



# Green Fungus Challenges in Post-COVID Health Landscape

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## Abstract

The rise of green fungal illnesses, particularly Aspergillosis, poses a significant problem in the post-COVID-19 health environment. Patients who have COVID-19 and have weakened immune systems or extended hospital stays are most extensively affected by these illnesses. The epidemiology, clinical symptoms, intricate diagnostic processes, available treatment options, and prognostic factors related to infections with green fungi are all examined in this article. As countries negotiate the COVID-19 pandemic's recovery phase, it also addresses the broader implications for public health policy, resource allocation, and healthcare infrastructure. Given the essential nature of green fungus and its potential to worsen current healthcare expenses, immediate action is required to address the issues it poses. Raising awareness, refining surveillance, and collaborating across disciplines are crucial for managing and reducing the effects of green fungus on post-COVID health systems. Prioritizing these actions will allow healthcare stakeholders to better protect patient well-being and build resilience against emerging infectious risks in the aftermath of the COVID-19 catastrophe.

**Keywords:** COVID-19, Green fungus, Aspergillosis, spores

**Significance** | Fungal diseases, worsened by COVID-19, pose a global health threat, demanding improved diagnosis, treatment, and collaborative efforts for containment.

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## Introduction

Fungal diseases remain a significant medical issue, considering as a worldwide threat to human health, affecting close to one billion individuals. The use of immunosuppressive treatments in the context of cancer treatment or transplantation, the growing use of contemporary medical equipment, such as catheters and implants, and the use of broad-spectrum antibiotics contribute to the continued rise in invasive fungal infections. The COVID-19 pandemic has exacerbated the current predicament by predisposing patients to additional life-threatening fungal infections in intensive care units (ICUs), making accurate diagnosis challenging. Treatment for COVID-19 is made more difficult by the coexisting respiratory symptoms. In COVID-19 patients, a prolonged hospital stay, the possibility of needing mechanical ventilation, lymphopenia, leukopenia, and a systemic hyperinflammatory response all contribute to the proliferation of fungus (Arastehfar et al., 2020). Furthermore, the World Health Organization (WHO) COVID-19 treatment guidelines recommend empirically prescribed broad-spectrum antibiotics to address potential bacterial co-infections, but only in cases of severe COVID-19 patients (World Health Organization, 2021). Most significant fungal illnesses are caused by one of four main causal organisms: *Aspergillus*, *Candida*, *Mucorales*, and *Cryptococcus*.

Although the mortality rate from fungal healthcare-associated invasive infections is unacceptably high, the number of deaths is probably underestimated because of inadequate epidemiological data and incorrect diagnoses (Bongomin et al., 2017). Invasive fungal infections cause significant clinical mortality and economic hardship, prompting extensive use of antifungal medications. Reducing morbidity and mortality from fungal infections requires

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antifungal therapy and prophylactic. However, the efficiency of restricted systemic antifungal medications has changed due to selective drug pressure, leading to less predictable antifungal susceptibility for certain species (Friedman & Schwartz, 2019).

Certain fungal species are prone to microbial resistance, which can be attributed to secondary resistance (acquired resistance in an otherwise susceptible strain following medication exposure) and intrinsic resistance (strains are naturally less susceptible to a certain antifungal treatment). Triazole-resistant *Aspergillus fumigatus* (Verweij et al., 2016), *Candida tropicalis*, *Candida parapsilosis* (Pfaller et al., 2019), multidrug-resistant (MDR) *Candida auris* (Chowdhary et al., 2018), and MDR *Candida glabrata* showing increasing prevalence globally (Haeley & Perlin, 2018) are the most notable species emerging worldwide and regarded as major concern for public health. The hunt for safer alternatives with lower toxicity, better pharmacodynamics and pharmacokinetics, and more specificity has been sparked by the limited spectrum activity and cross-resistance caused by comparable mechanisms of action across medications (Rocha et al., 2017).

This study presents an overview of newly developing fungal illnesses in COVID-19 patients, emphasizing the available antifungal therapies. We further explore some promising elements of developing novel antifungal drugs to address resistance problems. We concentrate on novel antifungal peptides in particular because other emerging alternatives, like quorum-sensing molecules, combination therapy of antifungals with non-antifungal drugs, and agents with new structure for a known target or entirely novel targets, have recently been reviewed by other authors (Kovács & Majoros, 2020).

#### Development of Fungal Infections during COVID-19

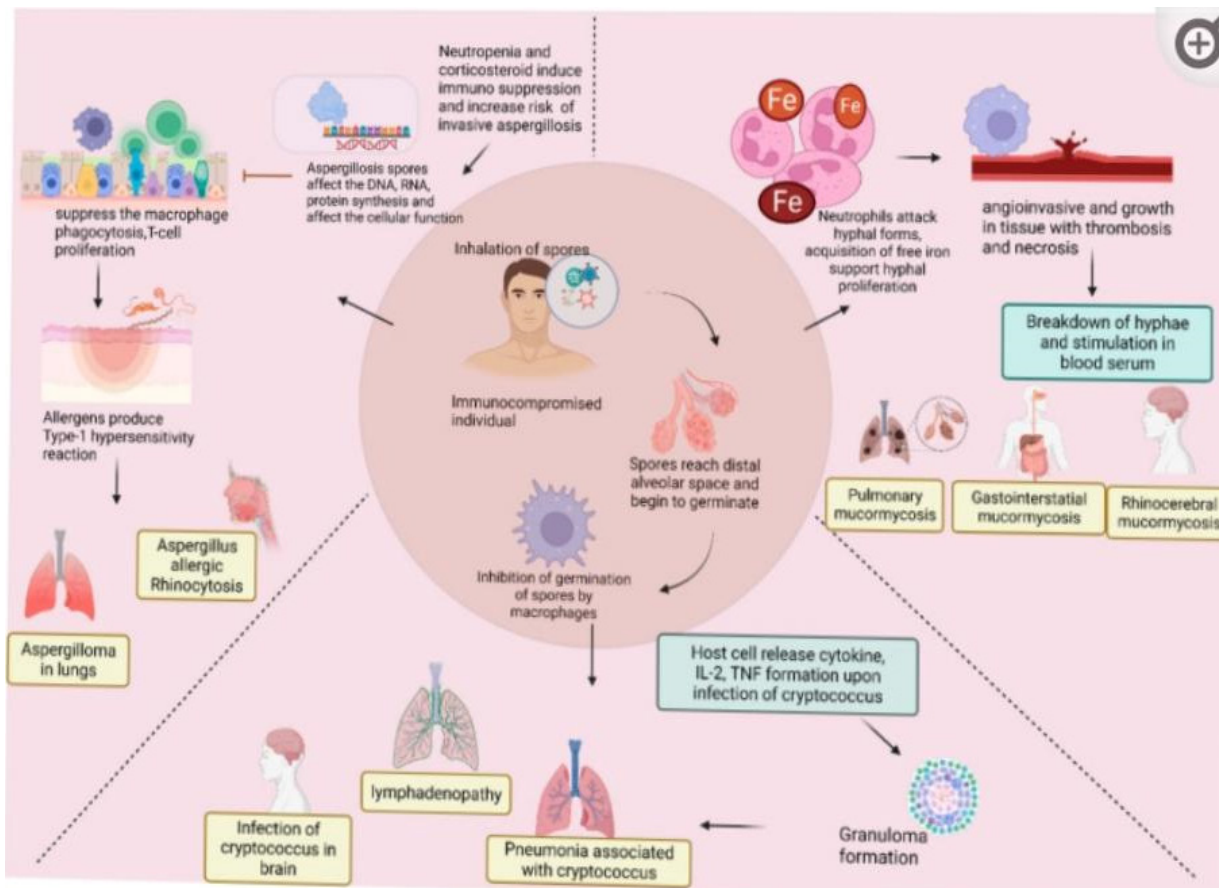
Aspergillosis, invasive candidiasis, mucormycosis, pulmonary alveolar infections, and other epidermal infections are among the frequent fungal diseases that patients often have. It is well-recognized that viral pneumonia can result in concurrent or secondary illnesses. A retrospective analysis found that 25% of H1N1 patients during the 2009 pandemic had a bacterial or fungal illness. In the instance of COVID-19 patients, a comparable pattern is noted (Chavda et al, 2021). Research has revealed that invasive fungal infections in COVID-19 patients have resulted in over 500 million cases and over six million deaths globally (Shishido et al, 2022). For COVID-19 patients, the rates of developing an opportunistic fungal secondary infection were found to be 49.7, 23.2, 19.8, 6.6, and 0.5%, respectively, in Asia, America, Europe, Africa, and Australia (Seyedjavadi et al, 2022).

Nowadays, COVID-19-positive people frequently experience a plethora of issues with secondary health infections, idiopathic infections, iatrogenic infections, superinfections, and coinfections (Kundu et al, 2022). Numerous risk factors make patients susceptible to fungal infections, including respiratory problems,

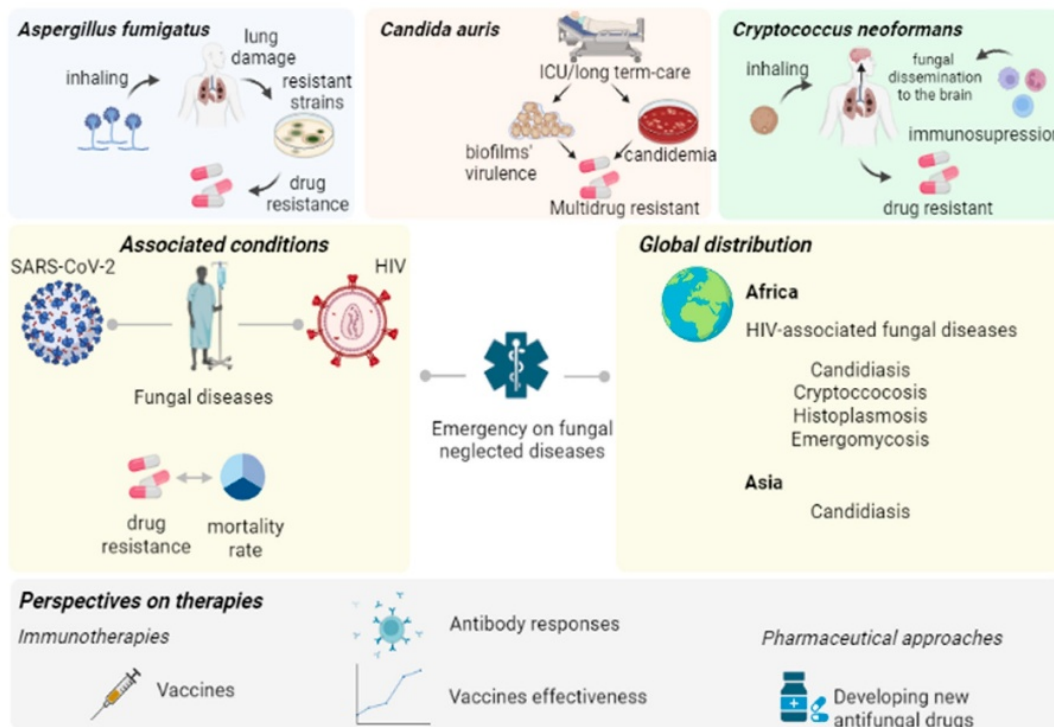
skin infections, black eye fungal infection, immunosuppression, the need for supplementary oxygen, monoclonal antibodies, steroid therapy, and so on. Adverse consequences that are closely linked to opportunistic fungal infections are experienced by COVID-19 patients. As a result, new terminology for coinfections has been developed, including COVID-19-associated mucormycosis (CAM), COVID-19-associated pulmonary aspergillosis (CAPA), and COVID-19-associated candidiasis (CAC) (Kundu et al, 2022). Some of the most common fungal infections seen in COVID-19 patients include aspergillosis, candidiasis, cryptococcosis, and mucormycosis. *Aspergillus* species, specifically *Candida auris*, *Cryptococcus neoformans*, and fungi from the Mucorales order, are responsible for these illnesses (Arastehfar et al, 2020). Figure 1 illustrates the pathophysiology of invasive aspergillosis, mucormycosis, and cryptococcus fungal infections. In figure show that when *Aspergillus* spores are inhaled and germinate in the lungs, causing invasive growth, invasive aspergillosis usually affects immunocompromised patients. If treatment is not received, the fungus spreads to other organs including the brain, heart, or kidneys, causing multi-organ failure due to lung tissue

#### Green Fungus

Green fungus, also known as Aspergillosis, can be found indoors and outdoors, with many individuals inhaling *Aspergillus* spores daily without experiencing illness (DeShazo et al., 1997). While inhaling these spores is generally not harmful to those with healthy immune systems, it can lead to lung or sinus infections in individuals with weakened immune systems, potentially spreading to other parts of the body and causing infectious pneumonia if left untreated (Russell et al., 2021). *A. fumigatus*'s conidia are small enough to allow for deep penetration into the alveolar region, it is most likely the most prevalent etiological agent in the world.. Despite its name, green fungus is not infectious and cannot be transmitted between humans or animals (Bassetti et al., 2020). Immunocompetent individuals' lungs often exclude *Aspergillus* spores by the action of innate immune system cells such neutrophils and macrophages (Hohl & Feldmesser, 2007). It typically thrives in environments with downward vegetation or stored grain, compost heaps, and the leaves of marijuana (Herbrecht et al., 2002). Symptoms of green fungus include fevers, wheezing, reduced smelling ability, fatigue, breath shortening, cough, runny nose, and headaches (Każmierczak-Siedlecka et al., 2020). Individuals susceptible to green fungus infections include those with lung conditions such as tuberculosis (TB), asthma patients prone to allergic bronchopulmonary aspergillosis (ABPA), individuals with sarcoidosis or TB-related lung illnesses developing chronic pulmonary aspergillosis, and those with compromised immune systems such as organ transplant recipients, high-dose corticosteroid users, or individuals undergoing cancer treatment



**Figure 1.** Mechanism of the pathogenesis of invasive aspergillosis, mucormycosis, and cryptococcus fungal infections and their complications (Courtesy from Biorender.com).



**Figure 2.** Schematic representation of the contagious and development of fungal diseases in humans. Aspergillosis, candidiasis destruction, pulmonary bleeding, and necrosis.

(Fox et al., 2020; Sivankalai & Sivasekaran, 2021). In figure 2 show of Aspergillosis, Candida and Cryptococcus fungus development and how to treat them.

### Factor of Fungus

Immunocompetent individuals' lungs often exclude *Aspergillus* spores by the action of innate immune system cells such neutrophils and macrophages (Hohl and Feldmesser, 2017). However, in immunocompromised people, *Aspergillus* species can induce a range of clinical symptoms. Spores that circulate in the environment can be inhaled or injected, and infection may result. This can cause allergic reactions or infectious disorders, which can spread from the respiratory system to the body as a disseminated or invasive infection (Latgé and Chamilo, 2019). According to Barnes and Marr (2006), invasive pulmonary aspergillosis (IPA) is a prevalent condition that causes substantial morbidity and death in critically ill patients. Hospitalized patients are more likely to get IPA due to a number of variables, such as corticosteroid therapy, antibiotics, and hematologic malignancy. IPA has also been linked to respiratory viral infections including influenza (Schauwvlieghe et al., 2018). Critically ill patients are susceptible to secondary infections with *Aspergillus* species because severe influenza and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pneumonia share immunopathological similarities (e.g., cytokine storm syndrome, epithelial damage within the airways, lymphopenia) (Khorramdelazad et al., 2021).

### A case of green Fungus

Green fungus is the latest among previously recorded black, white and yellow fungal instances. Madhya Pradesh's (MP) Indore was the first incidence of the illness. After a COVID-19 survivor of 34 years of age green fungus was diagnosed (Aspergillosis). He moved to Mumbai for treatment by the air ambulance. The individual who had recovered from coronavirus was tested for suspected infection with the black fungus (mucormycosis). However, he detected a green fungal infection in his lung, sinuses, and blood. The Sri Aurobindo Institute of Medical Sciences (SAIMS) Head of Chest Disease, Dr Ravi Dosi, informed PTI. "The patient got back. But then he began to get a high temperature and nasal bleeds. He was also quite weak because of loss of weight," He said Dr. Dosi. Doctors started to study the specifics of this new kind of the fungus (2019). While this is the first occurrence of MP, other regions of the country remain unclear to the medical community. A common mould, a form of fungus living inside and outside, is a source of green fungus also known as the aspergillosis. High temperature and nasal bleeding might trigger the illness. According to Dr Dosi, green fungus is also suspected of causing serious weight loss and weakness. He noted that further study is needed on whether the

form of the green fungal infection differs from that of other patients in those who have recovered from COVID-19 (2019).

### Biotechnology for Molecular Diagnosis of Aspergillosis (Green fungus)

The most reliable way to diagnose aspergillosis is to use methenamine-silver stain to show the presence of hyphal fragments in tissue biopsies. The hyphae frequently branch off of one another. Finding fungus in sputum might be challenging in cases of aspergilloma. Sputum smear results in invasive aspergillosis are frequently negative. Analyzing stained tissue sections is the most dependable way to diagnose acute invasive aspergillosis. Hematoxylin, eosin (H&E), and gomorimethenamine silver (GMS) can stain the histological section, and hyphae can be looked for. The ELISA technique was used to introduce rat anti-GM monoclonal antibodies, EB-A2, which identify the GM molecule's 1--- -5 BetaD-Galactofuranoside side chains. The current commercially available GM assay for the diagnosis of IA uses this sandwich ELISA technology. (Sandhya et al, 2019).

Regretfully, the GM assay's sensitivity is reduced while a patient is on *Aspergillus* antifungals, but its specificity for detection remains same (Larone et al, 2011) Compared to latex agglutination methods and enzyme immunoassays, these assays have higher sensitivity. Common radiological symptoms on the chest radiograph include cavitating lesions, patchy infiltrates, and nodular shadows. A computed tomography (CT) scan can help evaluate non-specific infiltrates in immunocompromised patients. In order to prevent the emergence of chronic problems and to minimize the death rates, it is essential to obtain an early diagnosis. The 'halo sign' on CT is now considered an early predictor of invasive pulmonary Aspergillosis (Hammond et al, 2011).

### Treatment

Preventing green fungus involves maintaining high hygiene standards and practicing oral and physical cleanliness to avoid uncommon fungal infections. Doctors recommend avoiding travel to dusty areas and minimizing exposure to polluted water. When visiting such locations, wearing an N95 breathing mask for added protection against inhaling fungal spores is advisable. Additionally, regular hand and face washing with soap and water after exposure to dust or filth can help reduce the risk of fungal transmission (Wiersinga et al., 2020; Doi et al., 2021). The first confirmed case of green fungus was reported in Jalandhar, Punjab, indicating the importance of monitoring and promptly reporting such cases. While speculation about additional cases has surfaced, their verification remains inconsistent. Various regions in India have documented instances of black, yellow, and white fungal infections, predominantly affecting COVID-19 patients. Mucormycosis, also known as black fungus, is the most prevalent fungal infection

among patients in post-recovery care. On June 15, 2021, India witnessed its first green fungus infection in a COVID-19 patient. The patient, a 34-year-old from Indore, was diagnosed with Aspergillosis, caused by the ubiquitous mold fungus *Aspergillus*, after battling a severe pulmonary infection for two months. Individuals with compromised immunity or preexisting pulmonary conditions are at higher risk of contracting Aspergillosis, which can lead to allergic responses, pulmonary infections, and other organ infections. Diabetic and steroid-treated COVID-19 patients are particularly vulnerable to various fungal infections, including green fungus (Singh, 2021).

The majority of opportunistic fungal Infections, namely mucormycosis, aspergillosis, and candidiasis, in this patient group have been misdiagnosed due to the complicated medical conditions of older COVID-19-positive individuals and the improper collection of their clinical samples (Silva et al, 2020). Additionally, this has had detrimental effects on their COVID-19 rehabilitation process.

Diverse strategies and techniques to the therapy of mucormycosis were established by the European Confederation of Medical Mycology (ECMM) and the Mycosis Study Group Education Research Consortium (Song et al, 2020) First and foremost, systemic antifungal medications like propiconazole and isavuconazole should be used as first-line therapy, followed by prompt and thorough surgical treatment. Allergy-induced and invasive aspergillosis are the two main classifications for managing SARS-CoV-2-associated pulmonary aspergillosis (CAPA). Invasive aspergillosis can be treated with lipid amphotericin B formulations, posaconazole, itraconazole, isavuconazole, and votinazole. Surgery can be necessary if the patient develops aspergilloma while receiving antifungal medication (Rahimi et al, 2016). A new echinocandin and bialfungin are now being tested in preclinical research and have showed early promise in mouse models as a once-a-week medication for IA prophylaxis (Ong et al, 2016). Since *C. auris* rarely responds to azoles or amphotericin B, echinocandins are typically used as a treatment. In order to maximize the effectiveness and minimize the toxicity of azoles, therapeutic drug monitoring ought to be necessary during treatment (Ellsworth et al, 2020). For the treatment of pneumocystis pneumonia infection, trimethoprim and sulfamethoxazole have been used in combination. Alternatively, moderate-to-severe pneumonia may also be treated with corticosteroids (Menon et al, 2020). Disease prevention may be aided by early infection detection and advised antifungal medication treatment.

Therefore, in order to treat fungal infections as soon as possible, appropriate early detection and antifungal treatment options become essential. Furthermore, proper planning must be done when laying out the treatment strategies, which should not only be the most cost-effective but also the most effective means of healing,

since the management of fungal infection in such patients costs a significant amount of money to both the public and private sectors annually. This is especially important for low- and middle-income nations, where a scarcity of resources greatly affects the accessibility and efficacy of therapeutic interventions. (Garre et al, 2022). In Table 1, the presently available treatment options for the invasive fungal infections of aspergillosis are summarized.

### Challenges

Additional risk factors are generally associated with the management of patients with severe COVID-19. High-dose corticosteroid therapy and *Aspergillus* co-infection have been linked in prospective and retrospective cohort studies using COVID-19 patients admitted to intensive care units (Bartoletti et al., 2021). Furthermore, since the significantly elevated level of IL-6 in severe COVID-19 patients has also been found to be a contributing factor in protection against *Aspergillus*, antiinterleukin-6 (IL-6) receptor treatment, such as tocilizumab therapy, which is widely used to treat COVID-19, seems to potentially confer higher risk for developing CAPA (Table 2) (Guaraldi et al., 2020). Given table give an idea of characteristics of COVID-19 which are linked to fungal infection. It show how the infection design in different forms and what results show. How we can control the infection.

Due to variations in diagnostic standards and the variety of respiratory specimen types obtained for mycological diagnoses, estimating the global burden of CAPA is challenging. Furthermore, observational studies have primarily been conducted in European nations, with scant data available from other continents (Feys et al., 2021). Regional variation in CAPA incidence has been reported, ranging from 0.54 to 42.1% when evaluating total CAPA incidence, based on examination of clinical data from multiple countries ( Takazono et al., 2021).

Lahmer et al. (2021) examined 32 patients who had severe pneumonia linked to COVID-19 and found that a high incidence of CAPA was present in COVID-19 patients (11/32; 34%). Jiang and al. found a similar incidence rate (8/19; 42.1%); however, only a small number of COVID-19 patients were included in both investigations (Jiang et al., 2022). Notwithstanding variations in the number of cases of CAPA that have been documented, COVID-19 raised the chance of getting an IPA, and CAPA was substantially linked to a higher death rate (up to 50%), highlighting the significance of widespread awareness and prompt diagnosis (Ezeokoli et al., 2021).

The International Society for Human and Animal Mycology (ISHAM) and the European Confederation of Medical Mycology (ECMM) propose isavuconazole or VOR as the first-line antifungal treatments for CAPA (Koehler et al., 2021). On the other hand, there are a number of recognized side effects associated with VOR medication, such as gastrointestinal upset and abnormalities of the

**Table 1. Fungus Treatment**

Fungal Infection	Available Treatments	Comment	Clinical Data
Aspergillosis	Voriconazole with the dose range of 6 mg/kg IV every 12 h per day, followed by 4 mg/kg every 12 h for 6–12 weeks. For Per oral administration 200 mg at every 12 h	<p>Voriconazole is available in tablet, IV, and suspension formulations for the treatment of invasive aspergillosis.</p> <p>Reported to cause liver and gastrointestinal abnormalities.</p> <p>Voriconazole has 96% oral bioavailability and causes high CNS penetration.</p>	<p>In phase II and III clinical trials, voriconazole showed exemplary clinical efficacy in human subjects.</p> <p>A randomized trial involving 144 patients. In a comparative study in which IV amphotericin B deoxycholate and voriconazole were given to different patients; after 12 weeks the survival rate was 70.8% in the voriconazole group and 57.9% in the amphotericin group</p>
	Isavuconazole in the dose range of 200 mg every 8 h per 6 doses, then 200 mg IV or oral daily for 6–12 weeks.	<p>Isavuconazole, a potent second-generation triazole available in capsule and IV formulations in the treatment of IA.</p> <p>Reduced efficacy as both Voriconazole and Isavuconazole are substrates for CYP3A4 enzyme in the liver. It reduces drug-drug interaction compared to other triazoles</p>	An Interventional open-label trial involving 149 patients investigated that Isavuconazole was found to be effective and generally well tolerated in international phase III clinical trials for the treatment of invasive aspergillosis fungal infection.
	Posaconazole was administered in the dose range in IV 300 mg twice daily and then 300 mg once daily for 6–12 weeks.	<p>Posaconazole is available in slowly released tablets, oral suspension, and IV formulation to treat refractory IA.</p> <p>If obtainable, only to be utilized as a second therapeutic option.</p>	<p>The FDA has authorized the use of posaconazole (Noxafil, Schering Corporation, Kenilworth, NJ) in immunocompromised patients as a preventative treatment against invasive Aspergillus and Candida fungi infections.</p> <p>An open-labeled trial stated the use of posaconazole as a salvage therapy for IA patients who were intolerant of previous antifungal treatment. The overall success rate was 42% for posaconazole</p>

**Table 2.** Comparison of the characteristics of COVID-19-associated fungal infections

Fungal infection	Cohort size	Identification/diagnosis	Risk factors and comorbidities	Co-infections	Antifungal treatment	Outcome
Aspergillosis	9	EORTC-MSG criteria and GM in BAL, serum; 8 case putative CAPA, 1 case probable CAPA	Myeloma, steroids	N/A	VOR, CAS therapy of 2 patients	4 died
	5	AspICU algorithm and GM in BAL or serum; putative CAPA	Arterial hypertension, diabetes mellitus, chronic obstructive pulmonary disease, obesity, hypercholesterolemia, steroids	Human metapneumovirus	VOR, ISZ, CAS	3 died
	5	Clinical signs and symptoms, an abnormal lung imaging, respiratory specimen culture positive for <i>Aspergillus</i> spp., GM in BAL or serum; putative CAPA	Diabetes mellitus, steroid and tocilizumab therapy	<i>K. pneumoniae</i> , <i>P.aeruginosa</i> , MRSA, <i>S. maltophilia</i> , MDR <i>Acinetobacter</i> spp	AMB, VOR	3 died (the cause of death was ARDS)
	6	Culture and GM in BAL; 3 possible and 3 probable CAPA	Cardiomyopathy, chronic obstructive pulmonary disease, corticosteroid therapy, asthma	N/A	VOR + ANI combination, AMB	4 died
	3	Culture, serum GM, serum BDG; 2 putative and 1 probable CAPA	Hypertension, diabetes mellitus type 2, pulmonary fibrosis, obesity, asthma, antibacterial therapy, tocilizumab therapy	<i>Haemophilus influenzae</i>	VOR	1 died
	7	AspICU algorithm, 4 proven CAPA cases	Obesity, hypercholesterolemia, arterial hypertension, diabetes mellitus, chronic kidney disease, acute myeloid leukemia, mechanical ventilation	N/A	VOR, ISZ therapy in 6 patients	4 died

**Table 3.** Recommendations for the management of fungal co-infections in COVID-19 patients

Fungal infection	First-line treatment	Second-line treatment	Alternative or salvage therapy	Reference
Aspergillosis	VOR-loading dose 6 mg/kg twice a day, followed by 4 mg/kg twice a day; or ISZ-loading dose 200 mg three times a day for six doses, followed by 200 mg once a day	liposomal AMB-3 mg/kg/day (except for patients with renal insufficiency)	POS or echinocandin + azole (e.g., ANI + VOR)	Koehler et al., 2021

liver. Since both medications are metabolized by the cytochrome P450 enzyme CYP3A4, VOR also has a number of drug-drug interactions, including remdesivir, which is typically used in the treatment of COVID-19 (McCreary and Pogue, 2020).

Monitoring plasma concentrations is necessary due to VOR's erratic metabolism, which has resulted in both subtherapeutic and dangerous doses in critically ill individuals. Its limited use in intensive care unit patients can be attributed to its toxicity, narrow therapeutic window, and interactions with other medications (Cadena et al., 2021; Tio et al., 2021). Isavuconazole is less toxic and has a better pharmacokinetic profile than VOR, but it also acts as a substrate for CYP3A4, which decreases its effectiveness. The alternative is liposomal amphotericin B, unless the patient has renal impairment linked to COVID-19. Posaconazole or echinocandins are substitute second-line treatments. Echinocandins should be used with other medications or as salvage therapy (Table 3; Koehler et al., 2021).

The case reports of triazole-resistant *A. fumigatus* infections in COVID-19 patients are another developing worry regarding the therapy of CAPA. Patients with invasive aspergillosis typically have a worse prognosis due to *Aspergillus* species' triazole-resistant strain, which varies greatly in geographic regions (from less than 1% in France to an estimated ~11% prevalence in the Netherlands) (Alanio et al., 2011). Arastehfar et al. (2020) reported that isolates may develop azole resistance as a result of either tandem repeat integrations of varying sizes in the *cyp51A* promoter, which induces point mutations in the gene (TR34/L98H, TR46/Y121F/T289A, and TR53), or as a result of prolonged azole treatment of patients in clinical settings.

Five cases of triazole-resistant *A. fumigatus* have been described, with four of them having the TR34/L98H mutation in the *cyp51A* gene. This mutation is linked to acquired environmental resistance, which often leads to panazole resistance (Borman et al., 2020). According to clinical data, most patients with azole-resistant infections had no prior history of azole prophylaxis or therapy (Meis et al., 2016). This environmental acquired resistance in the *cyp51A* gene is consistent with this finding. Triazole and multi-triazole resistance highlights the significance of early diagnosis and the pressing need for routine antifungal drug susceptibility testing of *Aspergillus* isolates by direct detection of *cyp51A* gene associated triazole resistance mutations on respiratory samples, or by quick and easy phenotypic method.

## Conclusion

Finally, the development of green fungus presents a severe challenge in the emerging post-COVID health landscape. This fungal infection has distinct clinical symptoms and presents treatment challenges. It primarily affects immunocompromised persons recuperating from COVID-19. Its rise highlights the need

for increased awareness and surveillance among medical professionals in order to quickly detect and treat cases. The intricacy of green fungus also emphasizes the value of multidisciplinary cooperation between experts in public health, mycologists, and infectious disease specialists in order to create thorough plans for diagnosis, prevention, and treatment.

Healthcare systems need to be alert and flexible in the wake of the COVID-19 pandemic in order to handle new risks like green fungus. This means improving the ability to diagnose, fortifying infection control protocols, and bringing focused antifungal treatments. Furthermore, continued study is needed to better understand the epidemiology, risk factors, and pathogenesis of green fungus, allowing for more effective management and prevention techniques in the future.

Finally, the management of green fungus demonstrates the interdependence of global health and the need for coordinated, evidence-based responses to emerging infectious diseases in the post-COVID era. Healthcare communities may effectively limit the impact of green fungus and protect public health globally by utilizing their pooled expertise and resources.

## Author contribution

J.J., S.S., G.N.B., B.S.S. conceptualized, reviewed the literature, and wrote the article.

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None declared

## Competing financial interests

The authors have no conflict of interest.

## References

- Agostoni et al(2020). Cardiac patient care during a pandemic: how to reorganise a heart failure unit at the time of COVID-19. *European journal of preventive cardiology*, 27(11), 1127-1132.
- Alanio, A., Dellière, S., Fodil, S., Bretagne, S., and Mégarbane, B. (2020). Prevalence of putative invasive pulmonary aspergillosis in critically ill patients with COVID-19. *Lancet Respir. Med.* 8, e48–e49.
- Alanio, A., Sitterle, E., Liance, M., Farrugia, C., Foulet, F., Botterel, F., et al. (2011). Low prevalence of resistance to azoles in *Aspergillus fumigatus* in a French cohort of patients treated for haematological malignancies. *J. Antimicrob. Chemother.* 66, 371–374.
- Ali, G. A., Husain, A., Salah, H., and Goravey, W. (2021). *Trichosporon asahii* fungemia and COVID-19 co-infection: an emerging fungal pathogen; case report and review of the literature. *IDCases* 25:e01244.
- Allaw, F., Kara Zahreddine, N., Ibrahim, A., Tannous, J., Taleb, H., Bizri, A. R., et al. (2021). First *Candida auris* outbreak during a COVID-19 pandemic in a tertiary-care center in Lebanon. *Pathogens* 10:157.



- Amin, A., Vartanian, A., Poladian, N., Voloshko, A., Yegiazaryan, A., Al-Kassir, A. L., et al. (2021). Root causes of fungal coinfections in COVID-19 infected patients. *Infect. Dis. Rep.* 13, 1018–1035.
- Arana, C., Cuevas Ramírez, R. E., Xipell, M., Casals, J., Moreno, A., Herrera, S., et al. (2021). Mucormycosis associated with COVID-19 in two kidney transplant patients. *Transpl. Infect. Dis.* 23:e13652.
- Arastehfar, A., Carvalho, A., van de Veerdonk, F. L., Jenks, J. D., Koehler, P., Krause, R., et al. (2020a). COVID-19 associated pulmonary aspergillosis (CAPA)—from immunology to treatment. *J. Fungi (Basel)* 6:91.
- Arastehfar, A., Lass-Flörl, C., Garcia-Rubio, R., Daneshnia, F., Ilkit, M., Boekhout, T., et al. (2020b). The quiet and underappreciated rise of drug-resistant invasive fungal pathogens. *J. Fungi (Basel)* 6:138.
- Baddley, J. W., Thompson, G. R., Chen, S. C.-A., White, P. L., Johnson, M. D., Nguyen, M. H., et al. (2021). Coronavirus disease 2019–associated invasive fungal infection. *Open Forum Infect. Dis.* 8:ofab510.
- Ballard, E., Yucel, R., Melchers, W. J. G., Brown, A. J. P., Verweij, P. E., and Warris, A. (2020). Antifungal activity of antimicrobial peptides and proteins against *Aspergillus fumigatus*. *J. Fungi (Basel)* 6:65.
- Bassetti et al (2020). Bacterial and fungal superinfections in critically ill patients with COVID-19. *Intensive care medicine*, 46(11), 2071–2074.
- Benhadid-Brahmi, Y., Hamane, S., Soyer, B., Mebazaa, A., Alanio, A., Chousterman, B., et al. (2022). COVID-19-associated mixed mold infection: a case report of aspergillosis and mucormycosis and a literature review. *J. Med. Mycol.* 32:101231
- Bermano et al (2021). Selenium and viral infection: are there lessons for COVID-19?. *British journal of nutrition*, 125(6), 618–627.
- Chowdhary, A., Tarai, B., Singh, A., and Sharma, A. (2020). Multidrug-resistant *Candida auris* infections in critically ill coronavirus disease patients, India, April–July 2020. *Emerg. Infect. Dis.* 26, 2694–2696.
- Dellière, S., Dudoignon, E., Fodil, S., Voicu, S., Collet, M., Ouilic, P.-A., et al. (2021). Risk factors associated with COVID-19-associated pulmonary aspergillosis in ICU patients: a French multicentric retrospective cohort. *Clin. Microbiol. Infect.* 27, 790.e1–790.e5.
- DeShazo et al (1997). Fungal sinusitis. *New England Journal of Medicine*, 337(4), 254–259.
- Doi et al (2021). The merits of entomophagy in the post COVID-19 world. *Trends in Food Science & Technology*.
- Duncan, V., Smith, D., Simpson, L., Lovie, E., Katvars, L., Berge, L., et al. (2021). Preliminary characterization of NP339, a novel polyarginine peptide with broad antifungal activity. *Antimicrob. Agents Chemother.* 65:e02345-20.
- Fernandez et al (2021). Ventilator-associated pneumonia involving *Aspergillus flavus* in a patient with coronavirus disease 2019 (COVID-19) from Argentina. *Medical mycology case reports*, 31, 19–23.
- Feys, S., Almyroudi, M. P., Braspenning, R., Lagrou, K., Spriet, I., Dimopoulos, G., et al. (2021). A visual and comprehensive review on COVID-19-associated pulmonary aspergillosis (CAPA). *J. Fungi (Basel)* 7:1067.
- Fox et al (2020). Pulmonary and cardiac pathology in African American patients with COVID-19: an autopsy series from New Orleans. *The Lancet Respiratory Medicine*, 8(7), 681–686.
- García-Bustos, V., Cabanero-Navalon, M. D., Ruiz-Saurí, A., Ruiz-Gaitán, A. C., Salavert, M., Tormo, M. Á, et al. (2021). What do we know about *Candida auris*? State of the art, knowledge gaps, and future directions. *Microorganisms* 9:2177.
- Gonzalez-Lopez et al (2020). Symptomatic Retinal Microangiopathy in a Patient with Coronavirus Disease 2019 (COVID-19): Single Case Report. *Ocular immunology and inflammation*, 1–3.
- Hammond, S. P., Bialek, R., Milner, D. A., Petschnigg, E. M., Baden, L. R., and Marty, F. M. (2011). Molecular methods to improve diagnosis and identification of mucormycosis. *J. Clin. Microbiol.* 49, 2151–2153.
- Hanley, B., Naresh, K. N., Roufosse, C., Nicholson, A. G., Weir, J., Cooke, G. S., et al. (2020). Histopathological findings and viral tropism in UK patients with severe fatal COVID-19: a post-mortem study. *Lancet Microbe* 1, e245–e253.
- Herbrecht et al (2002). Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *New England Journal of Medicine*, 347(6), 408–415.
- Hoenigl, M., Seidel, D., Carvalho, A., Rudramurthy, S. M., Arastehfar, A., Gangneux, J.-P., et al. (2022). The emergence of COVID-19 associated mucormycosis: a review of cases from 18 countries. *Lancet Microbe* S2666524721002378. <https://economictimes.indiatimes.com/news/india/green-fungus-what-we-know-so-far-about-this-new-ailment/articleshow/83596>
- <https://www.firstpost.com/health/green-fungus-found-in-recovering-covid-19-patient-all-you-need-to-know-about-this-life-threatening-infection-9724371.html>
- Jia et al (2016). Microbial-type terpene synthase genes occur widely in nonseed land plants, but not in seed plants. *Proceedings of the National Academy of Sciences*, 113(43), 12328–12333.
- Kaźmierczak-Siedlecka et al (2020). COVID-19-gastrointestinal and gut microbiota-related aspects. *European review for medical and pharmacological sciences*, 24(20), 10853–10859.
- Khorramdelazad, H., Kazemi, M. H., Najafi, A., Keykhaee, M., Zolfaghari Emameh, R., and Falak, R. (2021). Immunopathological similarities between COVID-19 and influenza: investigating the consequences of Co-infection. *Microb. Pathog.* 152:104554.
- Kilburn, S., Innes, G., Quinn, M., Southwick, K., Ostrowsky, B., Greenko, J. A., et al. (2022). Antifungal resistance trends of *Candida auris* clinical isolates in New York and New Jersey from 2016 to 2020. *Antimicrob. Agents Chemother.* 66:e02242-21.
- Koehler, P., Bassetti, M., Chakrabarti, A., Chen, S. C. A., Colombo, A. L., Hoenigl, M., et al. (2021). Defining and managing COVID-19-associated pulmonary aspergillosis: the 2020 ECMM/ISHAM consensus criteria for research and clinical guidance. *Lancet Infect. Dis.* 21, e149–e162.
- Lednický et al (2020). Viable SARS-CoV-2 in the air of a hospital room with COVID-19 patients. *International Journal of Infectious Diseases*, 100, 476–482.
- Machado, M., Estévez, A., Sánchez-Carrillo, C., Guinea, J., Escribano, P., Alonso, R., et al. (2022). Incidence of candidemia is higher in COVID-19 versus NonCOVID-19 patients, but not driven by intrahospital transmission. *JoF* 8:305.
- Magnasco, L., Mikulska, M., Giacobbe, D. R., Taramasso, L., Vena, A., Dentone, C., et al. (2021). Spread of carbapenem-resistant gram-negatives and *Candida auris*

during the COVID-19 pandemic in critically ill patients: one step back in antimicrobial stewardship? *Microorganisms* 9:95.

- Nasir, N., Farooqi, J., Mahmood, S. F., and Jabeen, K. (2020). COVID-19-associated pulmonary aspergillosis (CAPA) in patients admitted with severe COVID-19 pneumonia: an observational study from Pakistan. *Mycoses* 63, 766–770.
- Olivieri, C., Bugli, F., Menchinelli, G., Veglia, G., Buonocore, F., Scapigliati, G., et al. (2018). Design and characterization of chionodracine-derived antimicrobial peptides with enhanced activity against drug-resistant human pathogens. *RSC Adv.* 8, 41331–41346.
- Prestel, C., Anderson, E., Forsberg, K., Lyman, M., de Perio, M. A., Kuhar, D., et al. (2021). *Candida auris* outbreak in a COVID-19 specialty care unit —Florida, July–August 2020. *MMWR Morb. Mortal. Wkly. Rep.* 70, 56–57
- Russell et al (2021). Co-infections, secondary infections, and antimicrobial use in patients hospitalised with COVID-19 during the first pandemic wave from the ISARIC WHO CCP-UK study: a multicentre, prospective cohort study. *The Lancet Microbe.*
- Rutsaert, L., Steinfort, N., Van Hunsel, T., Bomans, P., Naesens, R., Mertes, H., et al. (2020). COVID-19-associated invasive pulmonary aspergillosis. *Ann. Intensive Care* 10:71.
- Sivankalai & Sivasekaran (2021). Mucormycosis (Black Fungus) Maiming Covid Patients: Scientometrics analysis through prism of Biblioshiny.
- Tabarsi, P., Khalili, N., Pourabdollah, M., Sharifynia, S., Safavi Naeini, A., Ghorbani, J., et al. (2021). Case report: COVID-19-associated Rhinosinusitis Mucormycosis caused by *Rhizopus arrhizus*: a rare but potentially fatal infection occurring after treatment with corticosteroids. *Am. J. Trop. Med. Hyg.* 105, 449–453
- van Arkel, A. L. E., Rijpstra, T. A., Belderbos, H. N. A., van Wijngaarden, P., Verweij, P. E., and Bentvelsen, R. G. (2020). COVID-19–associated pulmonary aspergillosis. *Am. J. Respir. Crit. Care Med.* 202, 132–135
- Welsh, R. M., Sexton, D. J., Forsberg, K., Vallabhaneni, S., and Litvintseva, A. (2019). Insights into the unique nature of the East Asian clade of the emerging Pathogenic yeast *Candida auris*. *J. Clin. Microbiol.* 57:e00007-19
- Wiersinga et al (2020). Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. *Jama*, 324(8), 782-793.
- Yang, X., Chen, W., Liang, T., Tan, J., Liu, W., Sun, Y., et al. (2021). A 20-year antifungal susceptibility surveillance (From 1999 to 2019) for *Aspergillus* spp. and proposed epidemiological cutoff values for *Aspergillus fumigatus* and *Aspergillus flavus*: a study in a tertiary hospital in China. *Front. Microbiol.* 12:680884.
- Zurl, C., Hoenigl, M., Schulz, E., Hatzl, S., Gorkiewicz, G., Krause, R., et al. (2021). Autopsy proven pulmonary mucormycosis due to *Rhizopus microsporus* in a Critically Ill COVID-19 patient with underlying hematological malignancy. *J. Fungi (Basel)* 7:88