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Post-COVID-19 Fungal Diseases and Emerging Antifungal Resistance

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Abstract

The COVID-19 pandemic had an impact on the incidence and management of fungal infections such as aspergillosis, Mucor mycosis, and Candidiasis. These infections were seen in that severely ill or requiring mechanical ventilation as the COVID-19 virus weakens the immune system and makes individuals more susceptible to fungal infections. In addition, the use of systemic corticosteroids to treat COVID-19 can also increase the risk of fungal infections, as steroids can suppress the immune system. Antifungal treatments, such as voriconazole, itraconazole, or posaconazole, may be used to treat fungal infections in individuals with COVID-19, and in some cases, surgical intervention may also be necessary to remove infected tissues. The treatment of invasive fungal infections is challenging due to the limited number of antifungal agents available and the increasing prevalence of antifungal-resistant strains of fungi.

Keywords: Candidiasis; Aspergillosis; Mucormycosis; Voriconazole; Posaonazole

Introduction

The COVID-19 pandemic had far-reaching impacts on health, not just from the virus itself, but also from its indirect effects, such as disruptions in healthcare systems, changes in medical practices, and increased susceptibility to other illnesses. One of these indirect effects is an increase in fungal diseases, which can cause a range of symptoms and complications of infections. Improved infection control measures, such as using HEPA air filter systems in hospitals, improved hygiene practices, and better management of healthcare systems, can help to reduce the risk of exposure to fungi and prevent the spread of fungal infections.

The COVID-19 pandemic had a significant increase in the number of patients with fungal infections, particularly in those who are hospitalized or critically ill [1]. In addition, COVID-19 has disrupted the delivery of healthcare services and limited access to diagnostic tests and treatments for fungal infections, which has made the management of these infections more challenging. Fungal infections such as invasive aspergillosis, Candidiasis, and Mucormycosis have

been reported in COVID-19 patients, especially in those with underlying medical conditions and those receiving immunosuppressive treatments. Fungal infections can occur in association with COVID-19, as the illness can weaken the immune system and increase the risk of developing other infections [2]. It is important for individuals who have been treated for COVID-19 to be vigilant for signs of fungal infections, such as cough, fever, shortness of breath, skin rash, or changes in mental status.

COVID-19 and Fungal Infections

COVID-19 has been associated with an increased risk of developing aspergillosis, candidiasis, and zygomycosis, also known as Mucor mycosis. Aspergillosis and zygomycosis are severe and potentially life-threatening fungal infections that can affect individuals with compromised immune systems. It can cause infections in the sinuses, lungs, skin, and other tissues and is often associated with high morbidity and mortality rates [3,4]. Candidiasis is a type of yeast infection that can affect the mouth, throat, skin, or genitals.

Candidiasis

Candida is a genus of yeast that can cause infections in humans. Thrush is a common oral yeast infection that affects the mouth and throat. Symptoms include white, creamy patches on the tongue and cheeks, redness, and discomfort when swallowing. Treatment includes antifungal medications applied directly to the affected area or taken orally. Vaginitis is a yeast infection of the vagina, and the symptoms include itching, burning, and a thick, white discharge. Treatment includes antifungal medications applied directly to the affected area or taken orally. Invasive Candidiasis is a serious systemic yeast infection that can spread throughout the body and the symptoms may include fever, fatigue, and a rash which may be treated with intravenous antifungal. Candida can also cause skin and nail infections, such as jock itch, ringworm, and athlete's foot, and the symptoms include itching, scaling, and redness [5,6].

Candida infections are treated with antifungal medications which include topical antifungal creams or oral antifungal medications. However, underlying conditions that increase the risk of developing a Candida infection, such as a weakened immune system, may also need to be treated in order to prevent future infections. There are many species of Candida that can cause infections, but the most common species isolated from clinical samples associated with COVID-19 viral infection are *Candida albicans*, *Candida auris*, *Candida tropicalis*, *Candida glabrata*, *Candida parapsilosis* and *Candida krusei* [5-7]. Candida infection can easily be identified by direct microscopy which shows budding cells with pseudo-hyphae formation may indicate Invasive Candidiasis as shown in Figure 1.

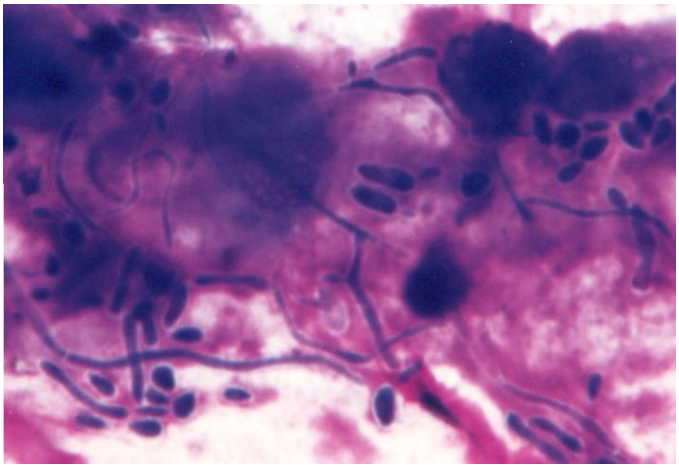

Figure 1: Microscopy of stained smear showing budding cells and pseudo-hyphae formation of *Candida albicans* from an invasive Candidiasis.

Treatment of Candidiasis depends on the severity and location of the infection. Mild to moderate cases can be treated with prescription antifungal medications, such as topical or oral azoles, or nystatin. Severe or systemic infections may require intravenous antifungal therapy with drugs such as amphotericin B or echinocandins [7,8]. Table 1 show the antifungal used to treat Candidiasis in adults.

Table 1: Antifungal treatment and common adult dosage for Candidiasis.

Treatment	Dosage
Fluconazole	Treating oral thrush is 50-100 mg once daily for 7-14 days. The typical dose for treating Vulvovaginal Candidiasis is 150 mg as a single dose.
Itraconazole	The typical dose for treating oral thrush is 200 mg once daily for 7-14 days. The typical dose for treating Vulvovaginal Candidiasis is 100 mg twice daily for 7-14 days.
Terbinafine	Treatment for Dermatophyte infections caused by Candida is 250 mg once daily.
Nystatin	Treatment for Cutaneous Candidiasis is 100,000 million units/g - 1 million units/g of cream or ointment applied to the affected area once or twice daily.

In addition to antifungal therapy, maintaining good hygiene and avoiding the use of antibiotics and other medications that suppress the immune system can also help prevent Candidiasis. In some cases, dietary changes, such as reducing sugar and carbohydrates, may also be recommended.

Aspergillosis

Aspergillosis is an infection caused by fungi of the genus Aspergillus which cause infections in the sinuses, lungs, skin, and other tissues of immunocompromised patients which leads to morbidity and mortality. Aspergillosis is a serious fungal infection that requires prompt and appropriate treatment. The treatment of aspergillosis typically involves antifungal medication and may also include surgical removal of infected tissue, if necessary. *Aspergillus fumigatus*, *Aspergillus niger*, *Aspergillus terreus*, and *Aspergillus sydowii* are commonly isolated from clinical specimens in association with COVID-19 viral infection causing aspergillosis [9]. Aspergillosis can easily be identified in stained smears and cultures. Figure 2 shows conidiophores with conidiospores and hyphae of the Aspergillus species. Aspergillus species have septate hyphae which can easily be identified from Zygomycetes which have aseptate hyphae.

Common antifungal medications used to treat aspergillosis include amphotericin B, administered Intravenously (IV), itraconazole, voriconazole, and Posaconazole, which is administrated orally. However, the use of Amphotericin is limited as it is potentially nephrotoxic [10-12]. In addition to antifungal medication and other treatments, patients with aspergillosis may also require supportive care, such as oxygen therapy, to help manage symptoms and prevent complications. It's important to work closely with a healthcare provider to develop an appropriate treatment plan for aspergillosis, as early and effective treatment is crucial for a positive outcome. It is important to monitor renal and hepatic parameters as the treatment has impacts on both organs.

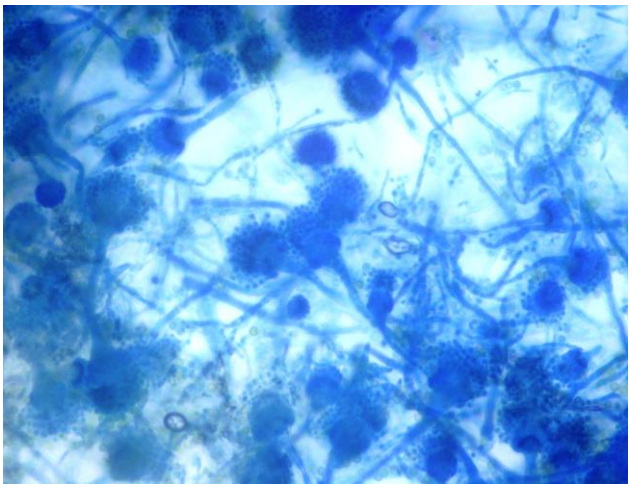

Figure 2: A direct microscopy preparation with lactophenol blue stain showing conidiophores, conidiospores, and hyphae of Aspergillus species.

Invasive aspergillosis can affect the lungs and other organs. The treatment involves the use of itraconazole, voriconazole, and isavuconazole (Table 2). Common side effects of these medications include nausea, vomiting, diarrhoea, headache, and liver dysfunction. Itraconazole, an azole antifungal, is widely used for the treatment of Aspergillus infections [11-13]. However, in recent years, the

emergence of itraconazole-resistant Aspergillus strains has become a major concern for the medical community [14-16].

Table 2: Antifungal treatment and common adult dosage for Aspergillosis.

Treatment	Dosage
Itraconazole	The typical adult dose is 200 mg twice daily.
Voriconazole	The typical adult dose is 200 mg twice daily.
Amphotericin B	1 mg/kg/day to 2 mg/kg/day. Amphotericin B can be given intravenously (into a vein) or as a lipid formulation.*.
Isavuconazole	200 mg three times daily*
Posaconazole	The typical adult dose is 200 mg to 400 mg once or twice daily.*.

*The treatment length depends on the infection's severity and location and the patient's overall health.

Zygomycosis (Mucormycosis)

The COVID-19 pandemic has increased the incidence of zygomycosis, and the most encountered fungi in association with COVID-19 are Rhizopus species, Mucor species, Absidia species, and Saksenaea species that can cause a variety of diseases in humans, including Mucor mycosis, rhino-orbital cerebral Mucor mycosis, cutaneous zygomycosis, gastrointestinal zygomycosis and disseminated zygomycosis [17-19].

Early diagnosis and prompt treatment are crucial for the best outcome. Fungal spores and aseptate hyphae can easily be identified in smears and cultures. Amphotericin B is a broad-spectrum antifungal often used as the first-line antifungal drug for treating Mucor mycosis, but due to its nephrotoxicity, other antifungal drugs, such as Posaconazole or Isavuconazole, may be used [21-23]. In addition to surgical intervention and antifungal medications, supportive care is also important for treating zygomycosis. This may include measures to control blood sugar levels in patients with diabetes, wound care, and management of any underlying medical conditions that may have contributed to the development of the fungal infection.

Amphotericin B is usually administered intravenously which may cause side effects such as kidney damage and fever [21]. Posaconazole and Isavuconazole are newer antifungal that are often used as a secondary treatment option for zygomycosis or in combination with Amphotericin B. Posaconazole is administrated orally and Isavuconazole is administered intravenously is well-tolerated and may cause side effects such as diarrhoea and abdominal pain [22-24]. Prompt diagnosis and aggressive treatment are crucial for the best outcome in patients with zygomycosis [25 -27] (Table 3).

Table 3: Antifungal treatment and common adult dosage for Zygomycosis (Mucor mycosis).

Treatment	Dosage
Amphotericin B	1 mg/kg/day to 2 mg/kg/day. Amphotericin B can be given intravenously (into a vein) or as a lipid formulation.*
Isavuconazole	200 mg three times daily*.
Posaconazole	The typical adult dose is 200 mg to 400 mg once or twice daily.*.

*The treatment of zygomycosis, also known as Mucormycosis, typically involves a combination of antifungal medications and supportive care. The choice of antifungal medication and the duration depend on the severity and location of the infection, as well as the patient's overall health status.

Antifungal Resistance

The most used antifungal drugs are azoles, polyenes, echinocandins, and allylamines. Azoles, such as itraconazole and voriconazole, are broad-spectrum antifungal drugs that target fungal cell membranes. These drugs are commonly used to treat superficial and systemic fungal infections. However, the widespread use of azoles has led to the emergence of resistance in some fungal species, making these drugs less effective in some cases. Polyenes, such as amphotericin B, target the fungal cell wall, causing fungal

cells to leak their contents. Polyenes are commonly used to treat systemic fungal infections, but they can cause side effects such as nephrotoxicity and infusion-related reactions. Echinocandins, such as caspofungin and micafungin, target the fungal cell wall, but through a different mechanism than polyenes. Echinocandins were commonly used for the treatment of invasive candidiasis, but the outcome is not satisfactory against aspergillosis. Allylamines, such as terbinafine, target the fungal cell membrane, causing the fungal cell to become leaky and eventually die. Allylamines are commonly used for the treatment of dermatophyte infections, but they are not effective against all types of fungi [28,29].

Resistance to antifungal medications is a growing concern in the treatment of fungal infections. Fungi can develop resistance to antifungal drugs, which can make treatment more difficult and increase the risk of treatment failure. The overuse or inappropriate use of antifungal drugs can lead to the selection of resistant strains of fungi. Poor patient compliance with antifungal treatment, such as not completing the full course of treatment or not taking the medication as prescribed, can also contribute to the development of antifungal resistance. Fungi can develop genetic mutations that make them resistant to antifungal drugs. To address the issue of antifungal resistance, it is important to use antifungal drugs appropriately and only, when necessary, to follow treatment regimens as prescribed, and to encourage the development of new antifungal drugs. In addition, the use of combination therapy, which involves using two or more antifungal drugs at the same time, may help to reduce the risk of resistance and improve treatment outcomes. Antifungal medications are often prescribed for extended periods of time, leading to the selection of resistant strains of fungi. To address the issue of fungal resistance, it is important to use antifungal medications appropriately to avoid overuse or misuse and only use them for confirmed fungal infections.

Hülle cells, a thick-walled fungal spore formation seen in association with itraconazole resistance aspergillosis case as shown in Figure 3. The formation of Hülle cells in association with antifungal resistance needs to be investigated further to confirm the resistance character of the spores to corresponding antifungal.

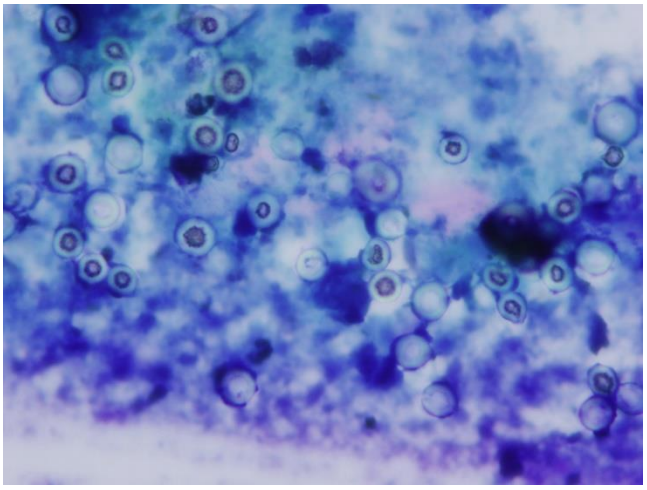

Figure 3: Imprint cytology from Aspergilloma after the treatment with itraconazole showed numerous Hülle cells with thick protective wall formation.

The resistance mechanism of itraconazole in Aspergillus species can arise due to the increased mechanisms of efflux pump activity, a mutation in the cytochrome P450 (CYP51) gene, and changes in cell wall permeability. Mutation of the CYP51 gene can lead to decreased sensitivity to azole like itraconazole, leading to treatment failure [30]. Recent studies found that itraconazole resistance rates among Aspergillus species in human infections have significantly increased [16,31]. This high rate of resistance has significant implications for the treatment of Aspergillus infections and highlights the need for new antifungal agents and strategies.

Voriconazole, isavuconazole, and Posaconazole are broad-spectrum antifungal belonging to the class triazole and commonly used for the treatment of invasive fungal infections, including infections caused by Aspergillus species. The Minimum Inhibitory Concentration (MIC) of posaconazole, isavuconazole, and voriconazole against Aspergillus species can provide valuable information about the drug's efficacy and studies have shown that posaconazole, isavuconazole, and voriconazole have high potency against Aspergillus species and has demonstrated excellent in vitro activity against both itraconazole-sensitive and itraconazole-resistant strains [10,15,22,23]. Recent

studies showed that the MIC values of posaconazole, isavuconazole, and voriconazole were found to have a lower MIC than itraconazole against all species tested [32-34]. This suggests that posaconazole, isavuconazole, and voriconazole may be a better choice for the treatment of Aspergillus infections, especially in cases where itraconazole resistance is present. However, there have been reports of voriconazole resistance in some fungal species, including Aspergillus. The mechanisms of voriconazole resistance in these species are not fully understood. Certain medications can interact with voriconazole and reduce its effectiveness, including some antibiotics, antacids, and proton pump inhibitors.

Fluconazole is a widely used antifungal medication against Candidiasis, but like all antifungal agents, it can face resistance from certain strains of fungi. Fungal resistance to Fluconazole occurs when the fungal cells develop mechanisms to pump out the drug before it has a chance to act [35]. This can result in reduced efficacy of fluconazole and a greater risk of fungal infections becoming more difficult to treat. The mechanisms of resistance in fluconazole can vary, with some strains of fungi producing enzymes that break down the drug, and others altering their cell membranes so the drug can't penetrate. Additionally, some fungal strains can develop mutations in the genes that the drug targets, rendering the drug ineffective. Fluconazole resistance is a growing concern, particularly in immunocompromised patients and those with chronic or recurrent infections.

Caspofungin is an antifungal drug in the class of echinocandins that is used to treat various fungal infections, including invasive Candidiasis, Esophageal Candidiasis, and aspergillosis. However, like other antifungal drugs, resistance to Caspofungin can develop in some fungal species. Resistance to Caspofungin can result from several mechanisms, including changes in the target enzyme, alterations in cell wall composition, and over expression of drug efflux pumps. These changes can result in decreased susceptibility to Caspofungin and decreased efficacy of treatment. Studies have shown that some species of Candida, such as *Candida glabrata*, are particularly prone to develop resistance to caspofungin, and treatment failure is common in patients with these infections [36]. In addition, Aspergillus species can also develop resistance to caspofungin, particularly in patients who have received long-term treatment with the drug [37].

A recent study found that the incidence of fungal infections in hospitals increased by 50% during the COVID-19 pandemic, compared to the previous years, and reported a twice increase in the number of patients with drug-resistant fungal infections during the pandemic [38]. These findings highlight the significant impact that the COVID-19 pandemic has had on the issue of fungal resistance and the need for continued attention and action to address this growing health threat.

Conclusion

The COVID-19 pandemic impacts a significant increase in the incidence and prevalence of fungal diseases and the main factor attributed was increased immunosuppression due to the decline in immunity by COVID-19, making individuals more susceptible to fungal infections. This is especially true for individuals who have received treatment for COVID-19, such as mechanical ventilation and corticosteroids. COVID-19 has led to an increase in hospitalization rates, which increases the risk of nosocomial infections, including fungal infections. The broad-spectrum triazoles including Voriconazole, Posaconazole, and Itraconazole are commonly used for the treatment of invasive fungal infections. The treatment of invasive fungal infections is challenging due to the limited number of antifungal agents available and the increasing prevalence of antifungal-resistant strains of fungi. The COVID-19 pandemic had a significant impact on the issue of fungal resistance. Prior to the pandemic, fungal resistance was already a growing concern, with increasing numbers of drug-resistant strains of fungi being reported. However, the pandemic has exacerbated this problem, leading to a further increase in the number of drug-resistant fungal infections. Compared to the situation prior to the pandemic, the issue of fungal resistance has become more pressing and more

widespread in the wake of COVID-19. The increased incidence of fungal infections, combined with the development of drug-resistant strains of fungi, has created a growing health threat that requires attention and action from the medical community. To address this growing health threat, it is important to use antifungal medications appropriately, improve hygiene and infection control practices, and invest in research into new treatments. By working together, we can help to ensure that effective treatments are available for those affected by fungal infections and reduce the risk of fungal resistance.

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