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Fungal Diseases in Humans: Epidemiology, Mechanisms, Diagnosis, Treatment, and Future Perspectives

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Abstract: Fungal diseases have become a major global public health issue, affecting both immunocompromised and immunocompetent populations. Opportunistic infections like candidiasis, aspergillosis, and cryptococcosis coexist with neglected endemic mycoses, especially in Latin America and Brazil, where Para coccidioidomycosis, histoplasmosis, and sporotrichosis pose significant burdens. Despite their substantial impact, fungal diseases remain underrecognized in global health plans, leading to limited resources for surveillance, diagnosis, and treatment. This review aims to provide a comprehensive overview of current knowledge on fungal diseases, covering their epidemiology, mechanisms of pathogenesis, diagnostic methods, treatment options, and future outlooks. The literature review includes studies published from 2000 to 2025, with a focus on recent findings from 2024–2025. Sources include peer-reviewed journals, global health reports, and institutional communications. Key topics examined include disease prevalence, antifungal resistance, host-pathogen interactions, diagnostic innovations, and treatment progress.

Keywords: Brazil, Global health, Immunocompetent, Morbidity, Mortality, Pathogenesis.

Research Paper

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1.0.INTRODUCTION

Fungal diseases have emerged as a major concern in global health over the past two decades, representing a complex burden that extends beyond clinical medicine into economic and social domains. Despite their importance, fungal infections have historically been overlooked in public health agendas, overshadowed by bacterial and viral diseases. However, with the growing population of immunocompromised patients and the rising number of emerging pathogens, mycoses now constitute a significant cause of morbidity and mortality worldwide (Marr *et al.*, 2002; Perfect *et al.*, 2003; Pfaller *et al.*, 2004; Pfaller and Diekema, 2010; Brown *et al.*, 2012).

The global burden of fungal diseases is alarming, ranging from superficial infections such as dermatophytosis and oral candidiasis to severe invasive mycoses like aspergillosis, cryptococcosis, mucormycosis, and systemic endemic infections, such as histoplasmosis and paracoccidioidomycosis. Mortality rates for invasive fungal infections remain high, often between 30% and 80%, even when patients receive antifungal treatment, reflecting both host vulnerability and limitations in current therapeutic options (Figure 1) (Bongomin *et al.*, 2017; Perfect, 2017; Pappas *et al.*, 2018; Richardson and Hoang, 2020; Lamoth and Kontoyiannis, 2022).

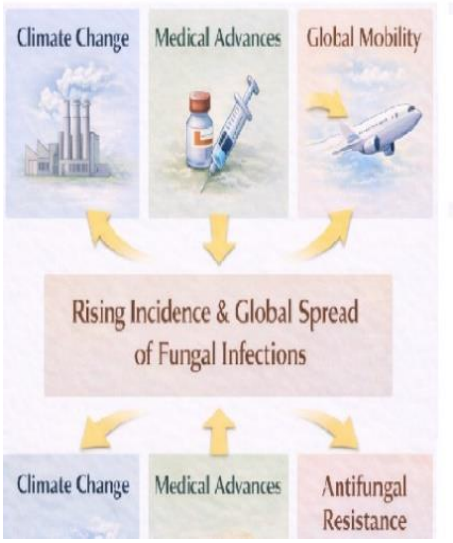

Figure 1: Fungal diseases are an increasing global health threat, affecting over 1.5 billion people annually and causing high mortality, particularly among immunocompromised individuals. Climate change, medical advances, global mobility, and antifungal resistance highlight the urgent need for improved diagnostics, therapies, and surveillance

Multiple factors contribute to the increasing relevance of fungal diseases. Advances in modern medicine, such as chemotherapy, hematopoietic stem cell transplantation, and solid-organ transplantation, have significantly improved patient survival but expanded the number of individuals at risk of invasive mycoses. Additionally, climate change and global mobility have contributed to the redistribution of pathogenic fungi, allowing previously localized species to colonize new environments and affect new populations. These changes, together with the emergence of multidrug-resistant fungi such as *Candidozyma auris* (Satoh & Makimura) Q.M. Wang, Yurkov, Boekhout & F.Y. Bai, 2024 (Serinales: Metschnikowiaceae), highlight the urgent need for innovative antifungal therapies, rapid diagnostic tools, and stronger epidemiological surveillance (Figure 2) (Brown *et al.*, 2012; Chowdhary *et al.*, 2017; Pappas *et al.*, 2018; Fisher *et al.*, 2022).

Figure 2: Fungal diseases are an escalating global health threat, driven by medical advances, climate change, global mobility, and the rise of antifungal resistance. These factors increase infection rates and mortality, underscoring the urgent need for improved diagnostics, therapies, and epidemiological surveillance

From a public health perspective, fungal infections remain largely underestimated and underreported, particularly in low- and middle-income countries where access to advanced diagnostic technologies and antifungal medications is limited. Addressing these challenges requires a comprehensive understanding of epidemiology, mechanisms of pathogenesis, diagnostic limitations, and treatment

strategies. Only through this integrated approach can the true impact of fungal diseases be reduced on a global scale (Garcia-Solache and Casadevall, 2010; Gauthier and Keller, 2013; Armstrong-James *et al.*, 2020; Rodrigues and Nosanchuk, 2020).

This article aims to provide a comprehensive and updated overview of human fungal diseases, focusing on their epidemiology, pathogenic mechanisms, diagnostic challenges, and therapeutic strategies.

2.0. METHODS

This review was developed through a structured and integrative approach, focusing on scientific publications and institutional reports addressing fungal diseases from January 2000 to May 2025. Databases such as PubMed, Scopus, Web of Science, and SciELO were systematically searched using keywords including "fungal infections," "epidemiology," "antifungal resistance," "diagnosis," and "therapy." In addition, priority documents published by the World Health Organization and national health agencies were included to ensure alignment with global health perspectives. Selection criteria prioritized peer-reviewed articles, consensus guidelines, systematic reviews, and original studies that directly addressed the epidemiology, pathogenesis, diagnosis, or treatment of mycoses.

To enrich the analysis with more recent perspectives, we also incorporated academic press releases and scientific communications from recognized institutions published in 2024 and 2025. Data extraction emphasized the regional distribution of fungal diseases, mechanisms of virulence and immune evasion, diagnostic performance, therapeutic efficacy, and trends in resistance. Information was then synthesized into thematic categories that guided the structure of this article, namely: introduction and objectives, epidemiological trends, mechanisms of infection, diagnostic strategies, therapeutic options, and future perspectives.

3.0. RESULTS AND DISCUSSION

3.1. Epidemiology of fungal diseases

The global burden reflects a wide range of clinical presentations, from superficial dermatophytoses to life-threatening systemic mycoses. Mortality rates for invasive infections remain high, often exceeding 30% and 80%, even when antifungal therapy is available. These infections are underestimated in public health policies, partly due to diagnostic limitations and underreporting, particularly in low- and middle-income countries (Denning and Bromley, 2015; Bongomin *et al.*, 2017; Armstrong-James *et al.*, 2020; Rodrigues and Nosanchuk, 2020).

In North America and Europe, invasive candidiasis and aspergillosis predominate, largely linked to advances in modern medicine such as chemotherapy, organ transplantation, and the use of immunosuppressive drugs. *Candida albicans* (Berkhout, 1923) (Saccharomycetales: Cryptococcaceae) remains the most common cause, but non-albicans species like *Candida glabrata* ((H.W. Anderson) S.A. Mey. and Yarrow, 1978) (Saccharomycetales: Saccharomycetaceae) and *Candida parapsilosis* (Langeron and Talice, 1932) (Serinales: Debaryomycetaceae) are increasingly prevalent, frequently associated with antifungal resistance. Invasive aspergillosis, caused mainly by *Aspergillus fumigatus* Fresenius, 1863 (Eurotiales: Trichocomaceae), remains a leading opportunistic infection in hematologic malignancy and transplant patients (Figure 3) (Garcia-Solache and Casadevall, 2010; Richardson and Hoang, 2020; Fisher *et al.*, 2022; Lamoth and Kontoyiannis, 2022).

Figure 3: The distribution of major invasive mycoses varies by region, reflecting differences in healthcare access, underlying conditions, and the emergence of resistant fungal pathogens worldwide

In sub-Saharan Africa, fungal diseases remain closely tied to the HIV/AIDS epidemic. Cryptococcal meningitis alone is estimated to cause over 180,000 deaths annually, despite being preventable and treatable. *Pneumocystis* Delanoë & Delanoë, 1912 (Pneumocystidales: Pneumocystidaceae) pneumonia, caused by *Pneumocystis jirovecii* Frenkel, 1976 (Pneumocystidales: Pneumocystidaceae), continues to be a major cause of morbidity and mortality among both children and adults with untreated HIV infection. Access to diagnostics and antifungal therapies exacerbates the problem in African healthcare systems (Brown *et al.,* 2012; Bongomin *et al.,* 2017; Richardson and Hoang, 2020; Rodrigues and Nosanchuk, 2020).

In Asia, mucormycosis has emerged as a severe and often fatal opportunistic infection, particularly in India, where a surge of cases occurred during the COVID-19 pandemic among diabetic patients receiving corticosteroid therapy. Furthermore, *Candida auris* Satoh & Makimura, 2009 (Saccharomycetales: Saccharomycetaceae), has become a multidrug-resistant fungal pathogen with hospital outbreaks across South and East Asia. Invasive candidiasis and aspergillosis are also frequently reported in tertiary hospitals, highlighting the dual burden of traditional opportunistic infections and emerging resistant fungi (Figure 4) (Chowdhary *et al.*, 2017; Lockhart *et al.*, 2017; Arastehfar *et al.*, 2020; Richardson and Hoang, 2020).

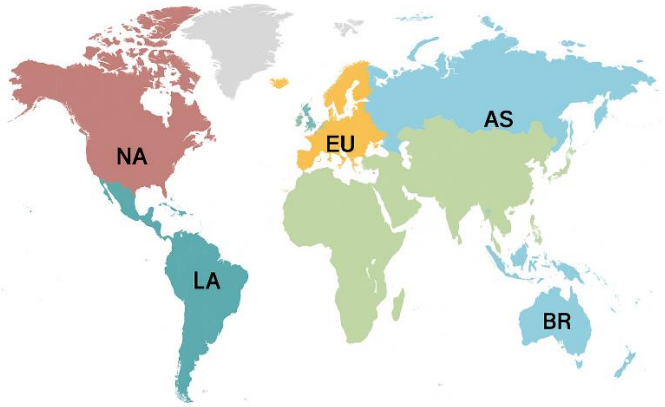

Figure 4: Global distribution of fungal diseases. Colored world map with regional abbreviations. For clarity, the regional abbreviations used are as follows: NA = North America, LA = Latin America, EU = Europe, AF = Africa, AS = Asia, and BR = Brazil, showing the distribution of the main fungal diseases prevalent in each area
Sources: WHO (2024) and USP (2024)

In Latin America, endemic systemic mycoses such as histoplasmosis, paracoccidioidomycosis, and coccidioidomycosis remain highly relevant. Histoplasmosis is one of the most common opportunistic infections in HIV/AIDS patients in the region, with mortality aggravated by diagnostic delays (Bongomin *et al.*, 2017; Shikanai-Yasuda *et al.*, 2017).

Paracoccidioidomycosis, a neglected tropical disease, predominantly affects rural male workers and is concentrated in Brazil, Colombia, and Venezuela (Perfect, 2017). Coccidioidomycosis, although historically associated with the southwestern United States, has been reported with increasing frequency in parts of Mexico and South America (Marr *et al.*, 2002; Pfaller *et al.*, 2004; Gauthier and Keller, 2013; Denning and Bromley, 2015).

In Brazil, fungal infections reflect both global and regional patterns. Superficial mycoses, such as dermatophytosis caused by *Trichophyton* spp. and *Microsporum* spp., are extremely prevalent in all regions (Rodrigues and Nosanchuk, 2020). Paracoccidioidomycosis remains one of the most characteristic systemic mycoses, particularly in the Southeast, South, and Midwest regions (Brown *et al.*, 2012; Armstrong-James *et al.*, 2020; Fisher *et al.*, 2022).

Histoplasmosis is widespread in river valleys and humid areas, often underdiagnosed in HIV-positive individuals. Cryptococcosis, caused by *Cryptococcus neoformans* (San Felice) Vuill. (1901) (Tremellales: Tremellaceae) and *Cryptococcus gattii* (Vanbreus. & Takashio) Kwon-Chung & Boekhout (1982) Tremellales: Tremellaceae), is a major opportunistic infection, particularly in urban centers. Hospital-based infections such as aspergillosis and invasive candidiasis are also significant in Brazilian tertiary centers (Table 1) (Pfaller and Diekema, 2010; Lockhart *et al.*, 2017; Pappas *et al.*, 2018; Esteves *et al.*, 2020; Lamoth and Kontoyiannis, 2022).

Table 1: Opportunistic fungal pathogens such as *Candida* spp., A*spergillus* spp., and *Cryptococcus neoformans* (San Felice) Vuill. (1901) are responsible for life-threatening infections, particularly in immunocompromised patients

Region	Predominant Fungal Diseases	Key Species / Groups
North America	Candidemia, Aspergillosis and Cryptococcosis	*Candida* spp., *Aspergillus fumigatus*1, and *Cryptococcus neoformans*
Latin America	Histoplasmosis, Paracoccidioidomycosis, and Sporotrichosis	*Histoplasma capsulatum*2, *Paracoccidioides* spp., and *Sporothrix schenckii*3
Europe	Candidemia and Aspergillosis	*Candida* spp., and *A. fumigatus*
Africa	Cryptococcosis, Histoplasmosis	*Cryptococcus neoformans* and Histoplasma *capsulatum*
Asia	Candidemia, Aspergillosis, and Mucormycosis	*Candida* spp., *Aspergillus* spp., and Mucorales
Brazil	Paracoccidioidomycosis, Histoplasmosis, and Sporotrichosis	*Paracoccidioides* spp., *H. capsulatum*, and *Sporothrix* spp.
Middle East	Candidemia and Aspergillosis	*Candida* spp. and *Aspergillus* spp.
Oceania	Candidemia, Aspergillosis, Cryptococcosis	*Candida* spp., *Aspergillus* spp., and *Cryptococcus gattii*
Southeast Asia	Talaromycosis and Candidemia	*Talaromyces marneffei* and *Candida* spp.
China	Candidemia, Aspergillosis, and Talaromycosis	*Candida* spp., Aspergillus *fumigatus*, and *Talaromyces marneffei*
Sub-Saharan Africa	Cryptococcosis and Histoplasmosis	*Cryptococcus neoformans* and *Histoplasma capsulatum*
Worldwide (Healthcare settings)	Candidemia, invasive yeast infections	*Candida auris*

3.2. Pathogenesis and mechanisms of infection

The pathogenicity of fungi results from a dynamic interaction between host defenses and fungal virulence factors. Unlike bacteria and viruses, fungi are eukaryotic organisms, which makes their biology closer to that of the human host and complicates therapeutic selectivity. Fungal infections occur when the equilibrium between host immunity and fungal presence is disrupted, either by immunosuppression, environmental exposure, or enhanced fungal adaptability. The ability of fungi to switch from commensal to pathogenic forms, as observed in *C. albicans*, exemplifies this delicate balance (Figure 5) (Garcia-Solache and Casadevall, 2010; Pappas *et al.*, 2018; Richardson and Hoang, 2020; Fisher *et al.*, 2022).

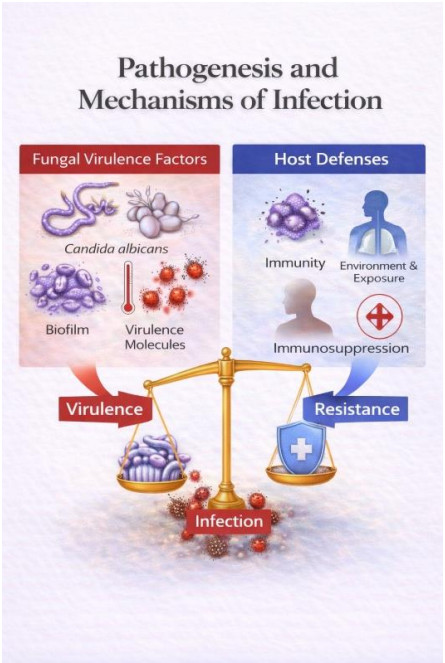

Figure 5: Fungal pathogenesis results from a dynamic imbalance between host immune defenses and fungal virulence factors, allowing commensal or environmental fungi to cause disease. Morphological plasticity, thermotolerance, and immune evasion enable fungal survival, dissemination, and tissue invasion, particularly in immunocompromised hosts

Among the key mechanisms of fungal pathogenicity are morphological plasticity, biofilm formation, thermotolerance, production of virulence molecules, and immune evasion strategies. Dimorphic fungi, such as *Histoplasma capsulatum/Ajellomyces capsulatus* Darling (1906)/(Kwon-Chung) McGinnis & Katz (1979) (Onygenales: Ajellomycetaceae) and *Paracoccidioides brasiliensis* (Splend.) F.P.Almeida (1930) (Onygenales: Ajellomycetaceae), switch from mycelial forms in the environment to yeast forms in the host, a transition that is essential for virulence (Shikanai-Yasuda *et al.,* 2017; Armstrong-James *et al.,* 2020; Rodrigues and Nosanchuk, 2020; Fisher *et al.,* 2022).

Opportunistic fungi like *Aspergillus fumigatus* Fresenius, 1863 (Eurotiales: Trichocomaceae) rely on small airborne conidia that reach the alveoli, evading mucociliary clearance and initiating infection in immunocompromised hosts, such as *Cryptococcus neoformans* (San Felice) Vuill. (Tremellales: Tremellaceae), and *Cryptococcus gattii* (Vanbreus. & Takashio) Kwon-Chung & Boekhout (2002) (Tremellales: Tremellaceae) possess a polysaccharide capsule that inhibits phagocytosis, while producing melanin that protects against oxidative stress, allowing persistence in the central nervous system (Rajasingham *et al.*, 2017; Esteves *et al.*, 2020; Fisher *et al.*, 2022).

Biofilm formation is a particularly important virulence factor in nosocomial infections. *Candida* spp., *Aspergillus* spp., and other opportunists form complex biofilms on medical devices, including catheters and prostheses, which confer resistance to antifungal drugs and host immune responses. These biofilms not only act as reservoirs for persistent infection but also promote horizontal gene transfer and antifungal resistance. Similarly, *C. auris,* an emerging pathogen, exhibits strong biofilm capacity and multidrug resistance, complicating hospital outbreak control (Figure 6) (Chowdhary *et al.*, 2017; Lockhart *et al.*, 2017; Richardson and Hoang, 2020; Fisher *et al.*, 2022).

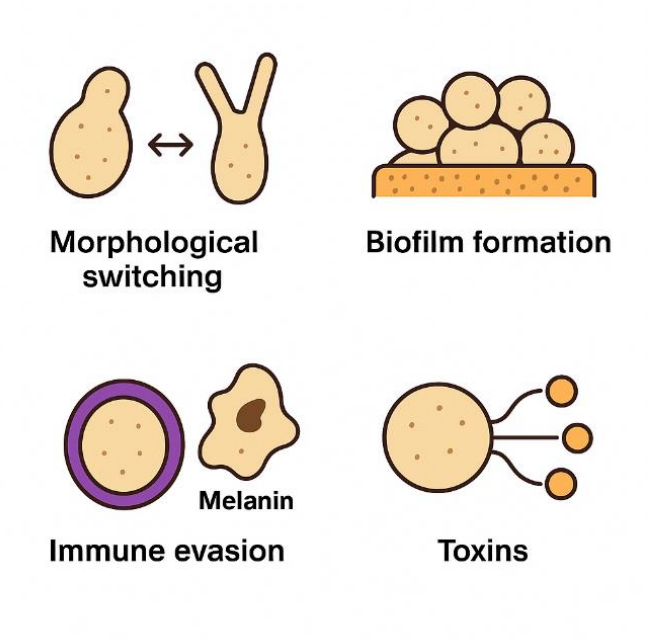

Figure 6: Mechanisms of fungal pathogenesis. Key mechanisms of fungal virulence include morphological switching of yeast hyphae, biofilm formation, immune evasion, capsule, melanin, and toxin/secondary metabolite production
Sources: Brown *et al.,* (2012) and Fisher *et al.,* (2022)

Fungi also exploit host immune deficiencies to establish infections. Patients with impaired cell-mediated immunity, such as those with HIV/AIDS or undergoing immunosuppressive therapy, are highly susceptible to invasive fungal infections (Brown *et al*., 2012; Arastehfar *et al.*, 2020; Singh *et al.,* 2021; Kontoyiannis, 2022)

Additionally, genetic factors can predispose individuals to fungal diseases: polymorphisms in pattern-recognition receptors like dectin-1 or Toll-like receptors reduce the host's ability to detect fungal components. These host–pathogen interactions determine not only the onset but also the severity of fungal infections (Table 2) (Garcia-Solache and Casadevall, 2010; Gauthier and Keller, 2013; Rodrigues and Nosanchuk, 2020).

Table 2: Endemic mycoses such as histoplasmosis, coccidioidomycosis, and paracoccidioidomycosis are geographically restricted infections that can affect both immunocompetent and immunocompromised individuals

Pathogen	Global Burden	Key Regions
Candida spp.	Candidemia leading cause of invasive mycoses	Worldwide
Aspergillus spp.	High mortality in immunocompromised patients	Worldwide
Cryptococcus spp.	The major cause of meningitis in HIV patients	Africa, Latin America
*Histoplasma capsulatum*1	Leading endemic mycosis	Americas
Paracoccidioides spp.	Neglected endemic mycosis	Brazil, Latin America
Mucorales sp.	High mortality mucormycosis	India, Asia
Coccidioides spp.	Important endemic mycosis; pulmonary disease and dissemination in risk groups	Southwestern USA, Mexico, Central/South America
Blastomyces spp.	Endemic dimorphic fungus causing pulmonary and disseminated disease	North America (Great Lakes, Ohio/Mississippi River valleys)
Talaromyces marneffei	Major endemic mycosis among people with HIV and other immunosuppressed hosts	Southeast Asia, Southern China
Pneumocystis jirovecii	Opportunistic pneumonia with substantial morbidity in immunocompromised patients	Worldwide
Sporothrix schenckii complex	Subcutaneous mycosis with outbreaks linked to zoonotic transmission	Latin America, parts of Asia
Candida auris	Emerging multidrug-resistant yeast associated with healthcare outbreaks	Worldwide (healthcare settings)
Fusarium spp.	Opportunistic mold infections: severe disease in neutropenic patients	Worldwide
Scedosporium and *Lomentospora* spp.	Difficult-to-treat mold infections, including in cystic fibrosis and transplant patients	Worldwide

3.3. Pathogenesis and clinical relevance

Brazil presents a dual fungal disease burden that juxtaposes hospital-acquired opportunistic infections with long-standing endemic mycoses shaped by ecology, land use, and social determinants. Paracoccidioidomycosis (PMC) and histoplasmosis remain highly prevalent in rural and riparian settings, while the genus *Aspergillus* Micheli ex Haller (1768) (Eurotiales: Aspergillaceae), *Candidemia* sp., and *Cryptococcus* Vuill. (1901) (Tremellales: Cryptococcacea) concentrate in urban tertiary centers and intensive care units. This pattern reflects interactions among environmental reservoirs, soil, bat/bird guano, feline epizootics, climatic variability, migration, and expanding populations at risk due to immunosuppression, diabetes, and complex medical care (Brown *et al.*, 2012; Shikanai-Yasuda *et al.*, 2017; Armstrong-James *et al.*, 2020; Rodrigues and Nosanchuk, 2020).

PCM is emblematic of Brazil and arises after inhalation of *P. brasiliensis* conidia that convert to pathogenic yeast at 37 °C; latency and reactivation in adulthood are common. Estrogen-mediated inhibition of mycelium-to-yeast transition helps explain sex differences, while Th1/Th2 balance modulates clinical form and severity. Agricultural exposure, deforestation, and soil disruption increase risk in the Southeast, South, and Midwest, with *Paracoccidioides lutzii* Vilela, de Hoog, Bagagli & L. Mend., 2014 (Onygenales: Ajellomycetaceae) also relevant in parts of the Midwest/North. Chronic pulmonary disease and mucocutaneous lesions predominate, demanding prolonged azole therapy and careful follow-up (Figure 7) (Queiroz-Telles *et al.*, 2017; Shikanai-Yasuda *et al.*, 2017; Rodrigues and Nosanchuk, 2020; Fisher *et al.*, 2022).

Figure 7: Brazil exhibits a dual fungal disease burden, combining endemic mycoses shaped by environmental and social determinants with hospital-acquired opportunistic infections. Regional patterns reflect ecological exposure, urbanization, immunosuppression, and healthcare practices, driving the distribution and clinical relevance of major fungal pathogens

Histoplasmosis is widely distributed in Brazil and often underdiagnosed, particularly in people living with HIV, where it mimics tuberculosis. Infection follows inhalation of microconidia from *Histoplasma capsulatum* Darling (1906) (Kwon-Chung) McGinnis & Katz (1979) (Onygenales: Ajellomycetaceae) in bat/bird-contaminated environments (caves, bridges, warehouses). Intracellular survival within macrophages and dissemination via the mononuclear phagocyte system underpin severe forms; rapid antigen testing and timely amphotericin B/azole therapy reduce mortality yet remain unevenly available (Wheat *et al.*, 2007; Adenis *et al.*, 2014; Queiroz-Telles *et al.*, 2017; Nacher *et al.*, 2020).

Cryptococcosis, caused by *C. neoformans* and *C. gattii*, is a leading opportunistic infection in Brazilian urban centers and also occurs in immunocompetent hosts, especially with *C. gattii* in the North/Amazon. Polysaccharide capsule, melanin production, and neurotropism favor central nervous system invasion; HIV-associated meningitis remains a major cause of death where screening and induction therapy are delayed (Trilles *et al.*, 2008; Hagen *et al.*, 2015; Rajasingham *et al.*, 2017; Rodrigues and Nosanchuk, 2020).

Zoonotic sporotrichosis driven by *Sporothrix brasiliensis* Marimon, Gené, Cano, and Guarro (2007) (Ophiostomatales: Ophiostomataceae) has expanded from Southeastern hubs, Rio de Janeiro, to multiple states, propelled by feline transmission and densely populated urban belts. High inoculum, dermotropic/lymphocutaneous spread, and severe disseminated disease in immunocompromised hosts characterize Brazil's hyperendemic scenario; control hinges on veterinary–public health integration and access to itraconazole/potassium iodide (Gremião *et al.*, 2017; Orofino-Costa *et al.*, 2017; Rodrigues *et al.*, 2020; Rodrigues and Nosanchuk, 2020).

Nosocomial candidemia and invasive aspergillosis mirror ICU expansion, widespread devices, broad-spectrum antibiotics, and corticosteroid use. Species shifts toward non-*albicans Candida* and biofilm-mediated tolerance complicate management, while *A. fumigatus* exploits alveolar immune defects and structural lung disease. Antifungal stewardship, diagnostics β-D-glucan, galactomannan, PCR, and infection-control capacity vary across regions, shaping outcomes (Table 3) (Colombo *et al.*, 2013; Nucci *et al.*, 2013; Pappas *et al.*, 2018; Lamoth and Kontoyiannis, 2022).

Table 3: Compiles major predisposing conditions that increase susceptibility to fungal infections, including HIV infection, organ transplantation, chemotherapy, and ICU stays. It also highlights populations at the highest risk of severe mycoses

Mechanism	Description	Examples
Morphological switching	Transition between yeast and hyphal forms, facilitating tissue invasion and immune evasion	*Candida albicans*
Biofilm formation	Structured microbial communities resistant to antifungals and host immune responses	*Candida* spp. and *Aspergil*lus spp.
Immune evasion	Capsule production, melanin synthesis, and antigenic variation that reduce host recognition	*Cryptococcus* spp.
Toxins / secondary metabolites	Production of metabolites that damage host tissues and impair immune function	*Aspergillus fumigatus*
Thermotolerance	Ability to grow at human body temperature, enabling survival in the host	*Candida albicans* and Cryptococcus *neoformans*
Nutrient acquisition	Specialized mechanisms for acquiring iron and other essential nutrients in the host environment	*Candida* spp. and *Aspergillus* spp.
Surface adhesins	Expression of adhesin proteins that promote attachment to host tissues and medical devices	*Candida albicans*
Oxidative stress resistance	Detoxification of reactive oxygen species produced by host immune cells	*Candida* spp. and *Aspergillus fumigatus*
Intracellular survival	Ability to persist and replicate within macrophages	*Cryptococcus neoformans* and *Histoplasma capsulatum*

3.4. Diagnosis of fungal diseases

Accurate and timely diagnosis is one of the greatest challenges in managing fungal diseases. Unlike bacterial infections, fungi often require complex culture conditions, longer incubation times, and specific laboratory expertise. Classical diagnostic methods, such as direct microscopy and culture, remain the gold standard, yet their sensitivity is limited and turnaround time delays therapeutic decisions. Microscopic visualization of yeast, hyphae, or spherules in tissue samples can be confirmatory, but sensitivity depends on operator experience and specimen quality (Figure 8) (Brown *et al.*, 2012; Denning and Bromley, 2015; Bongomin *et al.*, 2017; Lamoth and Kontoyiannis, 2022).

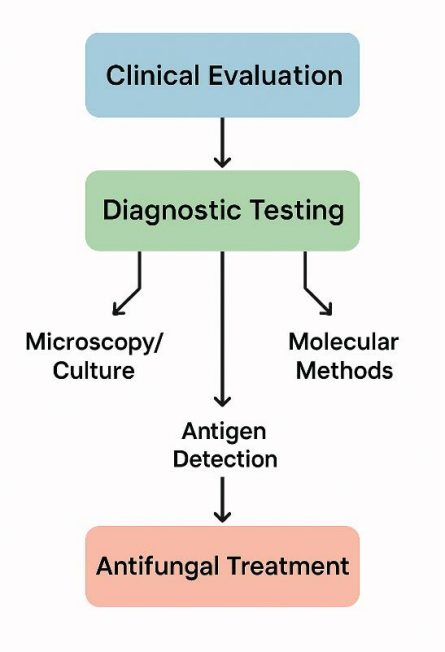

Figure 8: Diagnostic flowchart for fungal infections. Diagnostic approaches for fungal infections: starting from clinical suspicion and evaluation, followed by conventional methods, microscopy/culture, histopathology, antigen detection, molecular assays, C-reactive protein (CRP), sequencing, and imaging confirmation, leading to therapeutic decision-making

Sources: Lamoth and Kontoyiannis (2022) and Nacher *et al.,* (2024)

Culture methods allow species identification and antifungal susceptibility testing, but in many cases, such as mucormycosis or invasive aspergillosis, positive culture rates are low, leading to underdiagnosis. Invasive techniques such as bronchoalveolar lavage and biopsy are often required but may not be feasible in critically ill patients. Histopathology remains a cornerstone for tissue-invasive fungi, where the morphology of hyphae, septate vs. non-septate, can suggest etiological groups. Still, access to trained mycopathologists is limited in many regions (Perfect, 2017; Armstrong-James *et al.,* 2020; Rodrigues and Nosanchuk, 2020).

Non-culture-based diagnostics have transformed fungal diagnostics into high-income settings. Antigen detection tests, such as cryptococcal antigen lateral flow assay, galactomannan for aspergillosis, and β-D-glucan for invasive mycoses, offer rapid results and can be performed with minimal laboratory infrastructure. However, their sensitivity and specificity vary across patient populations, and cross-reactivity can complicate interpretation (Rajasingham *et al.*, 2017; Esteves *et al.*, 2020; Fisher *et al.*, 2022; Lamoth and Kontoyiannis, 2022).

Molecular assays, CRP-based, and sequencing are increasingly adopted, enabling species-level identification and detection of resistance markers, but their cost and need for specialized facilities limit widespread application in low- and middle-income countries. In Brazil and much of Latin America, diagnostic capacity remains uneven. While reference centers in São Paulo, Rio de Janeiro, and Porto Alegre employ molecular tests and antigen assays, most hospitals rely primarily on microscopy and culture (Colombo *et al.*, 2013; Nucci *et al.*, 2013; Shikanai-Yasuda *et al.*, 2017; Rodrigues and Nosanchuk, 2020).

For paracoccidioidomycosis, serology using double immunodiffusion remains the most common tool, but sensitivity varies by antigen source and disease form. Histoplasmosis is frequently misdiagnosed as tuberculosis, leading to delayed therapy and high mortality; rapid antigen detection is not yet routinely available outside research or pilot programs. Cryptococcal antigen testing is increasingly used in tertiary centers, yet routine screening of people living with HIV remains inconsistent. For invasive candidiasis and aspergillosis, blood culture and galactomannan testing are sporadically available, but turnaround time and costs hinder systematic use (Table 4) (Queiroz-Telles *et al.*, 2017; Armstrong-James *et al.*, 2020; Nacher *et al.*, 2020; Fisher *et al.*, 2022).

Table 4: Several antifungal drug classes are available, including azoles, echinocandins, and polyenes. Mechanisms of action, clinical applications, and emerging resistance profiles

Disease / Pathogen	Sample type	Diagnostic test(s)	Typical time to result	Main limitations
Invasive candidiasis	Blood, catheter tip	Blood culture; MALDI-TOF; PCR	2–7 days (culture); hours (PCR)	Low sensitivity; delay in culture positivity
Aspergillosis	BAL, serum	Galactomannan ELISA; PCR; histopathology	Hours–days	False positives (β-lactam antibiotics); invasive sampling needed
Cryptococcosis	CSF, sérum	India ink; cryptococcal antigen LFA; culture	Minutes–days	India ink has low sensitivity: antigen may not be routine in LMICs
Histoplasmosis	Urine, serum, tissue	Antigen detection; culture; serology	Minutes–weeks	Antigen not widely available in Brazil; culture is slow
Paracoccidioidomycosis	Serum, biopsy	Serology (immunodiffusion, ELISA); histopathology	Days–weeks	Variable sensitivity; cross-reactivity with other fungi
Mucormycosis	Tissue biopsy	Direct microscopy; culture; histopathology	Hours–days	Culture is often negative; invasive procedures are required
Sporotrichosis	Skin biopsy, exudate	Culture (gold standard); PCR; histopathology	Days–weeks	Culture slow; PCR not widely available
Pneumocystis pneumonia	BAL, induced sputum	Direct immunofluorescence; PCR; β-D-glucan	Hours–days	PCR is not standardized; low-resource settings lack access

3.5. Treatment and therapeutic challenges

The contemporary antifungal armamentarium comprises four cornerstone classes: polyenes, azoles, echinocandins, and flucytosine, supplemented by allylamines and iodides for selected dermato/subcutaneous mycoses; yet clinical outcomes

remain constrained by host factors, delayed diagnosis, drug toxicities, and rising resistance. Polyenes such as amphotericin B, particularly in liposomal formulations, retain broad fungicidal activity against yeasts, molds, and dimorphic fungi, and are pivotal in induction therapy for cryptococcal meningitis and severe endemic mycoses, but nephrotoxicity and infusion-related reactions limit duration and accessibility (Denning and Bromley, 2015; Richardson and Hoang, 2020; Lamoth and Kontoyiannis, 2022).

Azoles provide oral step-down options with species- and site-specific penetration of luconazole for genus *Candida* Berkh. (1923) (Serinales: Debaryomycetaceae), itraconazole for endemic mycoses, voriconazole for aspergillosis, posaconazole/isavuconazole for molds, yet are hampered by drug–drug interactions, CYP-mediated hepatotoxicity, and variable pharmacokinetics requiring therapeutic drug monitoring Echinocandins, caspofungin, micafungin, and anidulafungin have reshaped candidemia management due to potent activity against most *Candida* spp., including azole-resistant strains and biofilms; however, limited pulmonary/CNS penetration and intrinsic inactivity against *Cryptococcus* sp. and many dimorphic fungi narrow indications (Pfaller and Diekema, 2010; Brown *et al.*, 2012).

Flucytosine, synergistic with amphotericin B in cryptococcal meningitis induction, improves early fungicidal activity but demands close hematologic/hepatic monitoring and is vulnerable to rapid resistance when used as monotherapy. For subcutaneous/dermatophyte disease, itraconazole and terbinafine are first-line, while saturated potassium iodide remains an inexpensive, effective option for lymphocutaneous sporotrichosis in resource-limited settings (Gremião *et al.*, 2017; Orofino-Costa *et al.*, 2017; Rodrigues and Nosanchuk, 2020).

Resistance emerges via diverse mechanisms: azole resistance in *Candida* ERG11 mutations, upregulated efflux transporters, triazole resistance in *A. fumigatus* environmental azole fungicide exposure, CYP51A alterations, and echinocandin resistance through FKS hotspot mutations diminishing β-1,3-D-glucan synthase susceptibility. Biofilm-associated tolerance further reduces susceptibility across classes and contributes to device-related persistent infections. These trends elevate the role of antifungal stewardship, early source control device removal, debridement, optimized dosing guided by therapeutic drug monitoring, and strategic combination therapy in selected scenarios (Denning and Bromley, 2015; Bongomin *et al.*, 2017; Pappas *et al.*, 2018; Arastehfar *et al.*, 2020; Fisher *et al.*, 2022).

The pipeline and recently introduced agents broaden possibilities but require careful positioning. Novel mechanisms include glucan synthase inhibition via non-echinocandin scaffolds, Gwt1 inhibition targeting glycosylphosphatidylinositol anchor biosynthesis, and dihydroorotate dehydrogenase blockade for *Aspergillus*; early data suggest activity against refractory molds and *Candida*, including biofilm states, though access, cost, and resistance surveillance remain pressing. Ultimately, therapeutic success hinges on rapid species-level identification, susceptibility testing where feasible, and integration of host-directed strategies, including glycemic control, reduction of immunosuppression when possible, and timely neurosurgical/respiratory interventions (Table 5) (Figures 9-10) (Schwalb *et al.,* 2022; Fisher *et al.,* 2024; WHO, 2024; Arastehfar *et al.,* 2025; Richardson *et al.,* 2025).

Table 5: Presents estimates of disease burden, mortality, and the economic impact of fungal infections worldwide

Class	Key agents (examples)	Primary mechanism	Predominant spectrum / first-line uses	Major limitations/monitoring
Polyenes	Amphotericin B deoxycholate; Liposomal amphotericin B	Binds ergosterol - membrane pores (fungicidal)	Broad yeast/mold/dimorphic coverage; induction for cryptococcosis and severe endemic mycoses; salvage for molds	Nephrotoxicity with liposomal, electrolyte wasting, infusion reactions; IV only; access/cost
Azoles (triazoles)	Fluconazole Itraconazole Voriconazole Posaconazole Isavuconazole	Inhibit 14-α-lanosterol demethylase (ERG11) - blocks ergosterol synthesis (fungistatic/fungicidal species-dependent)	Fluconazole: *Candida* (non-*krusei*), crypto maintenance; Itraconazole: endemic mycoses, sporotrichosis; Voriconazole: aspergillosis; Posaconazole/Isavuconazole: molds, including Mucorales variable	CYP interactions, hepatotoxicity, QT effects, drug-specific, variable PK - TDM often needed; azole resistance (ERG11, efflux; cyp51A in *Aspergillus*
Echinocandins	Caspofungin Micafungin Anidulafungin	Inhibit β-1,3-D-glucan synthase (Fks complex) - cell wall	First-line for candidemia/invasive candidiasis (incl. many azole-R); activity vs	IV only; limited CNS/eye/urine penetration; intrinsic inactivity vs

Class	Key agents (examples)	Primary mechanism	Predominant spectrum / first-line uses	Major limitations/monitoring
		disruption (fungicidal vs *Candida*)	*Candida* biofilms; step-down to azole when stable	*Cryptococcus*, many dimorphic fungi; FKS mutations – resistance
Antimetabolite	Flucytosine (5-FC)	Converted to 5-FU - inhibits DNA/RNA synthesis	With amphotericin B for cryptococcal meningitis induction, occasionally with azoles for refractory yeasts	Rapid resistance if monotherapy; myelo/hepatotoxicity - drug levels + labs
Allylamine	Terbinafine	Inhibits squalene epoxidase	*Dermatophyte infections* (onychomycosis, tinea)	Hepatotoxicity (rare), interactions; limited role in invasive disease
Iodide (topical/systemic)	Saturated Solution of Potassium Iodide (SSKI)	Unclear (host/iodine effects)	*Lymphocutaneous sporotrichosis* resource-limited, step-up	GI intolerance; contraindications in thyroid disease; replaced by itraconazole where available

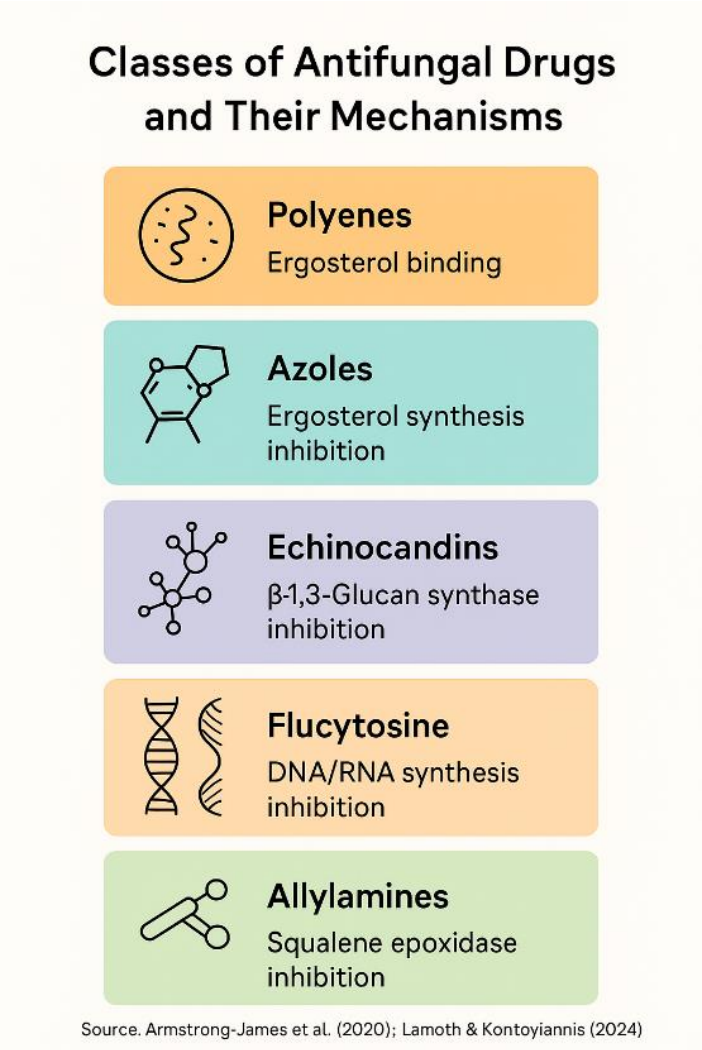

Figure 9: Classes of antifungal drugs and their mechanism. Infographic showing major antifungal classes: Polyenes ergosterol binding, Azoles ergosterol synthesis inhibition, Echinocandins β-1,3-glucan synthase inhibition), flucytosine DNA/RNA synthesis inhibition, and Allylamines squalene epoxidase inhibition
Sources : Armstrong-James *et al.,* (2020) and Lamoth & Kontoyiannis (2024)

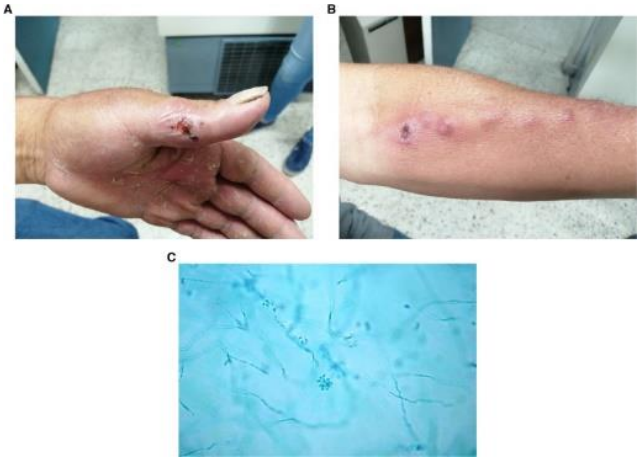

Figure 10: (A) Small, ulcerated lesion with surrounding erythema and edema in the left thumb, where minor trauma with a spike occurred. (B) Multiple erythematous subcutaneous nodules following lymphatic spread in the anterior left forearm. One nodule appears crusted. (C). *Sporothrix schenckii* (Hektoen & C.F. Perkins) Beurm. & Gougerot 1911 (Ophiostomatales: Ophiostomataceae) colonies showing branching narrow hyphae and the characteristic bouquet-like appearance of the microconidia
Source: Doi: 10.4269/ajtmh.21-1212

3.6. Future directions and perspectives (2024–2025)

The future of medical mycology is being shaped by converging pressures: rising antifungal resistance, expanding immunocompromised populations, climate-driven changes in fungal ecology, and persistent diagnostic gaps. In 2024–2025, global health agencies emphasized the need to integrate fungal diseases into international surveillance frameworks alongside bacterial AMR, recognizing that pathogens such as *C. auris* and azole-resistant *A. fumigatus* pose escalating threats. Reports highlighted that resistance surveillance is patchy outside Europe and North America, urging investment in genomic sequencing platforms, cross-border networks, and standardized antifungal susceptibility testing protocols (Fisher *et al.*, 2024; WHO, 2024; Arastehfar *et al.*, 2025; Chowdhary *et al.*, 2025).

Innovations in diagnostics are accelerating, with 2024–2025 studies demonstrating point-of-care molecular assays and next-generation antigen detection for cryptococcosis, histoplasmosis, and aspergillosis. Portable sequencing devices, Clustered Regularly Interspaced Short Palindromic Repeats) (CRISPR-based). Biosensors and multiplex PCR panels promise rapid identification of multiple pathogens and resistance markers directly from clinical samples. Yet challenges remain in ensuring affordability, decentralized availability, and performance validation in low-resource settings, particularly in Latin America and Africa (Figure 11) (Barrangou *et al.,* 2007; Doudna and Charpentier, 2014; Nacher *et al.*, 2024; Rajasingham *et al.*, 2024; Arastehfar *et al.*, 2025; Chowdhary *et al.*, 2025).

Figure 11: Future perspectives in fungal disease management. **Infographic illustrating future priorities: surveillance and resistance monitoring, diagnostic innovations, CRISPR, portable sequencing, new antifungals Fosmanogepix, Olorofim, immunotherapy monoclonal antibodies, vaccines, planetary health, climate-fungal interactions, and equity and stewardship**
Sources: Who, 2024, and Arastehfar *et al.,* 2055

Novel triterpenoid glucan synthase inhibitors, Gwt1 inhibitors fosmanogepix, and dihydroorotate dehydrogenase inhibitors are expected to expand the antifungal toolbox in the coming years. At the same time, immunotherapeutic approaches including monoclonal antibodies, checkpoint modulation, and fungal vaccines are gaining momentum as adjunctive strategies, particularly for cryptococcosis and endemic mycoses (Lamoth and Kontoyiannis, 2024; Arastehfar *et al.*, 2025; Chowdhary *et al.*, 2025; Ministry of Health, 2025).

From a planetary health perspective, climate change is driving shifts in fungal distribution and thermotolerance. Evidence from 2024–2025 underscores that rising global temperatures may select for pathogenic fungi with enhanced ability to survive at mammalian body temperature, potentially increasing the pool of emerging threats. Brazil and other tropical countries may see exacerbated risks, given their ecological diversity and rapid urbanization. Strengthening climate-health surveillance, integrating environmental sampling, and monitoring fungal emergence are now global priorities (Lamoth and Kontoyiannis, 2024; Nacher *et al.*, 2024; Rajasingham *et al.*, 2024; Richardson *et al.*, 2025).

Finally, stewardship and equity remain central. The WHO 2024–2025 roadmap emphasizes expanding access to essential antifungals, integrating fungal disease programs into HIV/TB platforms, and building laboratory capacity in low- and middle-income countries. For Brazil, perspectives include scaling up rapid diagnostics for histoplasmosis, implementing cryptococcal antigen screening in HIV clinics, and investing in regional reference laboratories for antifungal susceptibility testing. Without these measures, gains in innovation risk will remain confined to high-income settings, perpetuating diagnostic and therapeutic inequities (Table 6) (Arastehfar *et al.*, 2025; Chowdhary *et al.*, 2025; Richardson *et al.*, 2025; Rodrigues and Nosanchuk, 2025).

Table 6: Integrated One Health approaches and stronger surveillance systems are essential to address resistance and climate-driven risks. Equity in access and interdisciplinary collaboration remain central for global resilience

Priority domain	Key innovations (2024–2025)	Expected impact	Main challenges
Surveillance & Resistance	Global AMR integration; genomic sequencing hubs; harmonized AST protocols	Early detection of resistant *Candida auris*, azole-R *Aspergillus*	Limited capacity in LMICs; cost; data-sharing gaps
Diagnostics	CRISPR-biosensors; multiplex PCR; portable sequencing; improved antigen LFA for histoplasmosis/cryptococcosis	Rapid, decentralized detection; reduced mortality in HIV & ICU settings	Validation in diverse settings; affordability; training
Therapeutics	New classes: fosmanogepix, olorofim, ibrexafungerp; antifungal vaccines in development	Expanded treatment against MDR fungi; reduced toxicity; prevention potential	Regulatory approval; pricing; distribution inequities
Immunotherapy	Monoclonal antibodies; checkpoint modulation; adjunctive immunotherapies	Enhanced clearance in cryptococcosis and endemic mycoses	Complexity; cost; Safety monitoring
Planetary Health	Climate-driven fungal surveillance; ecological modeling	Anticipate emerging pathogens; link environment–health	Implementation across disciplines; sustainability
Equity/ Stewardship	WHO roadmap integration; scale-up of essential antifungals and rapid tests in LMICs	Reduce global disparities in fungal mortality	Funding gaps; political prioritization

3.7. Integration of scientific communication and public awareness (2024–2025)

In recent years, public communication channels have become increasingly important in disseminating knowledge about fungal diseases and their impact on society. Academic institutions in Brazil have strengthened their outreach efforts, highlighting the importance of fungal pathogens not only for clinical medicine but also for environmental and public health. For example, the University of São Paulo (USP) reported on emerging fungal threats and their links with climate change, emphasizing how rising temperatures and ecological disturbances facilitate the spread of opportunistic fungi into new ecosystems. These initiatives reinforce the connection between planetary health and medical mycology, bringing scientific debates into public awareness (Figure 12) (USP, 2024).

Figure 12: Integration of scientific communication, clinical practice, and public engagement strengthens awareness of fungal diseases and their societal impact. Universities, healthcare professionals, media, and community outreach collectively enhance surveillance, education, and responses to emerging fungal threats

Similarly, the University of Campinas has published updates on antifungal resistance, stressing the urgency of new therapeutic strategies and surveillance systems. These communications highlight how resistant pathogens such as *C. auris* are not confined to hospital settings but represent a growing public health concern in Brazil and worldwide. By bridging laboratory discoveries and societal implications, universities help build a critical understanding among healthcare professionals, policymakers, and the general population (Unicamp, 2025).

Beyond universities, specialized clinics have also contributed to public knowledge. For instance, has presented accessible educational resources linking fungal biology, host responses, and clinical manifestations, making complex medical topics understandable for broader audiences. Such initiatives demonstrate that integrating academic research with clinical practice and social communication is essential for tackling fungal diseases comprehensively. By combining scientific rigor with effective communication, these sources strengthen both community awareness and the healthcare system's ability to respond to fungal threats (Formare, 2025).

4.0. CONCLUSION

Fungal diseases remain a growing global health challenge, driven by expanding immunocompromised populations and environmental change. Opportunistic infections such as candidiasis, aspergillosis, and cryptococcosis coexist with endemic mycoses, especially in Brazil, creating a dual burden. Their pathogenesis involves mechanisms like morphological switching, biofilm formation, and immune evasion, which contribute to persistence, severity, and treatment resistance.

Despite advances, diagnosis is still limited by reliance on slow methods, while access to rapid molecular and antigen-based tests is uneven. Antifungal therapy, restricted to a few drug classes, faces toxicity, resistance, and emerging multidrug-resistant pathogens, underscoring the need for novel agents and immunotherapies. Future priorities include strengthening surveillance, expanding diagnostics, developing new drugs, and integrating fungal infections into public health agendas. For Brazil and other endemic regions, improving access and laboratory capacity will be crucial. Addressing fungal diseases requires global recognition that they are central to infectious disease medicine in the 21st century.

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