Review Article

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Fungal Infections in Humans: An Emerging Threat

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Abstract

Fungal pathogens and infections are an increasing global public health concern. People most at risk are those with underlying health problems or a weakened immune system, such as chronic lung disease, prior tuberculosis (TB), HIV, cancer, and diabetes mellitus. According to researchers over 5.7 crore Indians are affected by serious fungal conditions; around 4.1% of the Indian population is probably affected, which is similar to reports from other countries like China, Brazil, Korea, Senegal, and Germany. Over 300 million people worldwide suffer from major fungal illnesses, which cause 1.6 million deaths yearly. The World Health Organisation Fungal Priority Pathogen List (FPPL) intends to concentrate and direct additional research and policy measures to boost the international response to fungal infections and antifungal resistance.

Keywords: Fungi; WHO; FPPL; Fungal resistance.

INTRODUCTION

Millions of people around the world are known to be affected by fungi related disorders and have significant impact on health. However, the epidemiology of fungal infections varies between geographical areas and is influenced by a number of variables, such as at-risk persons, socioeconomic features, and fungal endemicity associated to geo-ecological parameters. When utilized as food (e.g., mushrooms, yeast, etc.) and medications (e.g. penicillin), fungi can be safe and even beneficial. Nevertheless, because of their opportunistic nature, fungi can also cause infections, which can range in severity from unfavourable (yeast infection, ringworm/athlete's foot, etc.) to fatal (Aspergillosis, Mucormycosis, Histoplasmosis, etc.) infections. Over 300 million people worldwide suffer from major fungal illnesses, which cause 1.6 million deaths yearly,[1] making fungi pathogens one of the most significant dangers to global health. Unbelievably, fungi kill four times as many people as malaria and kill as many people as tuberculosis each year.[2] However, they are still a neglected topic by public health authorities for instance, invasive mycoses weren't widely recognized as medically significant infections until the 1980s.[3] The serious fungal infections in humans are associated with

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conditions such as corticosteroid therapy, organ transplantation, cancer, AIDS, asthma.[1]

FUNGAL PRIORITY PATHOGENS

In response to the rise in antimicrobial resistance, WHO created its first list of priority bacterial infections in 2017.[4] This list served as a catalyst for increased global action, including the investigation and creation of novel therapies. WHO has now created the first list of fungal priority pathogens[4], which was influenced by the BPPL (Bacterial Priority Pathogen List). The World Health Organisation Fungal Priority Pathogen List (WHO FPPL) is the first global initiative to systematically prioritize fungal diseases, taking into accounts their unmet research and development requirements and perceived importance for public health. The WHO FPPL intends to concentrate and direct additional research and policy measures to boost the international response to fungal infections and antifungal resistance. The list was created using a multi-criteria decision analysis (MCDA) methodology. The prioritization process focused on fungal pathogens that can cause invasive acute and sub acute systemic fungal infections for which drug resistance or other treatment and management challenges exist. The pathogens included were ranked, then categorized into three priority groups like critical, high, and medium (Table 1).

Table 1: List of Fungal Priority Pathogens Categorized by WHO[4]

Critical group	High group	Medium group
Cryptococcus neoformans	Nakaseomyces glabrata	Scedosporium spp
Candida auris	Histoplasma spp	Lomentospora prolificans
Aspergillus fumigatus	Eumycetoma causative agents	Coccidioides spp
Candida albicans	Mucorales	Pichia kudriavzeveii (Candida krusei)
	Fusarium spp	Cryptococcus gattii
	Candida tropicalis	Talaromyces marneffei
	Candida parapsilosis	Pneumocystis jirovecii
		Paracoccidioides spp.

Fungal Infection Burden in India

India is the second most populous country in the world and the seventh-largest country by land area. This tropical country has unique and diverse geographical characteristics, with mountains, plains, plateaus, and numerous rivers, in addition to being surrounded on three sides by vast stretches of ocean. Many fungal infections are endemic in India. Recently experimenters from All India Institute of Medical Sciences (AIIMS), New Delhi, AIIMS Kalyani, West Bengal, and Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, along with The University of Manchester, UK, estimate over 5.7 crore Indians are affected by serious fungal conditions. Around 4.1% of the Indian population is probably affected, which is similar to reports from other countries like China, Brazil, Korea, Senegal, and Germany.[5] This total burden of serious fungal infections is >10 times the annual incidence of tuberculosis in India, indicating an enormous population of patients affected by fungal diseases.[6] The various type of serious fungal infections are summarized in following cases (Table 2).

Table 2: Different Fungal Infections with number of cases in India[6]

Infection	Total no. of Cases	Rate / 100000 Population
RVCC	24370566	1749
IA	250935	18
CPA	1738913	125
SAFS	1363142	97.8
ABPA	1197913	86.0
Fungal rhinosinusitis	1518005	109
Mucormycosis	195076	14.0
Candidemia	188035	13.5
Candida peritonitis ICU + Surgery	18803	1.35
Candida peritonitis CAPD	85	0.004
Esophageal candidiasis	266612	19.1
Cryptococcal meningitis	11526	0.83
Pneumocystis pneumonia	58378	4.19
Talaromycosis	2825	0.2
Fungal keratitis	1017182	73.0
Tinea capitis	25053332	1798
Total Serious Fungal Infection	57251328	4109

RVCC (*Recurrent vulvovaginal candidiasis*), **IA** (*Invasive aspergillosis*), **CPA** (*Chronic pulmonary aspergillosis*), **ABPA** (*Allergic bronchopulmonary aspergillosis*), **SAFS** (*Severe asthma with fungal sensitization)*, **CAPD** *(chronic ambulatory pulmonary dialysis)*

Factors Contribute to the Rise in the Burden of Fungal Infections

Some of the factors that contribute to the rise in the burden of fungal infections are well understood. Major contributors are, shape shifting in a warming world, antifungal resistance, lack of knowledge resources, and lack of coordination.[7]

1) Shape shifting in a Warming World

There are some fungi that have lived peacefully with humans as part of their microbiome but are now becoming invasive. One such is the *Candida* species, which lives on moist surfaces like the mucosa of the gut, mouth, vagina, and skin in humans and causes superficial dermatophyte infection.[8] Climate change directly impacts the ability of fungi to cause damage to the human host. Recently, the multi-resistant pathogen *Candida auris* has emerged as a serious global threat to human health, causing infections resistant to all major classes of antifungal drugs in immuno-compromised patients.[9] *Candida auris* differs from most other Candida species in several aspects. it is hypothesized to have a nonhuman environmental reservoir with possible dispersal by birds. This yeast is considered as the first "novel" pathogen to have evolved in response to climate change[10], although this remains speculative and awaits conclusive substantiation. The indispensable suppositions for its emergence include expanded farming and aquaculture which increased the contact with humans, and contaminate the environment with fungicides. *Candida auris* is particularly problematic in healthcare settings where it colonizes and spreads to cause nosocomial outbreaks, and it is remarkably resistant to antifungals and disinfectants.

2) Antifungal Resistance

The fungicide overuse in agriculture, overuse and over prescription of antifungals in healthcare, and failure of patients to finish the entire course of antifungal treatments led to the development of resistance in fungi. Fungal genomes are relatively small compared to animals and plants and, hence, can acquire mutations easily. However, when it comes to drug discovery, it is important to understand that very few antifungals actually can be used as therapeutics. This is because fungi are eukaryotes, and many of the cellular targets overlap with the cellular machinery of their hosts. Notably, this is in contrast to the unique cellular targets presented by bacteria. To further complicate this issue, fungicides are regularly overused in agriculture to treat crops and livestock. As humans and animals end up consuming antifungals as medicines, they might also inhale/ingest fungal spores from the environment, thus disrupting the microbiome by tampering with the equilibrium and potentially prompting the evolution of resistance. Further, the tendency to not finish the antifungal course and improper disposal of drugs are also key drivers of resistance. Inadequate dosing may facilitate selective pressure that drives the evolution of the very fungi being targeted for treatment.[11]

3) Lack of Knowledge and Resources

Lack of knowledge among health care professionals and diagnostic tools also appears to be contributing to the load of invasive fungal infections. At nearly 40% of *candida auris* is very high and there is little awareness among clinicians about it.[12] Some of fungal diseases resemble bacterial infections, mostly seen with *Mycobacterium tuberculosis* and *Aspergillus* spp. *Aspergillus* infection is misdiagnosed as TB, those who have recovered from TB are susceptible to *Aspergillus* because of scars in the lungs.[13] The availability of mycology laboratories in India is abysmal. Every state needs at least one for fungal disease. Currently, there are only 9 such laboratories in India. The first one was established in the PGIMER, Chandigarh in 1996 with the support of the Indian Council of Medical Research. This is also the WHO collaborating centre.[8]

4) Lack of Coordination

A specific assessment of the prevalence and incidence of each fungal infection worldwide is unclear due to a lack of cooperation between national and international institutions, and statistics are scarce in the majority of nations, particularly in the developing world.[14] In comparison to financing for other infectious diseases that generate comparable mortality, research funding for fungi infections is certainly modest. For instance, research on the fifth deadliest infectious disease, cryptococcal meningitis, receives 4.3 times less funding than the illness brought on by the bacterial infection Neisseria meningitis.[15] Knowledge generation is directly impacted by decreased funding for fungal disease research and innovation. For instance, 8,827 and 5,687 scientific articles, focused and published on tuberculosis and malaria in 2017, respectively. Fungal diseases, on the other hand, were much less investigated, with 213 papers on cryptococcosis, 80 on Para coccidioidomycosis,

51 on chromoblastomycosis, 53 on mycetoma, and 56 on sporotrichosis produced in the same period.[15] These figures are presumably linked to intimidating data, similar as the forenamed lack of vaccines able to prevent fungal disease, less effective diagnostics, and a dearth of anti-fungal medicines in development.

Challenges to Antifungal Drug Development

Increased antifungal resistance leads to the reduced efficacy of fungal disease treatments. At the patient level, treatment failure may translate to prolonged infection or even death. As a result, scientists are actively searching for new drug candidates, but several factors challenge antifungal drug development in ways that are unique from other antimicrobials. The major problem lies with the similarity in human and fungal genomes, for example, it is suggested that common brewer's yeast (*Saccharomyces cerevisiae*) has about 30% human like proteins, making it one of the most similar lower eukaryotes to humans.[16] This means that some drugs and drug doses can be harmful to humans due to similar enzymes and metabolic pathways. It can be difficult to identify fungal species through conventional laboratory methods. For example, *Candida auris* is often misidentified as other Candida species, which make infections onerous to treat and/or result in faulty treatment. Several fungi exist as part of the normal microbiota and act as opportunistic pathogens, primarily in immuno-compromised patients. That means that most of the time, the fungi won't be problematic, and developing treatments for the unique conditions in which they do cause infection requires additional consideration.[11]

Strategies to Control Fungal Infections in Human Beings

A growing hazard to public health comes from resistant fungus. Everyone has a part in contributing in preventing resistant fungal diseases, including researchers, medical professionals, and the general public.[17]

Prevention increases your ability to stop and treat infections that are resistant to antifungals and healthcare associated infections. By collaborating with the public, business, and medical professionals, you may encourage responsible usage of antifungals may be encouraged. One health surveillance system expands testing and monitoring capabilities for antifungal resistance and discovers trends and patterns in healthcare and agricultural settings by cooperating with federal and state agencies. The awareness of the numerous variables that lead to the emergence, transmission, and ongoing existence of infections that are resistant to antifungals need improvement. The advanced diagnostic and laboratory facilities to diagnose antifungal resistant infections and to enhance surveillance, infection control, and treatment choices, novel laboratory tests and clinical diagnostics should be created and validated. Collaboration between nations working with global partners to identify, stop, and manage fungi that are resistant to antifungals anywhere in the world should be strengthened.[17]

Recent Initiatives for Control of Fungal Infections

To raise awareness of the value of antifungal stewardship, reducing antifungal drug resistance, and identifying serious fungal diseases early enough in the course of a patient's illness to provide lifesaving treatment, the CDC and partners created fungal awareness week, which is observed in early October.[17] The UK government released its plan in January 2019 for AMR to be contained and under control by 2040. The vision acknowledges that an issue as large and complex as AMR requires a long-term strategy that steadily improves our comprehension of AMR and what controls it. The Department is funding basic and applied research in India's Infectious Disease Biology-1 (Bacterial and Fungal Diseases) course to better understand and eventually offer solutions for therapeutics, diagnostics, and preventive measures for infectious diseases caused by bacterial and fungal pathogens, including areas of global concern like Tuberculosis (including MDR and XDR TB) and AMR (Anti-Microbial Resistance).

CONCLUSION

Fungal infections frequently go undetected. They are among the most challenging disorders to treat, even after being discovered. They are now stealthily expanding around the world, preying on people's weakening immune systems and exploiting the high prevalence of diabetes. The necessity for public health initiatives to lower the frequency and mortality of various infectious diseases is highlighted by the understanding that fungi infections play a significant role in the mortality of a number of ailments. Focusing on enhancing diagnostics is a clinical requirement just as crucial as developing novel antifungal

medications because a late diagnosis is associated with a poor outcome. Additionally, it is vitally necessary to create diagnostic tests that are affordable and transportable to low-income nations in field hospital settings.

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