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The Evolution of Fungal Infections in the 21st Century

I. Introduction

Fungal infections can be traced back as far as thousands of years ago. Due to the lack of understanding towards it in the past, diagnosis and treatment were difficult. Thanks to the advancement of technology, scientists and doctors were able to learn more about the field of mycology, which, in turn, allowed for earlier and better identification and treatment of fungal infections.

Despite so, research in fungal infections is still found to be lacking, especially when compared to bacterial, viral and even parasitic research, even when the mortality rate for fungal infections tends to be higher than that of bacterial infections (Greener, 2022). A study in 2024 showed that the mortality rate by fungal infection on the liver was 93%, which was significantly more severe than the 52% mortality rate by bacterial infection (Khan et al., 2024). Furthermore, due to various important historical events throughout the 21st century, fungal diseases are secretly on the rise, while the public may still be unaware of it. Other than climate change and global warming expanding the geographical ranges for fungal growth, the COVID-19 pandemic also assisted opportunistic fungal pathogens in infecting humans, and our current counter-measurements towards fungal diseases are looking less and less effective due to overuse of drugs and fungal mutations.

Therefore, this article aims to point out the status of our battle with fungal diseases and how recent events made it even more challenging for scientists to treat them, in hopes to bring more attention to the rising threat of invasive fungal infections.

II. Literature Review

(i) COVID-19-Associated Fungal Infections

Before COVID-19, fungal infections were caused by weaker immune systems, either due to age, genetics or even post-surgery recovery, or long-time exposure to moldy environments. Fungal pathogens are mostly opportunistic, so the occasional news of fungal infection cases usually does not attract much attention.

In 2019, COVID-19 was first detected and was declared by the World Health Organization (WHO) as a pandemic outbreak in 2020. It is a virus

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that mainly attacks the respiratory system, while also resulting in other body health issues. As of 3rd August 2025, there are a total of 778 million cases reported to WHO (WHO, 2025). While COVID-19 victims were fighting against the virus, unexpectedly, they could also be affected by different fungal infections.

In general, there are three main types of COVID-1-associated fungal infections: COVID-19-associated pulmonary aspergillosis (CAPA), COVID-19-associated mucormycosis (CAM) and COVID-19-associated candidiasis (CAC) (Figure 1).

CAPA, in particularly, was the most prevalant type, estimating to make up for 10% of the COVID-19 patients (Martin et al., 2022). During the early stages of the pandemic, direct medical examination in the airway was rarely done to minimize the risk of COVID-19 transmission, but this also means that the detection of CAPA was easily missed as aspergillosis mainly targets the respiratory system, similar to COVID-19. Other clinical methods, such as blood tests, also lacked the sensitivity to detect CAPA. *Aspergillus fumigatus* is an infamous member within the *Aspergillus* genus known for its higher resistance to common antifungal treatments and was the major common cause for CAPA. Furthermore, late detection of CAPA usually results in an almost 80% death rate (Martin et al., 2022). The above

	CAPA	CAM	CAC
Prevalence	Prevalence about 10% among invasively ventilated patients with COVID-19[4]	Prevalence of 0.27% among hospitalized patients with COVID-19 in India[15]; limited evidence from Europe suggests prevalence about 1–2% among invasively ventilated patients with COVID-19 (ref. [14])	Unknown; outbreaks reported from 12 countries in the Americas, Europe and Middle East[18,52]
Infectious agents (!, of particular concern)	*A. fumigatus* predominant[4]! Azole-resistant *A. fumigatus*	*Rhizopus* spp. predominant[14,16]	*C. albicans* predominant[53]! *C. auris*
Sites of infection	Lungs[21]	ROM, ROCM[14,16] Pulmonary[14] Gastrointestinal[14] Disseminated[14]	Bloodstream[52] Abdomen
Therapy	Voriconazole or isavuconazole as first-line treatment for possible, probable and proven CAPA[21] Liposomal amphotericin B, posaconazole or echinocandins as second line[21]	Surgical debridement[14] Liposomal amphotericin B[14] If renal compromise, intravenous isavuconazole or intravenous posaconazole[48]	Caspofungin or micafungin as first line[52,53] Liposomal amphotericin B as second line[53]
Challenges	Reluctance to perform aerosol-generating procedures, such as autopsies and bronchoscopies Azole-resistant aspergillosis awareness (not tested if not suspected)	Diagnostics in ICU setting (BAL, gut biopsy)[14] Reluctance to perform aerosol-generating procedures, such as autopsies and bronchoscopies, awareness (not tested if not suspected)	High rate of multidrug resistance for *C. auris*[18] Misleading identifications, ability to form biofilms, reluctance to perform autopsies

Figure 1. Summary of CAPA, CAM and CAC
Source: Hoenigl et al., 2022

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highlights the importance for medical officers to be aware of potential CAPA, so as to ensure patients can be provided with swift and precise treatment during their entire recovery period.

CAM, on the other hand, is an infection of fungal of the order *Mucorales*, such as *Rhizopus* sp., while under COVID-19 infections. It first gained attention in India, and the outbreak resulted in a mislabelling of the "black fungus" pandemic due to causing the victim's skin to appear black. Infection by the order *Mucorales* in India was originally high, even prior to the COVID-19 pandemic. The surge of this infection in India during the pandemic, especially during the second wave, was related to environmental factors and the overuse of drugs. It was estimated that the burden India suffers from CAM was around 70 times higher than other countries (Martin et al., 2022). However, this does not mean CAM was only an issue in India as CAM cases were also reported in Asia, Europe and even America (Martin et al., 2022). On the other hand, this could indicate that the severity and impact of CAM might be underestimated in other countries, creating an even larger gap between our understanding of CAM versus the reality.

CAC is an infection associated with the yeast species *Candida albicans*. Originally found in Japan in 2009, fungal infection cases involving this yeast have been increasing over the years globally, and it was first reported in a COVID-19 patient in February 2020 (Martin et al., 2022). Most members in the *Candida* family are known to effortlessly grow on various surfaces, including skin and ventilation surfaces, becoming one of the opportunistic yeast that risk causing additional infection on patients with a prolonged stay in hospitals. It is common for COVID-19 patients to be administered into the ICU (Intensive Care Unit) ward, so these patients may also be at risk to CAC. Studies have also shown that candida-associated infection were at least twice more likely within COVID -19 patients than non-COVID-19 patients (Martin et al., 2022), thus the potential complications of CAC should not be taken lightly.

(ii) Distribution Expansion

Climate change has been a common topic of discussion in the 21st century. The increase in global temperature has resulted in a plethora of impacts, including the shift in weather patterns and the rising sea levels. The thermal

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stress also pushed the evolution of all kinds of organisms to adapt to this new environment, including fungi.

The normal core temperature of the human body is roughly around 37.0°C (Geneva et al., 2019), and studies showed that starting from 30°C, for each 1°C increase in temperature, another 6% of fungal species cannot tolerate such temperatures (Robert & Casadevall, 2009). Therefore, it is likely that fungi did not originally adapt to environmental temperature that is similar to the temperature of the human body and only certain family or species of fungi, such as *Aspergillus* sp., would be considered as human pathogens (Seidel, 2024). However, with the global temperature rising every year, fungi are gradually encouraged to become more heat-resistant and adapt better to the hotter climate, inevitably allowing them to become opportunistic towards humans, leading to not only more fungal infection cases caused by heat-tolerant species, but also more reported infection cases by fungi that traditionally were not considered pathogenic. The stress adaptation to heat in fungi was actually observed in a study when studying the urban heat-island effect, where the dense tall buildings ended up trapping more heat in urban areas, and fungi sampled in the urban areas were found to be able to tolerate 2°C higher than the ones in the nearby rural area, despite being the same species (McLean, 2005).

There are already several examples of emerging pathogens. Fungi from the genus *Fusarium* was mostly associated with plant pathogens, and would only cause infections to humans who had particularly weaker immune system. However, in recently years, reported cases of eye and skin infection from *Fusarium* are slowly on the rise, especially in tropical regions (Cighir, A., 2023). *Candida auris*, another yeast species from the *Candida* genus, is another example of an emerging human pathogen that originated as a plant decomposer. Similar to the urban heat-island effect, researchers discovered that *C. auris* isolated from mammlian samples shown greater heat tolerant and grew faster compared to those isolated from the environment (McLean, 2005), further suggesting that strains of this species evolved to become human pathogens due to their adaptation towards heat.

There are many more species, other than those from *Fusarium* and *Candida* genus, that used to be considered as rare species that cause infection in humans

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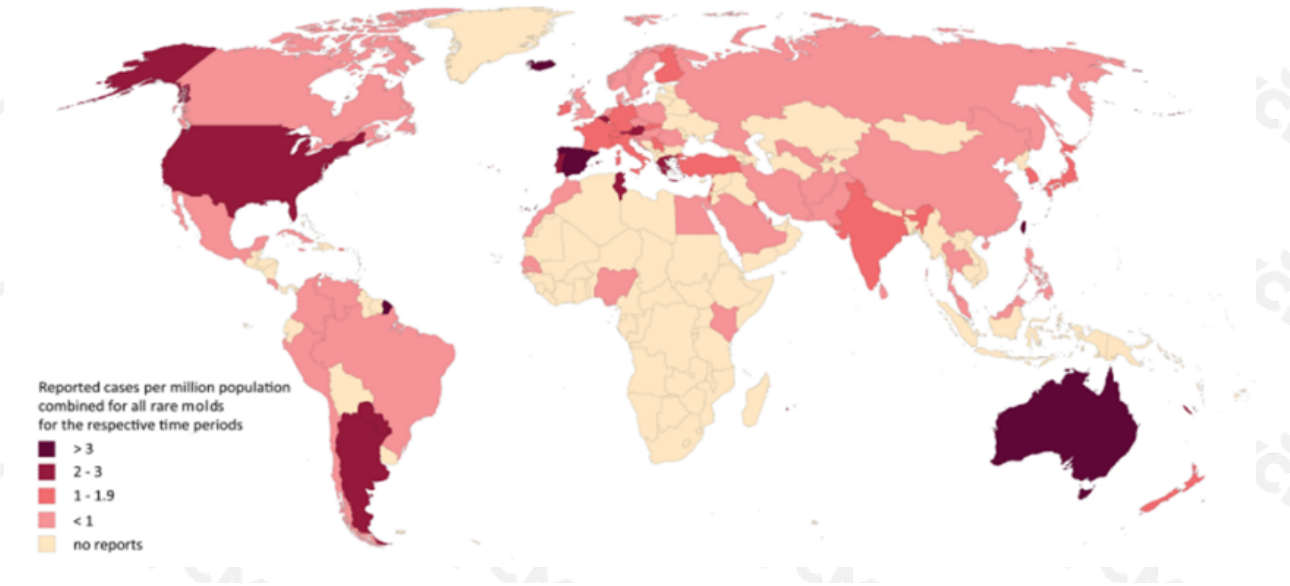

Figure 2. Distribution of Reported Rare Mold Infections
Source: Seidel et al., 2024

because of the lower occurrence frequency. However, a study in 2021 showed that several countries received more reported infection cases by these rare mold species, such as Australia, America, Argentina and France, in which for every 1 million population, there were more than 3 reported cases of rare mold infections (Sprute et al., 2023) (Figure 2). In order to combat the newly-evolved fungal pathogens, WHO established a priority list in 2022 that specifies fungal species that could pose a greater threat towards human health, including *C. auris* and *Fusarium oxysporum*, a species from the *Fusarium* genus that was mostly known as a banana pathogen. This list is the evidence of the collaborative effort with global researches to help direct and drive the future of fungal diseases to alleviate its burdens on mankind, but some scientists remarked on some of the limitations of this list, such as the lack of geographical considerations for different species and the potential geographical bias of survey participants (Casalini et al., 2024).

(iii) Greater Anti-fungal Drug Resistance

With the aid from WHO in the form of the fungal pathogen priority list, one of the most obvious solutions to counter fungal pathogens is to develop drugs against them, but this is easier said than done.

Antifungal agents can be classified based on how they neutralize fungal pathogens, commonly by how they

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destroy the cell membrane or cell wall (Fang et al., 2023). Amphotericin B deoxycholate (AMB-d) is one of the most commonly used treatments for several types of life-threatening fungal infections, including those by *Aspergillus* and *Candida* (Pate & Zito, 2025), but its effectiveness is reduced when used on specific species, such as *A. fumigatus* and *C. auris*. Even though the resistant trait of some *A. fumigatus* strains was already known in the past, there are reports showing that more infections by this species show resistance towards antifungal agents. A data survey dedicated towards this topic in Denmark found that the prevalance of resistance rose from 4.5% in 2007 and 2009 to 7.3% in 2018 (Risum et al., 2022), providing concrete evidence that fungal pathogens can become even more resistant and more widespread than before.

There are various mechanisms in how species attain their anti-fungal resistant abilities. Some fungal strains have the ability to reduce the drug concentration in their cells by producing more certain proteins that can actively remove the chemicals of the drug, lowering the effectiveness of treatment (Fang et al., 2023). Another similar method to reduce drug concentrations is by actively producing more of the target molecules that the drug targets. Strains of *A. fumigatus* is one of the reported species that resists AMB-d by expressing more of the gene Cyp51A (Fang et al., 2023). Since AMB-d can target protein with Cyp51A, the drug will bind with these target proteins to break them down, but *A. fumigatus* can produce more than the usual dose of AMB-d can bind to, effectively diluting the drug concentration and reducing its effectiveness.

It is also possible for a species to be resistant to multiple drugs. C. auris is not only invasive and widespread, but also resistant to most antifungal treatment, and some strains were even reported to be resistant to all currently available antifungals (Greener, 2022). These strains of fungi could be pushed to develop resistance due to overuse of the same treatment. Sometimes, treatment was still being administered to patients who could be infected, but were not diagnosed with infection yet, which can further provide opportunities for fungi to mutate and develop into a new strain that is resistant to it (Greener, 2022). Furthermore, these antifungal agents may not be limited to medical use only, as they can also be used as fungicide in agriculture (Fang et al., 2023), hence

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further increasing the risks of fungi developing resistance to current antifungal agents.

III. Conclusion

Although the advancement of technology has allowed us to discover more about the intricate nature of fungi, there are still plenty more that scientist do not know. With different stress factors promoting new opportunity and location for infection and even evolving into a new and resistant strain, the battle against the rising of fungal infection may be becoming even more difficult.

Hence, it is imparative for more researchers to acknowledge the importance of studying fungi and fungal infection. WHO's fungi pathogen priority list marks a significant development in our battle against fungal infections by providng a clear direction on which species are more urgent to work with, despite the possible bias of the data collected. However, this also indicated that there is a lack of centralized databases on fungal infection around the globe, even in developed countries such as the US (Rayens and Norris, 2022).

Awareness of fungal infections from both the medical field and the public is essential. Though the surge in reported cases was only observed recently, infection cases were only reported because the public was aware of potential symptoms and visited a medical facility, meaning it is entirely possible that the change already happened long ago and its impact has become widespread enough to be noticed. Thus, research in this area should be further hastened before the gap of our understanding on fungi widens even further than ever.

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