UNIVERSA MEDICINA

pISSN: 1907-3062 / eISSN: 2407-2230

Univ Med 2024;43:102-113

DOI: https://doi.org/10.18051/UnivMed.2024.v43.102-113

REVIEW ARTICLE

Emerging and reemerging human fungal pathogens that affect people with weakened immune systems: a systematic review

Amere Genet and Abayeneh Girma

[1] Department of Biology, College of Natural and Computational Science, Mekdela Amba University, P.O. Box 32, Tulu Awuliya, Ethiopia

gabayeneh2013@gmail.com

Date of first submission, December 12, 2023
Date of final revised submission, March 22, 2024
Date of acceptance, April 1, 2024

Cite this article as: Genet A, Girma A. Emerging and reemerging human fungal pathogens that affect people with weakened immune systems: a systematic review. Univ Med 2024;43:102-113

ABSTRACT

BACKGROUND

Emerging and reemerging human fungal pathogens are becoming more closely associated with morbidity and mortality, with 13 million infections and 1.5 million deaths per year. They are most often associated with critically ill and immunosuppressed patients. Therefore, this systematic review focused on emerging and reemerging human fungal pathogens that affect immunosuppressed individuals.

METHODS

A systematic literature search was performed using PubMed, ScienceDirect, Web of Science, Google Scholar, and other sources (Google engine and manual search using a reference list). The data were extracted in a structured format prepared using Microsoft Excel.

RESULTS

Cryptococcus neoformans, *Candida auris*, *Aspergillus fumigatus*, *Candida albicans*, Nakaseomyces glabrata (*Candida glabrata*), *Histoplasma* spp., Mucorales (*Rhizopus* spp., *Mucor* spp., *Lichtheimia* spp., and others), *Fusarium* spp., *Candida tropicalis*, *Candida parapsilosis*, *Pichia kudriavzevii* (*Candida krusei*), *Talaromyces marneffei* and *Pneumocystis jirovecii* were emerging and reemerging fungal pathogens reported among critically ill and immunocompromised patients including but not limited to HIV patients and patients with infectious diseases such as influenza, COVID-19, and tuberculosis as well as chronic conditions or co-morbidities such as asthma, hepatic cirrhosis, cancer, diabetes, cystic fibrosis (CF), transplant recipients, and chronic obstructive pulmonary disease (COPD). Climate change, agricultural activities, occupational hazards, deforestation, migratory trends of people, soil dispersion, decreased immunity of patients, biofilm development, medication tolerance, and resistance to antifungal therapies are all factors that contribute to the emergence of fungal diseases.

CONCLUSION

This review makes recommendations for policymakers, public health experts, and other stakeholders to improve the response to these fungal infections, including laboratory capacity and surveillance, fostering sustainable research and innovation, implementing public health initiatives, and limiting the development of antifungal drug resistance.

Keywords: Fungal pathogens, antifungal drug resistance, reemerging fungal pathogens, invasive fungal infections, immunocompromised patients, emerging fungal pathogens

INTRODUCTION

Human fungal pathogens are a serious threat to public health as they are increasingly associated with morbidity and mortality.[1] Globally, they are responsible for more than 13 million infections and 1.5 million deaths per year.[2-5] Most often, fungal infections are significantly associated with critically ill and immunocompromised patients, with increasing mortality rates, despite having historically been associated with severe infections in immunosuppressed individuals and in those admitted to the intensive care unit (ICU).[6] Critically ill and immunocompromised individuals are easily exposed to species such as *Cryptococcus*, *Candida*, *Aspergillus*, *Pneumocystis*, *Fusarium*, and Mucorales, while they are also affected by dimorphic fungi such as *Histoplasma* and *Talaromyces*.[7]

Human fungal infections range from mucocutaneous infections that are not life-threatening to serious invasive infections that affect almost any organ or system of the body. [5] Infections of the skin, hair, nails, mucosal surfaces, and allergic reactions are examples of superficial infections or mycosis caused by primary or opportunistic human fungal pathogens. Invasive fungal infections (IFIs), which affect internal organs, are progressive and usually fatal. The infection with human fungal pathogens in HIV patients is the result of a decrease in the activity of $CD4^+$ lymphocytes due to defects in cell-mediated immunity.[2,4,8] Additionally, infectious diseases such as influenza,[9] COVID-19,[10] and tuberculosis [11] as well as chronic conditions or co-morbidities such as asthma,[12] cirrhosis,[13] cancer,[14] diabetes,[15] cystic fibrosis (CF),[16] transplant recipients,[17] and chronic obstructive pulmonary disease (COPD) [9] are the risk factors that complicate fungal infectious diseases. Infectious and non-infectious diseases increase hospitalization days and cost, mortality rates, and antifungal resistance, and decrease treatment options.

Climate change, agricultural activities, occupational hazards, deforestation, human migration patterns, soil dispersion, patient immunosuppression, improved infection detection, and diagnostic tests are all factors that contribute to the emergence of fungal diseases.[18,19] The increasing incidence of fungal morbidity and mortality is directly associated with antifungal resistance, tolerance to antifungal drugs, and biofilm formation.[1] Antifungal tolerance is the emergence of partial growth after 24 hours that can be shown in susceptibility tests, including at inhibitory drug concentrations.[20] Comparatively, antifungal resistance is the absence of a detectable toxic impact on treating human fungal pathogens. For the treatment of fungal infections, only limited classes of antifungals (considering their mode of action), notably polyenes, azoles, echinocandins, allylamines, and flucytosine are available. Allylamines are used to treat superficial infections, but the four remaining drug classes are excellent against invasive mycoses. However, beyond their side effects (in terms of their toxicity, spectrum, hazards, and pharmacokinetic properties), currently it is common to see resistance to one or more of the above clinically prescribed antifungal drugs.[4]

The impact of important fungal pathogens (*Cryptococcus neoformans, Candida auris, Aspergillus fumigatus, Candida albicans, Nakaseomyces glabrata (Candida glabrata), Histoplasma* spp., Mucorales *(Rhizopus* spp., *Mucor* spp., *Lichtheimia* spp. and others*), Fusarium* spp., *Candida tropicalis, Candida parapsilosis, Pichia kudriavzevii (Candida krusei), Talaromyces marneffei,* and *Pneumocystis jirovecii*) as well as the extent of the public health risk caused by fungal infectious diseases and the antimicrobial resistance (AMR) of significant pathogens is becoming a global issue.[21,22]

The significant reasons may be a week-long laboratory capacity and surveillance system, research and innovative activities, and implementing public health initiatives in each country. Therefore, this review aims to emphasize the clinically significant fungal pathogens, risk factors, antifungal resistance, and the importance of preventive and diagnostic strategies to protect public health.

METHODS

Formulation of research questions and problems

This systematic review was guided by the following question: "What are the emerging and reemerging human fungal pathogens that affect people with weakened immune systems?" The problem was formulated when searching for and assessing the impacts of human fungal pathogens on human health. Due to their diverse impacts, the

study focused on examining the impact of emerging and reemerging human fungal pathogens on immunocompromised patients. Several research articles on emerging and reemerging human fungal pathogens among immunocompromised individuals were systematically searched and collected in different databases. Many published articles were available separately, and a detailed review was essential to incorporate all of the results to reach a conclusion and prevent any information conflicts, ambiguities, or misconceptions.

Data source and search strategy

A systematic literature search of published and unpublished primary articles related to the emerging and reemerging fungal pathogens was conducted using PubMed, ScienceDirect, Web of Science, Google Scholar, and other sources (Google engine and manual search using a reference list). The systematic search was conducted using the following keywords and phrases: "emerging fungal pathogens", "reemerging fungal pathogens", "fungal pathogens", "invasive fungal infections", "antifungal drug resistance", "immunocompromised patients", "immunosuppressed individuals". The study was carried out from April 1, 2023 to July 1, 2023. The search process was presented in accordance with the PRISMA 2020 flow diagram guidelines,[23] together with the included and excluded items and reasons for exclusion **(Figure 1).** A review protocol was developed and registered with the Center for Open Science with registration number osf-registrations-m8gzk-v1, and it is available from https://archive.org/details/osf-registrations-m8gzk-v1.

Study selection and eligibility criteria

All collected studies were exported to the EndNote citation manager to avoid duplications and then assessed for eligibility to be included in this systematic review using a prepared Microsoft Excel assessment format.

Inclusion criteria

Studies concerning emerging and reemerging fungal pathogens among immunocompromised patients were considered eligible to be included in this review. Articles reporting type of human fungal pathogen, associated disease, affected organs/systems, treatment options. and antifungal resistance data were included. Only literature written in English language was included**.** Both published and unpublished literature available from 2000 to 2023 was included.

Exclusion Criteria

Articles with insufficient information, records with missing outcomes of interest, personal opinions, editorial reports, letters to the editors, correspondence, and proceedings were excluded.

Data extraction

All studies obtained using the search strategies were exported to Endnote version 8 software and duplicates were removed. Finally, all studies were exported to a Microsoft Excel spreadsheet. The titles and abstracts of studies retrieved and those from additional sources were screened to identify studies that satisfied the inclusion criteria. Then, the full text of potentially eligible studies was assessed. The fungal pathogens and references, associated disease, affected organs/systems, treatment options, and antifungal resistance data were included in the data extraction format of Table 1. Additionally, in Table 2, antifungal classes and references, effect on microbial cells, mechanisms of action, and resistance mechanisms were included. Two reviewers (AmG, and AbG) independently assessed the qualities of the articles. Discrepancies were resolved through discussion.

RESULTS

Characteristics of the included studies

A total of 500 articles were obtained from the electronic databases through a primary search. Due to duplication, detected by the automation tool Endnote X8, and being out of scope, 113 articles were removed. The remaining 387 articles were evaluated by reading their titles and abstracts. During title and abstract evaluation, 110 articles were excluded, and of the 277 remaining articles, 83 were not retrieved. Subsequently 194 articles were selected for further evaluation by reading their full texts, following which 16 articles met the inclusion criteria and were included in the systematic review (Figure 1). Of these included studies, 10 and 6 studies were included in Tables 1 and 2. Emerging and reemerging fungal pathogens among immunocompromised patients.

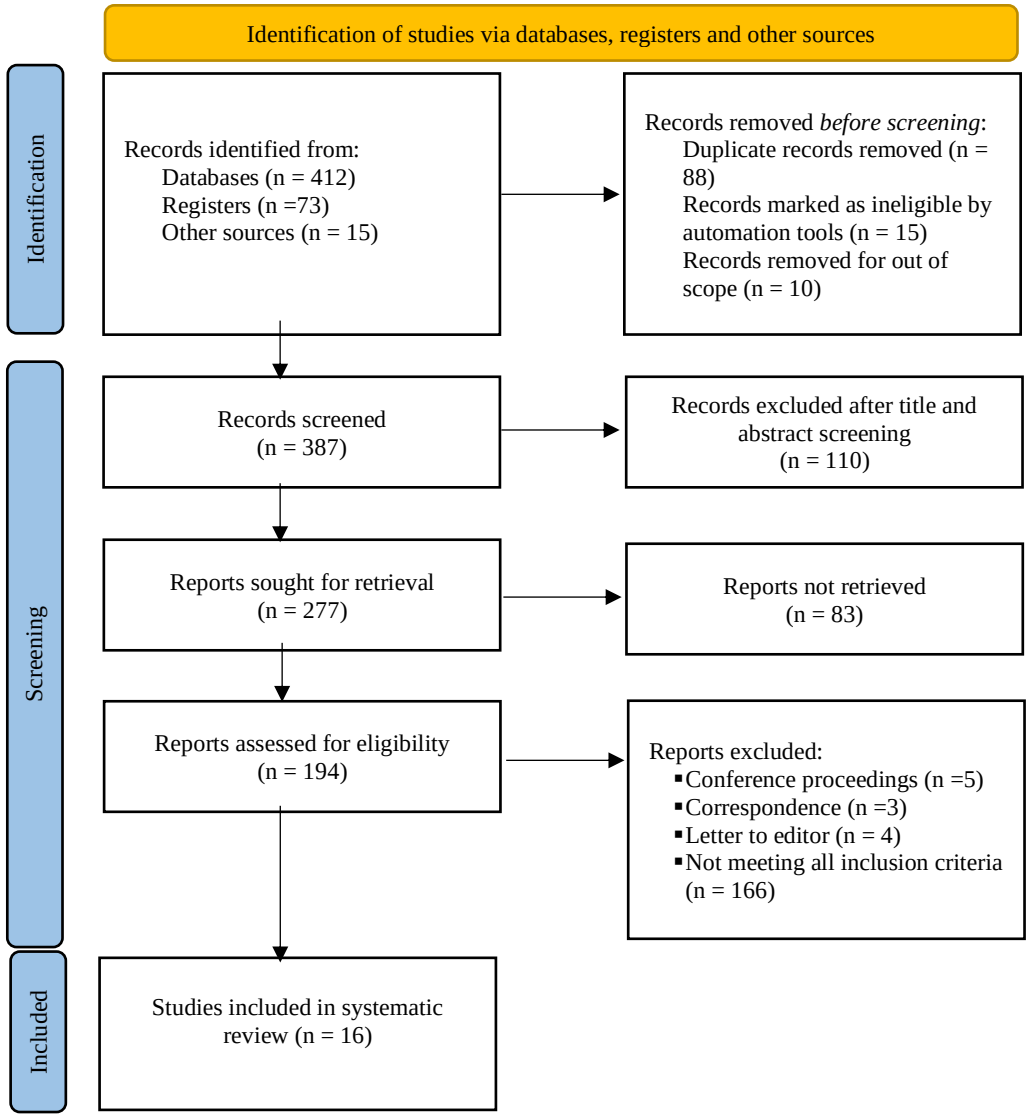

Figure 1. Flow diagram for study selection strategy as per PRISMA guidelines

Cryptococcus neoformans

Cryptococcus neoformans is a globally distributed opportunistic yeast pathogen found in soil and decaying wood environments and causes the disease known as 'cryptococcosis' (Table 1). It primarily infects human lungs when the pathogen is inhaled from the environment through the respiratory route and then spreads to the central nervous system and blood and causes cryptococcal meningitis and cryptococcemia, respectively.[24]

Candida auris

Candida auris is a globally distributed yeast pathogen that can cause the disease called "invasive candidiasis". *C. auris* infects the blood (candidemia), heart, central nervous system, eyes, bones, and internal organs of the human body.[25-27]

Aspergillus fumigatus

Aspergillus fumigatus is an environmental mold that infects humans and causes aspergillosis (ranging from allergic reaction, colonization, and semi-invasive disease to acute invasive aspergillosis). It is ubiquitous in nature and as such, is easily inhaled from the environment, predominantly affecting the respiratory system (e.g., lung) causing pulmonary disease, and disseminating to other systems (e.g., central nervous system).[28, 29]

Candida albicans

Candida albicans is a pathogenic yeast distributed around the world (Table 1). It is part of the healthy human microbiome (mouth, throat, gut, vagina, and skin) that can cause infections of the mucosae (oropharyngeal candidiasis, esophageal candidiasis, vulvovaginal candidiasis, and cutaneous candidiasis) or produce invasive candidiasis (blood (candidemia), heart, central nervous system, eyes, bones, and internal organs).[30]

***Nakaseomyces glabrata* (*Candida glabrata*)**

Nakaseomyces glabrata (Candida glabrata) is a globally distributed commensal yeast that can cause invasive candidiasis second only to *C. albicans* in incidence. It infects the blood (candidemia), heart, central nervous system, eyes, bones and/or internal organs. Immunocompromised patients are vulnerable groups for this pathogenic yeast. Echinocandins are the usual treatment option for invasive candidiasis.[31, 32]

***Histoplasma* spp**

Histoplasma spp are globally distributed dimorphic fungi living as a mold in the environment (soil, bird droppings, and bat droppings) as well as a yeast-like organism at human body temperature, that causes histoplasmosis infections. It initially affects the lung and spreads to the CNS, blood, and other parts of the body.[33]

Mucorales

Mucorales is a large group of pathogenic molds (*Rhizopus* spp., *Mucor* spp., *Lichtheimia* spp., and others) that are distributed worldwide and cause an infection called 'mucormycosis'. Spore inhalation is the route of human infection. Invasion of the pathogen can also occur through skin breaks, burns, and soft-tissue injuries. They primarily affect the lungs and sinuses and spread to other parts of the body (eye, CNS, and gastrointestinal tract). Immunocompromised patients (with cancer, diabetes mellitus, neutropenia, trauma, and transplants) are the vulnerable groups for invasive mucormycosis. Mucorales are treated by amphotericin B, but they are inherently resistant to the antifungal agents fluconazole, voriconazole, and echinocandins.[22,32,34]

***Fusarium* spp.**

Fusarium spp. are pathogenic filamentous fungi that are distributed globally, but mostly in tropical countries. They primarily infect the respiratory system and the eyes (keratitis) of humans, but can also spread to the CNS and other organs of the body. Because of their adventitious sporulation, they also cause fungemia. Immunocompromised patients with hematological malignancies or post-hemopoietic stem cell transplantation (HSCT), allogeneic HSCT, acute myeloid leukemia, cytomegalovirus reactivation, and presence of skin lesions, are the risk groups of this infection. The infection is treated by azoles but the fungi are inherently resistant to most antifungal agents.[22, 35]

Candida tropicalis

Candida tropicalis is a globally distributed yeast, being part of the healthy human and animal microbiome but unfortunately capable of causing invasive candidiasis (blood (candidemia), heart, CNS, eyes, bones and internal organs). Those with critical illness and decreased host immunity are at risk for this pathogen. Echinocandins are the treatment option for this infection since they are resistant to azole antifungal agents (fluconazole, itraconazole, voriconazole, and posaconazole).[31, 32]

Candida parapsilosis

Candida parapsilosis is an emerging globally distributed yeast that is part of the healthy human and animal microbiome but unfortunately can cause invasive candidiasis (blood (candidemia), heart, CNS, eyes, bones, and internal organs).[36,37]

Pichia kudriavzevii (Candida krusei)

Pichia kudriavzevii (Candida krusei) is a member of the human microbiota, but it can invade mucosae and become an opportunistic pathogenic yeast (oropharyngeal candidiasis, esophageal candidiasis, vulvovaginal candidiasis, and cutaneous candidiasis). Critically ill and immunocompromised patients are the at-risk groups for this pathogen that may cause a serious nosocomial infection. Echinocandins are the primary treatment option for this pathogen, but other antifungals (e.g., azoles) may be used. Intrinsic resistance is recorded for the fluconazole antifungal agent.[31,32]

Talaromyces marneffei

Talaromyces marneffei is a dimorphic pathogenic fungus found in the environment (eg, soil, decaying wood) and causes the disease talaromycosis. It primarily infects the host's lungs (respiratory system) due to spore inhalation, and spreads to the CNS, blood, and other parts of the human body. Critically ill and immunocompromised patients (HIV/AIDS, cancer) or organ transplant patients are the vulnerable groups for invasive talaromycosis. Amphotericin B, itraconazole, or voriconazole are the recommended antifungal drugs for this infection.[22,32]

Pneumocystis jirovecii

Pneumocystis jirovecii is an opportunistic fungal pathogen that spreads globally and causes *Pneumocystis jirovecii* pneumonia (PJP). It is transmitted from person to person by air. Immunocompromised patients (HIV/AIDS, cancer, iatrogenic immunosuppression for solid organ transplantation (especially renal), autoimmune and inflammatory diseases, and nephrotic syndrome) are the most affected groups of this pathogen.[22,38]

Table 1. Emerging and reemerging human fungal pathogens that affect people with weakened immune systems

Fungal pathogens and Ref.	Associated disease	Affected organs or systems	Treatment options	Antifungal resistance data
Cryptococcus neoformans [5,34]	• Cryptococcosis	○ Lungs ○ Central nervous system (cryptococcal meningitis) ○ Blood (cryptococcemia)	✓ Fluconazole ✓ Amphotericin B in combination with flucytosine (severe cases)	◆ Unknown
Candida auris [25, 26, 48]	• Invasive candidiasis	○ Blood (candidemia) ○ Heart ○ Central nervous system ○ Eyes ○ Bones ○ Internal organs	✓ Echinocandins	◆ Fluconazole ◆ Amphotericin B ◆ Echinocandins
Aspergillus fumigatus [5,29, 34, 49]	• Invasive aspergillosis	○ Respiratory system ○ Central nervous system	✓ Liposomal amphotericin B	◆ Unknown
Candida albicans [31, 32, 34]	• Oropharyngeal candidiasis • Esophageal candidiasis • Vulvovaginal candidiasis • Cutaneous candidiasis • Invasive candidiasis	○ Human microbiota (mouth, throat, gut, vagina, and skin) ○ Blood (candidemia), heart, central nervous system, eyes, bones, and internal organs	✓ Echinocandins	◆ Unknown
Nakaseomyces glabrata (*Candida glabrata*) [31, 32]	• Invasive candidiasis	○ Blood (candidemia), heart, central nervous system, eyes, bones and/or internal organs	✓ Echinocandins	◆ Unknown
Histoplasma spp. [22, 34]	• Histoplasmosis	○ Lungs, central nervous system, blood, and other parts of the body	✓ No medication (healthy patients) ✓ Amphotericin B followed by itraconazole (severe cases)	◆ Moderate

			✓ Itraconazole (Moderate and chronic cases)	
Mucorales (*Rhizopus* spp., *Mucor* spp., *Lichtheimia* spp., and others) [32, 34]	• Mucormycosis	○ Lungs and sinuses, eye, central nervous system, and gastrointestinal tract	✓ Amphotericin B	◆ Inherently resistant to fluconazole, voriconazole and echinocandins
Fusarium spp. [22, 35]	• Fusariosis	○ Respiratory system, the eyes (keratitis), central nervous system and other organs	✓ Amphotericin B	◆ High
Candida tropicalis [31, 32]	• Invasive candidiasis	○ Blood (candidemia), heart, central nervous system, eyes, bones and internal organs	✓ Echinocandins	◆ Fluconazole ◆ Itraconazole ◆ Voriconazole ◆ Posaconazole
Candida parapsilosis [31, 32]	• Invasive candidiasis	○ Blood (candidemia), heart, central nervous system, eyes, bones and internal organs	✓ Echinocandins	◆ Moderate
Pichia kudriavzevii (*Candida krusei*) [31, 32]	• Oropharyngeal candidiasis • Esophageal candidiasis • Vulvovaginal candidiasis • Cutaneous candidiasis • Invasive candidiasis	○ Human microbiota (mouth, throat, gut, vagina, and skin)	✓ Echinocandins	◆ Moderate
Talaromyces marneffei [22, 32]	• Invasive talaromycosis	○ Lungs, central nervous system, blood, and other parts of the body	✓ Amphotericin B, itraconazole or voriconazole	◆ Low
Pneumocystis jirovecii [5, 32, 34]	• *Pneumocystis jirovecii* pneumonia (PJP)	○ Lungs	✓ Cotrimoxazole	◆ Unknown

DISCUSSION

Antifungal drug resistance mechanism and consequences

Currently, clinicians prescribe five classes of antifungal drugs (polyenes, azoles, echinocandins, allylamines, and pyrimidine analogs). These antifungal drugs commonly target the ergosterol biosynthesis pathway, the fungal cell wall, or the synthesis of fungal nucleic acids (DNA / RNA).[39] However, beyond the side effects, it is common to see resistance to one or more of the above clinically prescribed antifungal drugs using different survival strategies, *viz.* (i) drug target mutations that reduce their affinity for the drug, (ii) overexpression of the targeted protein by altering the promoter region of the gene, (iii) expression of an efflux system to reduce the drug concentration inside the fungal cell, (iv) drug degradation and (v) pleiotropic drug responses. [31] According to studies on the molecular causes of resistance to azoles in yeast, the ergosterol biosynthetic pathway, for example, undergoes four major changes after the action of azoles: (1) a decrease in affinity of azoles for their target, (2) an increase in the number of azole targets, (3) an alteration of the ergosterol biosynthetic pathway, and (4) a reduction in intracellular azole accumulation.[40-42] [Table 2]

Table 2. Antifungal drug resistance mechanisms of human fungal pathogens.

Antifungal classes and Ref.	Effect on microbial cells	Mechanism of action	Resistance Mechanisms
Polyenes [50]	Fungicidal	▪ Alteration of membrane function by binding to ergosterol	• Reduction of ergosterol concentration in the cell membrane due to defects in the ERG3 or ERG6 gene
Azoles [50-52]	Fungistatic	▪ Alteration of ergosterol biosynthesis by blocking 1,4-α-lanosterol demethylase	• Drug efflux by multi-drug transporters (ABC transporters) • Decrease in drug affinity through mutation in Erg11p or overexpression of ERG11 gene
Echinocandins [53]	Fungistatic or fungicidal	▪ Alteration of cell wall biosynthesis by inhibiting 1,3-β-D glucan synthase	• Mutation in Fks1 and Fks2 binding units
Allylamines [54]	Fungistatic	▪ Inhibition of ergosterol biosynthesis by inhibiting squalene epoxidase	• Interference from multidrug transporters • Mutations in the squalene epoxidase gene
Pyrimidine analogs [55]	Fungicidal	▪ Inhibition of nucleic acids (RNA and DNA) synthesis	• Mutation in cytosine permease and deaminase

Contributing factors for emerging antifungal resistance

The emergence of novel and antifungal-resistant infectious diseases in people, plants, and animals is accelerated by host shifts (e.g., human exposure, changing at-risk groups), globalization, urbanization, trade, agrochemical practice (e.g. fungicides), climate change, increase in environmental hotspot areas, change in microbiota and virulence, habitat disruption, and biodiversity loss (Figure 2).[40] Due to these factors, new fungal pathogens can emerge in human populations by coming into contact with naive hosts in their geographic niches.[43,44] Additionally, the overuse of antifungal agents in agriculture and medicine has caused a worldwide outbreak of drug-resistant fungal pathogens, which has outpaced the development of new antimicrobial therapies.[44] As the effects of anthropogenic environmental modification and climate change are felt on our planet, new fungal pathogens will continue to appear and disappear.

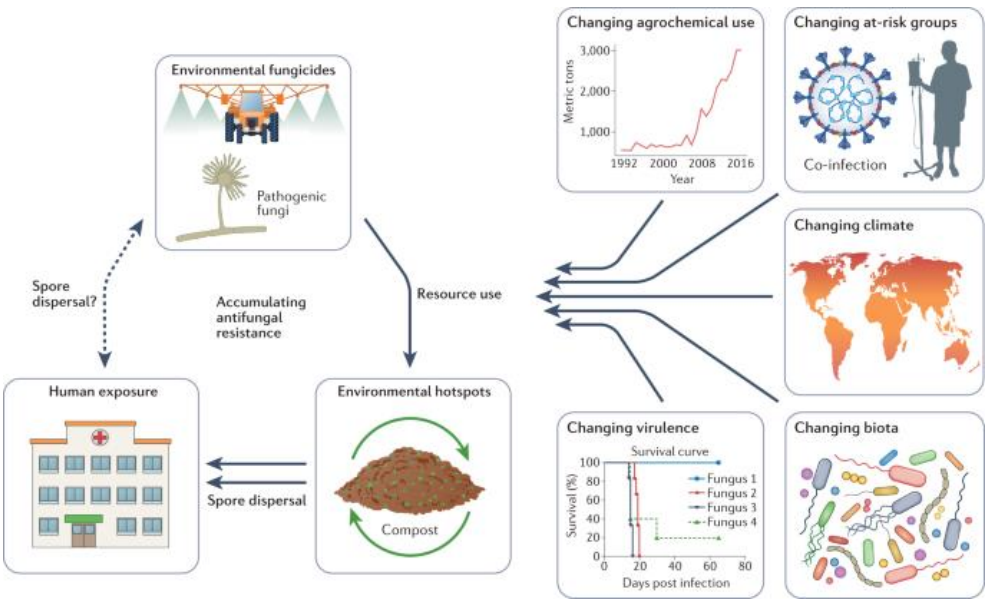

Figure 2. Contributing factors for emerging antifungal resistance [56]

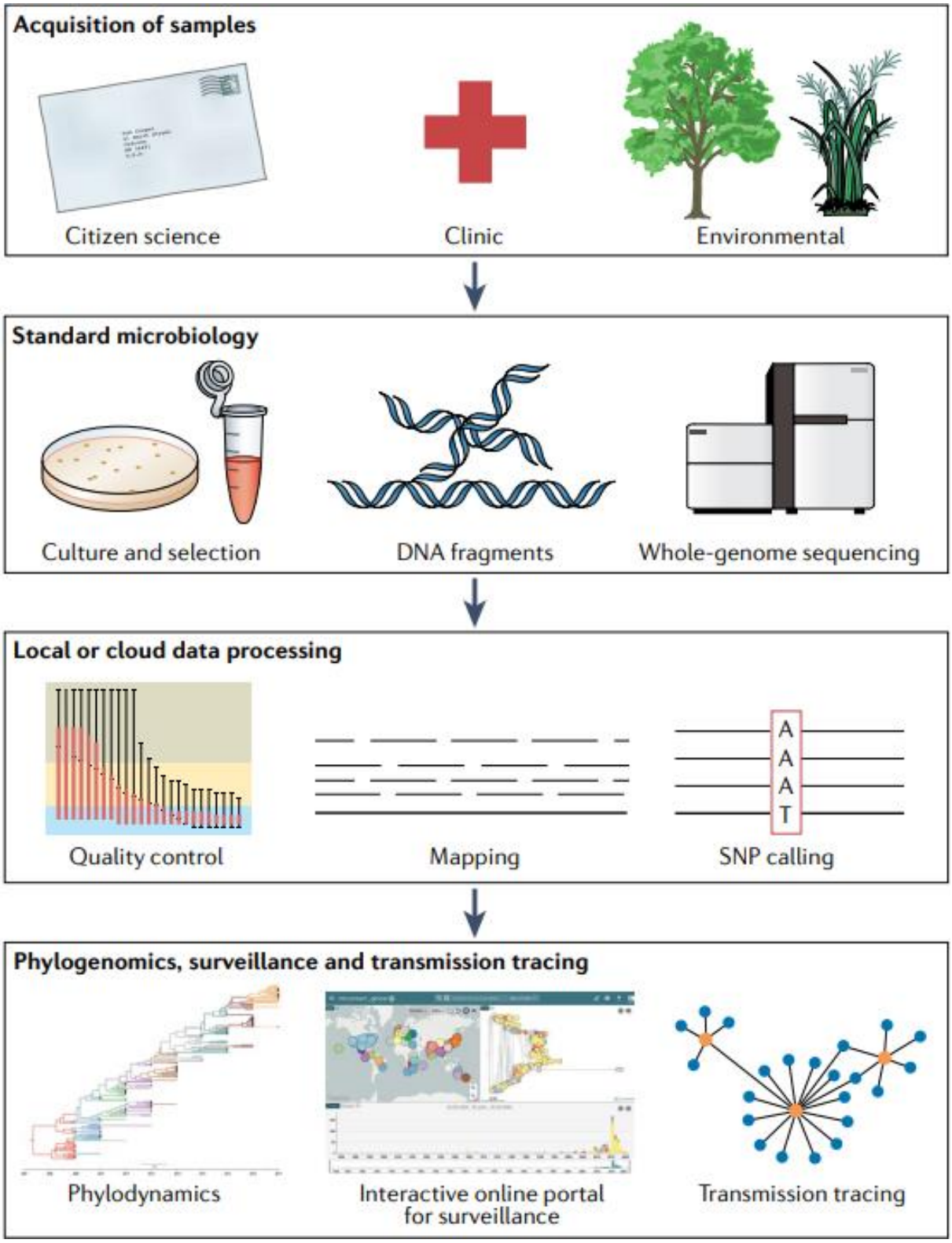

Figure 3. Resistance detection, tracking, and surveillance [56]

Resistance detection, combat, and surveillance

Fungal samples can be obtained from the environment or medical facilities, as well as by interacting with the public as "citizen scientists".[45] From these materials, traditional known microbiological techniques can cultivate and select isolates that are prepared for genomic DNA extraction. To create a sequencing library for whole genome sequencing (WGS), these DNA fragments are employed. There are numerous

technologies for sequencing that can produce both long-read and short-read sequence data. Before mapping to a reference genome, the raw sequencing data needs to be quality-controlled, either locally or using cloud computing. High-confidence single nucleotide polymorphisms (SNPs) can be used to deduce the evolutionary origins of alleles linked to drug resistance. Tracing transmission episodes is made possible by phylodynamic inference and the creation of interactive Internet portals (such as Nextstrain [46] or Microreact [47]) that are accessible to academics and physicians.
[Figure 3]

CONCLUSION

Fungal infections are a growing global public health concern, particularly among critically ill and immunosuppressed patients. Anthropological environmental factors contribute to the global expansion of both the incidence and geographic range of fungal infections. Because of the rapid emergence of antifungal resistance and a lack of access to effective diagnostic and treatment options, fungi pose a growing and unpredictable threat to global health. This document makes recommendations for policymakers, public health experts, and other stakeholders to improve the response to these fungal infections, including limiting the development of antifungal drug resistance. Despite increasing concern, fungal infections receive little attention and funding, patients have limited access to quality diagnostics and treatment, and there is an absence of high-quality information on the prevalence of fungal diseases.

Conflict Of Interest

The authors declare that there are no conflicts of interest.

Funding statement

This work did not receive specific grants from funding agencies in the public, commercial or nonprofit sectors.

Author Contributions

AmG: Conceptualization; methodology; resources; data curation; validation; visualization; project administration; writing - original draft. AbG: Conceptualization; methodology; data curation; investigation; supervision; validation; visualization; writing - review and editing. Both authors read and approved the final version of the manuscript.

Data availability statement

The data presented in this study are available within the article.

Declaration of Use of AI in Scientific Writing

None.

REFERENCES

1. Garvey M, Meade E, Rowan NJ. Effectiveness of front line and emerging fungal disease prevention and control interventions and opportunities to address appropriate eco-sustainable solutions. Sci Total Environ 2022;851(Pt 2):158284. https://doi.org/10.1016/j.scitotenv.2022.158284.
2. Rayens E, Norris KA, editors. Prevalence and healthcare burden of fungal infections in the United States, 2018. Open Forum Infect Dis 2022;9:ofab593. doi: 10.1093/ofid/ofab593.
3. Su H, Han L, Huang X. Potential targets for the development of new antifungal drugs. J Antibiot (Tokyo) 2018;71:978-991. doi: 10.1038/s41429-018-0100-9.
4. Garvey M, Rowan NJ. Pathogenic drug resistant fungi: a review of mitigation strategies. Int J Mol Sci 2023;24:1584. doi: 10.3390/ijms24021584.
5. Bongomin F, Gago S, Oladele RO, Denning DW. Global and multi-national prevalence of fungal diseases—estimate precision. J Fungi (Basel) 2017;3:57. doi: 10.3390/jof3040057.
6. Huang J, Liu C, Zheng X. Clinical features of invasive fungal disease in children with no underlying disease. Sci Rep 2022;12:208. doi: 10.1038/s41598-021-03099-w.
7. Oliveira M, Oliveira D, Lisboa C, Boechat JL, Delgado L. Clinical manifestations of human exposure to fungi. . J Fungi (Basel) 2023;9:381. doi: 10.3390/jof9030381.
8. Firacative C. Invasive fungal disease in humans: are we aware of the real impact? Mem Inst Oswaldo Cruz 2020;115:e200430. doi: 10.1590/0074-02760200430.
9. Xu L, Chen B, Wang F, et al. A higher rate of pulmonary fungal infection in chronic obstructive pulmonary disease patients with influenza in a large tertiary hospital. Respiration 2019;98:391-400. https://doi.org/10.1159/000501410.
10. Hoenigl M, Seidel D, Sprute R, et al. COVID-19-associated fungal infections. Nature Microbiol 2022;7:1127-40. https://doi.org/10.1038/s41564-022-01172-2.
11. Ekeng BE, Davies AA, Osaigbovo II, Warris A, Oladele RO, Denning DW. Pulmonary and extrapulmonary manifestations of fungal infections misdiagnosed as tuberculosis: the need

for prompt diagnosis and management. J Fungi 2022;8:460. https://doi.org/10.3390/jof8050460.
12. Hughes KM, Price D, Torriero AA, Symonds MR, Suphioglu C. Impact of fungal spores on asthma prevalence and hospitalization. Int J Mol Sci 2022;23:4313. https://doi.org/10.3390/ijms23084313.
13. Verma N, Singh S, Singh M, et al. Global epidemiological burden of fungal infections in cirrhosis patients: a systematic review with meta-analysis. Mycoses 2022;65:266-84. https://doi.org/10.1111/myc.13387.
14. Ruhnke M, Cornely OA, Schmidt-Hieber M, et al. Treatment of invasive fungal diseases in cancer patients—Revised 2019 Recommendations of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO). Mycoses 2020;63:653-82. https://doi.org/10.1111/myc.13082.
15. Lao M, Li C, Li J, Chen D, Ding M, Gong Y. Opportunistic invasive fungal disease in patients with type 2 diabetes mellitus from Southern China: clinical features and associated factors. J Diabetes Investig 2020;11:731-44. doi: 10.1111/jdi.13183.
16. Schwarz C, Eschenhagen P, Bouchara J. Emerging fungal threats in cystic fibrosis. Mycopathologia 2021;186:639-53. https://doi.org/10.1007/s11046-021-00574-w.
17. Hosseini-Moghaddam SM, Ouédraogo A, Naylor KL, et al. Incidence and outcomes of invasive fungal infection among solid organ transplant recipients: a population-based cohort study. Transpl Infect Dis 2020;22:e13250. doi: 10.1111/tid.13250.
18. Konsoula A, Tsioutis C, Markaki I, Papadakis M, Agouridis AP, Spernovasilis N. *Lomentospora prolificans:* an emerging opportunistic fungal pathogen. Microorganisms 2022;10:1317. https://doi.org/10.3390/microorganisms10071317.
19. Spallone A, Schwartz IS. Emerging fungal infections. Infect Dis Clin North Am 2021;35:261-77. doi: 10.1016/j.idc.2021.03.014.
20. Gow NAR, Johnson C, Berman J, et al. The importance of antimicrobial resistance in medical mycology. Nat Commun 2022;13:5352. doi: 10.1038/s41467-022-32249-5.
21. Alastruey-Izquierdo A. WHO fungal priority pathogens list to guide research, development and public health action. Geneva: World Health Organization; 2022.
22. Parums DV. Editorial: The World Health Organization (WHO) fungal priority pathogens list in response to emerging fungal pathogens during the COVID-19 pandemic. Med Sci Monit 2022;28:e939088. doi: 10.12659/MSM.939088.
23. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.
24. Lin YY, Shiau S, Fang CT. Risk factors for invasive *Cryptococcus neoformans* diseases: a case-control study. PloS One 2015;10:e0119090. https://doi.org/10.1371/journal.pone.0119090.
25. Calvo B, Melo AS, Perozo-Mena A, et al. First report of *Candida auris* in America: clinical and microbiological aspects of 18 episodes of candidemia. J Infect 2016;73:369-74. https://doi.org/10.1016/j.jinf.2016.07.008.
26. Chowdhary A, Sharma C, Meis JF. *Candida auris*: a rapidly emerging cause of hospital-acquired multidrug-resistant fungal infections globally. PLoS Pathogens 2017;13:e1006290. https://doi.org/10.1371/journal.ppat.1006290.
27. Lockhart SR, Etienne KA, Vallabhaneni S, et al. Simultaneous emergence of multidrug-resistant *Candida auris* on 3 continents confirmed by whole-genome sequencing and epidemiological analyses. Clin Infect Dis 2017;64:134-40. https://doi.org/10.1093/cid/ciw691.
28. Zhou D, Korfanty GA, Mo M, et al. Extensive genetic diversity and widespread azole resistance in greenhouse populations of *Aspergillus fumigatus* in Yunnan, China. mSphere. 2021;6:e00066-21. doi: 10.1128/mSphere.00066-21.
29. Rhodes J, Abdolrasouli A, Dunne K, et al. Population genomics confirms acquisition of drug-resistant *Aspergillus fumigatus* infection by humans from the environment. Nature Microbiol 2022;7:663-74. https://doi.org/10.1038/s41564-022-01091-2.
30. Talapko J, Juzbašić M, Matijević T, et al. *Candida albicans*—the virulence factors and clinical manifestations of infection. J Fungi 2021;7:79. https://doi.org/10.3390/jof7020079.
31. Denning DW. Antifungal drug resistance: an update. Eur J Hosp Pharm 2022 ;29:109-12. doi: 10.1136/ejhpharm-2020-002604.
32. Denning DW, Perlin DS, Muldoon EG, et al. Delivering on antimicrobial resistance agenda not possible without improving fungal diagnostic capabilities. Emerg Infect Dis 2017 ;23:177-83. doi: 10.3201/eid2302.152042.
33. Rodrigues AM, Beale MA, Hagen F, et al. The global epidemiology of emerging *Histoplasma* species in recent years. Stud Mycol 2020;97:100095. doi: 10.1016/j.simyco.2020.02.001.
34. Brown GD, Denning DW, Gow NA, Levitz SM, Netea MG, White TC. Hidden killers: human fungal infections. Sci Transl Med 2012;4:165rv13. doi: 10.1126/scitranslmed.3004404.
35. Tlamçani Z, Er-Rami M. Fungal opportunist infection: common and emerging fungi in immunocompromised patients. J Immunol Tech Infect Dis 2013;2:2-7.
36. Trofa D, Gácser A, Nosanchuk JD. *Candida parapsilosis*, an emerging fungal pathogen. Clin

Microbiol Rev 2008;21:606-25. https://doi.org/10.1128/CMR.00013-08.
37. Tóth R, Nosek J, Mora-Montes HM, et al. *Candida parapsilosis*: from genes to the bedside. Clin Microbiol Rev 2019;32:10.1128/cmr. 00111-18. https://doi.org/10.1128/CMR.00111-18
38. Bateman M, Oladele R, Kolls JK. Diagnosing *Pneumocystis jirovecii* pneumonia: a review of current methods and novel approaches. Med Mycol 2020;58:1015-28. https://doi.org/10.1093/mmy/myaa024.
39. Ivanov M, Ćirić A, Stojković D. Emerging antifungal targets and strategies. Int J Mol Sci 2022;23:2756. doi: 10.3390/ijms23052756.
40. Kaur J, Nobile CJ. Antifungal drug-resistance mechanisms in *Candida* biofilms. Curr Opin Microbiol 2023;71:102237. doi: 10.1016/j.mib.2022.102237.
41. Branco J, Miranda IM, Rodrigues AG. *Candida parapsilosis* virulence and antifungal resistance mechanisms: a comprehensive review of key determinants. J Fungi 2023;9:80. https://doi.org/10.3390/jof9010080.
42. Angiolella L. Virulence regulation and drug-resistance mechanism of fungal infection. Microorganisms 2022;10:409. doi: 10.3390/microorganisms10020409.
43. Heffernan C. Climate change and multiple emerging infectious diseases. Vet J 2018;234:43-7. doi: 10.1016/j.tvjl.2017.12.021.
44. Fisher MC, Hawkins NJ, Sanglard D, Gurr SJ. Worldwide emergence of resistance to antifungal drugs challenges human health and food security. Science 2018;360:739-42. https://doi.org/10.1126/science.aap7999.
45. Shelton JM, Fisher MC, Singer AC. Campaign-based citizen science for environmental mycology: the "science solstice" and "summer soil-stice" projects to assess drug resistance in air and soilborne *Aspergillus fumigatus*. bioRxiv 2020:2020.06. 11.146241. https://doi.org/10.1101/2020.06.11.146241.
46. Hadfield J, Megill C, Bell SM, et al. Nextstrain: real-time tracking of pathogen evolution. Bioinformatics 2018;34:4121-3. https://doi.org/10.1093/bioinformatics/bty407.
47. Argimón S, Abudahab K, Goater RJ, et al. Microreact: visualizing and sharing data for genomic epidemiology and phylogeography. Microb Genom 2016;2:e000093. https://doi.org/10.1099/mgen.0.000093.
48. Rudramurthy SM, Chakrabarti A, Paul RA, et al. *Candida auris* candidaemia in Indian ICUs: analysis of risk factors. J Antimicrob Chemother 2017;72:1794-801. doi: 10.1093/jac/dkx034.
49. van der Linden JW, Snelders E, Kampinga GA, et al. Clinical implications of azole resistance in Aspergillus fumigatus, The Netherlands, 2007–2009. Emerg Infect Dis 2011;17:1846. https://doi.org/10.3201/eid1710.110226.
50. Srinivasan A, Lopez-Ribot JL, Ramasubramanian AK. Overcoming antifungal resistance. Drug Discov Today Technol 2014;11:65-71. doi: 10.1016/j.ddtec.2014.02.005.
51. Mathé L, Van Dijck P. Recent insights into Candida albicans biofilm resistance mechanisms. Curr Genet 2013;59:251-64. doi: 10.1007/s00294-013-0400-3.
52. Lupetti A, Danesi R, Campa M, Del Tacca M, Kelly S. Molecular basis of resistance to azole antifungals. Trends Mol Med 2002 ;8:76-81. doi: 10.1016/s1471-4914(02)02280-3.
53. Perlin DS. Resistance to echinocandin-class antifungal drugs. Drug Resist Updat 2007;10:121-30. doi: 10.1016/j.drup.2007.04.002.
54. Ryder N, Leitner I. Synergistic interaction of terbinafine with triazoles or amphotericin B against Aspergillus species. Med Mycol 2001;39:91-5. https://doi.org/10.1080/mmy.39.1.91.95.
55. Perlin DS. Current perspectives on echinocandin class drugs. Future Microbiol 2011;6:441-57. https://doi.org/10.2217/fmb.11.19.
56. Fisher MC, Alastruey-Izquierdo A, Berman J, et al. Tackling the emerging threat of antifungal resistance to human health. Nat Rev Microbiol 2022;20:557-71. https://doi.org/10.1038/s41579-022-00720-1.