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

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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 comorbidities 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. Globally, they are responsible for more than 13 million infections and 1.5 million deaths per year. 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). 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.

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. 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. Additionally, infectious diseases such as influenza, COVID-19, and tuberculosis as well as chronic conditions or co-morbidities such as asthma, cirrhosis, cancer, diabetes, cystic fibrosis (CF), transplant recipients, and chronic obstructive pulmonary disease (COPD) 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. The increasing incidence of fungal morbidity and mortality is directly associated with antifungal resistance, tolerance to antifungal drugs, and biofilm formation. Antifungal tolerance is the emergence of partial growth after 24 hours that can be shown in susceptibility tests, including at inhibitory drug concentrations. 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.

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.

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.
Emerging and re-emerging fungal pathogens

**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).\(^{28,29}\)

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

Records identified from:
- Databases (n = 412)
- Registers (n = 73)
- Other sources (n = 15)

Records removed before screening:
- Duplicate records removed (n = 88)
- Records marked as ineligible by automation tools (n = 15)
- Records removed for out of scope (n = 10)

Records screened (n = 387)

Reports sought for retrieval (n = 277)

Reports excluded after title and abstract screening (n = 110)

Reports assessed for eligibility (n = 194)

Reports not retrieved (n = 83)

Reports excluded:
- Conference proceedings (n = 5)
- Correspondence (n = 3)
- Letter to editor (n = 4)
- Not meeting all inclusion criteria (n = 166)

Studies included in systematic review (n = 16)
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 (e.g., 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

<table>
<thead>
<tr>
<th>Fungal pathogens and Ref.</th>
<th>Associated disease</th>
<th>Affected organs or systems</th>
<th>Treatment options</th>
<th>Antifungal resistance data</th>
</tr>
</thead>
</table>
| *Cryptococcus neoformans*\(^{(5,34)}\) | Cryptococcosis | o Lungs  
o Central nervous system (cryptococcal meningitis)  
o Blood (cryptococccemia) | ✓ Fluconazole  
✓ Amphotericin B in combination with flucytosine (severe cases) | • Unknown |
| *Candida auris*\(^{(25,26,48)}\) | Invasive candidiasis | o Blood (candidemia)  
o Heart  
o Central nervous system  
o Eyes  
o Bones  
o Internal organs  
o Respiratory system  
o Central nervous system | ✓ Echinocandins | • Fluconazole  
• Amphotericin B  
• Echinocandins |
| *Aspergillus fumigatus*\(^{(5,29,34,49)}\) | Invasive aspergillosis | o Human microbiota (mouth, throat, gut, vagina, and skin)  
o Blood (candidemia), heart, central nervous system, eyes, bones, and internal organs | ✓ Liposomal amphotericin B | • Unknown |
| *Candida albicans*\(^{(31,32,34)}\) | Oropharyngeal candidiasis  
Esophageal candidiasis  
Vulvovaginal candidiasis  
Cutaneous candidiasis  
Invasive candidiasis | | ✓ Echinocandins | • Unknown |
| *Nakaseomyces glabrata* (Candida glabrata)\(^{(31,32)}\) | Invasive candidiasis | o Blood (candidemia), heart, central nervous system, eyes, bones and/or internal organs | ✓ Echinocandins | • Unknown |
| *Histoplasma spp.*\(^{(22,34)}\) | Histoplasmosis | o Lungs, central nervous system, blood, and other parts of the body | ✓ No medication (healthy patients)  
✓ Amphotericin B followed by itraconazole (severe cases) | • Moderate |
<table>
<thead>
<tr>
<th>Fungal Group</th>
<th>Antifungal Drug Resistance Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucorales (Rhizopus spp., Mucor spp., Lichtheimia spp., and others)</td>
<td>(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.</td>
</tr>
<tr>
<td>Fusarium spp.</td>
<td>Inherently resistant to fluconazole, voriconazole and echinocandins</td>
</tr>
<tr>
<td>Candida tropicalis</td>
<td>Fluconazole, Itraconazole, Voriconazole, Posaconazole</td>
</tr>
<tr>
<td>Candida parapsilosis</td>
<td>Moderate</td>
</tr>
<tr>
<td>Pichia kudriavzevi (Candida krusei)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Talaromyces marneffei</td>
<td>Low</td>
</tr>
<tr>
<td>Pneumocystis jirovecii</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

**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). 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,
Emerging and re-emerging fungal pathogens

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

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

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). Due to these factors, new fungal pathogens can emerge in human populations by coming into contact with naive hosts in their geographic niches. 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. 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

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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". 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
Emerging and re-emerging fungal pathogens

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.

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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.

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