pntd.0007964
6. Wu, Y., Hu, S., Wu, C., Gu, F., & Yang, Y. (2022). Probiotics: Potential Novel Therapeutics Against Fungal Infections. Frontiers in Cellular and Infection Microbiology, 11. https://doi.org/10.3389/fcimb.2021.793419
7. Fisher, M. C., Stajich, J. E., Blehert, D. S., Kronstad, J. W., Boone, C., Casadevall, A., Wright, G. D., Stukenbrock, E. H., Gurr, S. J., Heitman, J., Cowen, L. E., Cuomo, C. A., Gow, N. A. R., Jin, H., Sheppard, D. C., Denning, D. W., Taylor, J. W., Klein, B. S., & Kahmann, R. (2020). Threats Posed by the Fungal Kingdom to Humans, Wildlife, and Agriculture. mBio, 11(3). https://doi.org/10.1128/mbio.00449-20
8. Thambugala, K. M., Daranagama, D. A., Tennakoon, D. S., Jayatunga, D. P. W., Hongsanan, S., & Xie, N. (2024). Humans vs. Fungi: An Overview of Fungal Pathogens against Humans. Pathogens (Basel, Switzerland), 13(5), 426. https://doi.org/10.3390/pathogens13050426
9. Cutler, J. E., Deepe, G. S., & Klein, B. S. (2006). Advances in combating fungal diseases: vaccines on the threshold. Nature Reviews. Microbiology, 5(1), 13–28.
10. Osset-Trénor, P., Proft, M., & Pascual-Ahuir, A. (2023). Fungal Drug Response and Antimicrobial Resistance. Journal of Fungi, 9(5), 565. https://doi.org/10.3390/jof9050565
11. Liu, F., Chen, Y., Huang, Y., Jin, Q., & Ji, J. (2024). Nanomaterial-based therapeutics for enhanced antifungal therapy. Journal of Materials Chemistry. B, 12(37), 9173–9198. https://doi.org/10.1039/d4tb01484g
12. Roy, M., Shamsuzzaman, M., Karhana, S., & Khan, M. A. (2023). Recent drug development and treatments for fungal infections. Brazilian Journal of Microbiology, 54(3), 1695–1716. https://doi.org/10.1007/s42770-023-00999-z
13. Niño-Vega, G. A., Padró-Villegas, L., & López-Romero, E. (2024). New Ground in Antifungal Discovery and Therapy for Invasive Fungal Infections: Innovations, Challenges, and Future Directions. Journal of Fungi, 10(12), 871.
14. Li, Y., Qiao, Y., Ma, Y., Xue, P., & Ding, C. (2025). AI in fungal drug development: opportunities, challenges, and future outlook. Frontiers in Cellular and Infection Microbiology, 15.
15. Mccormick, T. S., & Ghannoum, M. (2024). Time to Think Antifungal Resistance Increased Antifungal Resistance Exacerbates the Burden of Fungal Infections Including Resistant Dermatomycoses. Pathogens and Immunity, 8(2), 158–176.
16. Izadi, A., Paknia, F., Roostaee, M., Mousavi, S. A. A., & Barani, M. (2024). Advancements in nanoparticle-based therapies for multidrug-resistant candidiasis infections: a comprehensive review. Nanotechnology, 35(33), 332001.
17. Perlin, D. S. (2009). Antifungal drug resistance: do molecular methods provide a way forward? Current Opinion in Infectious Diseases, 22(6), 568–573.
18. Denning, D. W. (2022). Antifungal drug resistance: an update. European Journal of Hospital Pharmacy, 29(2), 109–112.
19. Williams, C. C., Gregory, J. B., & Usher, J. (2024). Understanding the clinical and environmental drivers of antifungal resistance in the One Health context. Microbiology (Reading, England), 170(10).
20. Marie, C., & White, T. C. (2009). Genetic basis of antifungal drug resistance. Current Fungal Infection Reports, 3(3), 163–169. https://doi.org/10.1007/s12281-009-0021-y
21. Osset-Trénor, P., Proft, M., & Pascual-Ahuir, A. (2023). Fungal Drug Response and Antimicrobial Resistance. Journal of Fungi, 9(5), 565.
22. Carvalho, A., Carvalho, A., Arastehfar, A., Arastehfar, A., Groll, A. H., Lamoth, F., Lamoth, F., Thompson, G. R., Thompson, G. R., Heylen, J., Heylen, J., Gangneux, J.-P., Gangneux, J.-P., Jenks, J. D., Jenks, J. D., Gold, J. A. W., Wauters, J., Wauters, J., Prattes, J., … Chiller, T. (2024). Novel antifungals and treatment approaches to tackle resistance and improve outcomes of invasive fungal disease. Clinical Microbiology Reviews, 37(2).
23. Mccormick, T. S., & Ghannoum, M. (2024). Time to Think Antifungal Resistance Increased Antifungal Resistance Exacerbates the Burden of Fungal Infections Including Resistant Dermatomycoses. Pathogens and Immunity, 8(2), 158–176.

24. Kanamori, H., Rutala, W. A., Weber, D. J., & Sickbert-Bennett, E. E. (2015). Review of fungal outbreaks and infection prevention in healthcare settings during construction and renovation. Clinical Infectious Diseases, 61(3), 433–444.
25. Shah, K., Shah, P., & Deshpande, M. (2024). Healthcare-associated fungal infections and emerging pathogens during the COVID-19 pandemic. Frontiers in Fungal Biology, 5.
26. Jenks, J. D., White, P. L., Kidd, S. E., Goshia, T., Fraley, S. I., Hoenigl, M., & Thompson, G. R. (2023). An update on current and novel molecular diagnostics for the diagnosis of invasive fungal infections. Expert Review of Molecular Diagnostics, 23(12), 1135–1152.
27. Perlroth, J., Choi, B., & Spellberg, B. (2007). Nosocomial fungal infections: epidemiology, diagnosis, and treatment. Medical Mycology, 45(4), 321–346.
28. Fridkin, S. K., & Jarvis, W. R. (1996). Epidemiology of nosocomial fungal infections. Clinical Microbiology Reviews, 9(4), 499–511.
29. Ghosh, P. N., Bates, K. A., & Fisher, M. C. (2018). Diagnosing Emerging Fungal Threats: A One Health Perspective. Frontiers in Genetics, 9(e6968).
30. Faraji Rad, Z. (2022). Microneedle Technologies for Food and Crop Health: Recent Advances and Future Perspectives. Advanced Engineering Materials, 25(4), 2201194.
31. Brauer, V. S., Rezende, C. P., De Paula, R. G., Gupta, V. K., Almeida, F., Nayaka, S. C., Rangappa, K. S., & Pessoni, A. M. (2019). Antifungal Agents in Agriculture: Friends and Foes of Public Health. Biomolecules, 9(10), 521. https://doi.org/10.3390/biom9100521
32. Banerjee, S., Chakrabarti, A., & Denning, D. W. (2021). One Health aspects & priority roadmap for fungal diseases: A mini-review. The Indian Journal of Medical Research, 153(3), 311–319.
33. Fisher, M. C., Stajich, J. E., Blehert, D. S., Kronstad, J. W., Boone, C., Casadevall, A., Wright, G. D., Stukenbrock, E. H., Gurr, S. J., Heitman, J., Cowen, L. E., Cuomo, C. A., Gow, N. A. R., Jin, H., Sheppard, D. C., Denning, D. W., Taylor, J. W., Klein, B. S., & Kahmann, R. (2020). Threats Posed by the Fungal Kingdom to Humans, Wildlife, and Agriculture. mBio, 11(3).
34. Gow, N. A. R., & Netea, M. G. (2016). Medical mycology and fungal immunology: new research perspectives addressing a major world health challenge. Philosophical Transactions of the Royal Society B: Biological Sciences, 371(1709), 20150462.
35. Fones, H. N., Gurr, S. J., Kay, W. T., Bebber, D. P., Chaloner, T. M., & Steinberg, G. (2020). Threats to global food security from emerging fungal and oomycete crop pathogens. Nature Food, 1(6), 332–342.
36. Case, N. T., Berman, J., Blehert, D. S., Cramer, R. A., Cuomo, C., Currie, C. R., Ene, I. V., Fisher, M. C., Fritz-Laylin, L. K., Gerstein, A. C., Glass, N. L., Gow, N. A. R., Gurr, S. J., Hittinger, C. T., Hohl, T. M., Iliev, I. D., James, T. Y., Jin, H., Klein, B. S., … Cowen, L. E. (2022). The future of fungi: threats and opportunities. G3 (Bethesda, Md.), 12(11).
37. Wang, M., Brooks, A., Paini, D., Ota, N., & Kriticos, D. J. (2021). A general trait-based modelling framework for revealing patterns of airborne fungal dispersal threats to agriculture and native flora. New Phytologist, 232(3), 1506–1518.
38. Derevnina, L., Kellner, R., Giannakopoulou, A., Kamoun, S., Van West, P., Chaparro-Garcia, A., Petre, B., De La Concepcion, J. C., Dagdas, Y. F., Sarowar, M. N., & Pennington, H. G. (2016). Emerging oomycete threats to plants and animals. Philosophical Transactions of the Royal Society B: Biological Sciences, 371(1709), 20150459
39. Fisher, M. C., Gurr, S. J., & Gow, N. A. R. (2016). Tackling emerging fungal threats to animal health, food security and ecosystem resilience. Philosophical Transactions of the Royal Society B: Biological Sciences, 371(1709), 20160332.
40. Xu, J. (2022). Assessing global fungal threats to humans. mLife, 1(3), 223–240.
41. Fones, H. N., Gurr, S. J., Kay, W. T., Bebber, D. P., Chaloner, T. M., & Steinberg, G. (2020). Threats to global food security from emerging fungal and oomycete crop pathogens. Nature Food, 1(6), 332–342.
42. Carolus, H., Van Dijck, P., Pierson, S., & Lagrou, K. (2020). Amphotericin B and Other Polyenes-Discovery, Clinical Use, Mode of Action and Drug Resistance. Journal of Fungi (Basel, Switzerland), 6(4), 321.

43. Van Daele, R., Wauters, J., Van Hecke, S., Mercier, T., Spriet, I., Brüggemann, R., & Maertens, J. (2019). Antifungal drugs: What brings the future? Medical Mycology, 57(Suppl 3), S328–S343.
44. Sheehan, D. J., Sibley, C. M., & Hitchcock, C. A. (1999). Current and emerging azole antifungal agents. Clinical Microbiology Reviews, 12(1), 40–79.
45. Prasad, R., Rawal, M. K., & Shah, A. H. (2016). Antifungals: Mechanism of Action and Drug Resistance. Advances in Experimental Medicine and Biology, 892, 327–349.
46. Seyedmousavi, S., Tolooe, A., Hedayati, M. T., Ilkit, M., Verweij, P., & Rafati, H. (2016). Systemic Antifungal Agents: Current Status and Projected Future Developments. Methods in Molecular Biology (Clifton, N.J.), 1508, 107–139. https://doi.org/10.1007/978-1-4939-6515-1_5
47. Lamoth, F., Kontoyiannis, D. P., & Lewis, R. E. (2022). Investigational Antifungal Agents for Invasive Mycoses: A Clinical Perspective. Clinical Infectious Diseases, 75(3), 534–544
48. 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., Almaghrabi, R. S., Abuzaid, A. A., Altowaileb, J. A., Al Ibrahim, M., Alsalman, E. M., Alsalman, F., Alghounaim, M., Bueid, A. S., Al-Omari, A., & Mohapatra, R. K. (2023). Potential Strategies to Control the Risk of Antifungal Resistance in Humans: A Comprehensive Review. Antibiotics, 12(3), 608.
49. Gupta, A. K., & Venkataraman, M. (2021). Antifungal resistance in superficial mycoses. Journal of Dermatological Treatment, 33(4), 1888–1895.
50. Pemán, J., Cantón, E., & Espinel-Ingroff, A. (2009). Antifungal drug resistance mechanisms. Expert Review of Anti-Infective Therapy, 7(4), 453–460.
51. Macedo, D., Berrio, I., Escandon, P., Gamarra, S., & Garcia-Effron, G. (2024). Mechanism of azole resistance in Candida vulturna, an emerging multidrug resistant pathogen related with Candida haeumulonii and Candida auris. Mycoses, 67(7).
52. Perlin, D. S., Zhao, Y., & Shor, E. (2015). Update on Antifungal Drug Resistance. Current Clinical Microbiology Reports, 2(2), 84–95. https://doi.org/10.1007/s40588-015-0015-1
53. White, T. C., Marr, K. A., & Bowden, R. A. (1998). Clinical, cellular, and molecular factors that contribute to antifungal drug resistance. Clinical Microbiology Reviews, 11(2), 382–402.
54. Jay, A., Jordan, D. F., Gerstein, A., & Landry, C. R. (2025). The role of gene copy number variation in antimicrobial resistance in human fungal pathogens. Npj Antimicrobials and Resistance, 3(1).
55. Arikan-Akdagli, S., Meis, J. F., & Ghannoum, M. (2018). Antifungal Resistance: Specific Focus on Multidrug Resistance in Candida auris and Secondary Azole Resistance in Aspergillus fumigatus. Journal of Fungi, 4(4), 129.
56. Smith, D. J., Toda, M., Lyman, M., Benedict, K., Chow, N. A., Wu, K., Medina, N., Litvintseva, A. P., Lockhart, S. R., Sexton, D. J., Gold, J. A. W., Chiller, T., Jackson, B. R., & Jordan, A. (2023). Public Health Research Priorities for Fungal Diseases: A Multidisciplinary Approach to Save Lives. Journal of Fungi, 9(8), 820.
57. Woods, M., Geddes-Mcalister, J., & Mcalister, J. A. (2023). A One Health approach to overcoming fungal disease and antifungal resistance. WIREs Mechanisms of Disease, 15(4).
58. Perlin, D. S. (2009). Antifungal drug resistance: do molecular methods provide a way forward? Current Opinion in Infectious Diseases, 22(6), 568–573.
59. Kanafani, Z. A., & Perfect, J. R. (2008). Resistance to Antifungal Agents: Mechanisms and Clinical Impact. Clinical Infectious Diseases, 46(1), 120–128.
60. Williams, C. C., Gregory, J. B., & Usher, J. (2024). Understanding the clinical and environmental drivers of antifungal resistance in the One Health context. Microbiology (Reading, England), 170(10).
61. Osset-Trénor, P., Proft, M., & Pascual-Ahuir, A. (2023). Fungal Drug Response and Antimicrobial Resistance. Journal of Fungi, 9(5), 565.
62. Fisher, M. C., Alastruey-Izquierdo, A., Xu, J., Zwaan, B., Bromley, M., Gurr, S. J., Cornely, O. A., Verweij, P. E., White, P. L., Brüggemann, R., Berman, J., Rhodes, J., Sheppard, D. C., Bowyer, P., Warris, A., Garber, G., Harrison, T. S., Kuijper, E., Bignell, E. M., & Bicanic, T. (2022).

Tackling the emerging threat of antifungal resistance to human health. Nature Reviews Microbiology, 20(9), 557–571.

63. Mccormick, T. S., & Ghannoum, M. (2024). Time to Think Antifungal Resistance Increased Antifungal Resistance Exacerbates the Burden of Fungal Infections Including Resistant Dermatomycoses. Pathogens and Immunity, 8(2), 158–176.
64. Pfaller, M. A., Castanheira, M., Jones, R. N., & Messer, S. A. (2015). Antifungal susceptibilities of Candida, Cryptococcus neoformans and Aspergillus fumigatus from the Asia and Western Pacific region: data from the SENTRY antifungal surveillance program (2010-2012). The Journal of Antibiotics, 68(9), 556–561.
65. Mudenda, S. (2024). Global Burden of Fungal Infections and Antifungal Resistance from 1961 to 2024: Findings and Future Implications. Pharmacology & Amp; Pharmacy, 15(04), 81–112.
66. Gupta, A. K., Carviel, J. L., Piguet, V., Talukder, M., & Cooper, E. A. (2023). Combatting antifungal resistance: paradigm shift in the diagnosis and management of onychomycosis and dermatomycosis. Journal of the European Academy of Dermatology and Venereology, 37(9), 1706–1717.
67. Langfeldt, A., Gold, J. A. W., & Chiller, T. (2022). Emerging Fungal Infections: from the Fields to the Clinic, Resistant Aspergillus fumigatus and Dermatophyte Species: a One Health Perspective on an Urgent Public Health Problem. Current Clinical Microbiology Reports, 9(4), 46–51.
68. Odoj, K., Garlasco, J., Pezzani, M. D., Magnabosco, C., Ortiz, D., Manco, F., Galia, L., Foster, S. K., Arieti, F., & Tacconelli, E. (2024). Tracking Candidemia Trends and Antifungal Resistance Patterns across Europe: An In-Depth Analysis of Surveillance Systems and Surveillance Studies. Journal of Fungi (Basel, Switzerland), 10(10), 685.
69. Fisher, M. C., & Denning, D. W. (2023). The WHO fungal priority pathogens list as a game-changer. Nature Reviews. Microbiology, 21(4), 211–212.
70. Fisher, M. C., Alastruey-Izquierdo, A., Xu, J., Zwaan, B., Bromley, M., Gurr, S. J., Cornely, O. A., Verweij, P. E., White, P. L., Brüggemann, R., Berman, J., Rhodes, J., Sheppard, D. C., Bowyer, P., Warris, A., Garber, G., Harrison, T. S., Kuijper, E., Bignell, E. M., & Bicanic, T. (2022). Tackling the emerging threat of antifungal resistance to human health. Nature Reviews Microbiology, 20(9), 557–571.
71. Yamin, D., Akanmu, M. H., Al Mutair, A., Alhumaid, S., Rabaan, A. A., & Hajissa, K. (2022). Global Prevalence of Antifungal-Resistant Candida parapsilosis: A Systematic Review and Meta-Analysis. Tropical Medicine and Infectious Disease, 7(8), 188.
72. Kumar Nigam, P. (2015). Antifungal drugs and resistance: Current concepts. Our Dermatology Online, 6(2), 212–221.
73. Howard, K. C., Dennis, E. K., Garneau-Tsodikova, S., & Watt, D. S. (2020). A comprehensive overview of the medicinal chemistry of antifungal drugs: perspectives and promise. Chemical Society Reviews, 49(8), 2426–2480.
74. Perlin, D. S. (2009). Antifungal drug resistance: do molecular methods provide a way forward? Current Opinion in Infectious Diseases, 22(6), 568–573.
75. Maubon, D., Garnaud, C., Sanglard, D., Calandra, T., & Cornet, M. (2014). Resistance of Candida spp. to antifungal drugs in the ICU: where are we now? Intensive Care Medicine, 40(9), 1241–1255.
76. Sanglard, D. (2016). Emerging Threats in Antifungal-Resistant Fungal Pathogens. Frontiers in Medicine, 3(Suppl 6).
77. Ahuja, A., & Bajpai, M. (2024). Nanoformulations Insights: A Novel Paradigm for Antifungal Therapies and Future Perspectives. Current Drug Delivery, 21(9), 1241–1272.
78. Carolus, H., Verbeeck, T., Pierson, S., Lobo Romero, C., Chen, A., Goossens, L., Sofras, D., Biriukov, V., Steenackers, H., Van Dijck, P., Berman, J., Lagrou, K., Van Den Berg, P., Boccarella, G., Gabaldón, T., Jacobs, S., & Vantyghem, I. (2024). Collateral sensitivity counteracts the evolution of antifungal drug resistance in Candida auris. Nature Microbiology, 9(11), 2954–2969

79. Sheng, C., & Zhang, W. (2011). New Lead Structures in Antifungal Drug Discovery. Current Medicinal Chemistry, 18(5), 733–766.
80. Liu, N., Dong, G., Sheng, C., Tu, J., & Wang, Y. (2018). Emerging New Targets for the Treatment of Resistant Fungal Infections. Journal of Medicinal Chemistry, 61(13), 5484–5511
81. Mccormick, T. S., & Ghannoum, M. (2024). Time to Think Antifungal Resistance Increased Antifungal Resistance Exacerbates the Burden of Fungal Infections Including Resistant Dermatomycoses. Pathogens and Immunity, 8(2), 158–176.

HOW TO CITE: Haider Abbas*, Amulya Singh, Arpit Maurya, Kavya Singh, Dr. Anupam Singh, Emerging Multidrug-Resistant Fungal Pathogens: Epidemiology, Mechanisms, and Novel Therapeutic Solutions, Int. J. Sci. R. Tech., 2025, 2 (11), 726-737. https://doi.org/10.5281/zenodo.17739885