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Fungal Infections Linked to COVID-19: A Critical Need for Alternative Therapeutic Strategies?

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Abstract

The clinical course of patients with viral respiratory disorders, particularly those hospitalised to intensive care units, may be complicated by secondary fungal infections. Hospitalised COVID-19 patients are more likely to develop fungal co-infections, which can worsen the prognosis of the illness due to misdiagnosis, which frequently leads to ineffective treatment and a high mortality rate. Fungal infections linked to COVID-19, primarily caused by Aspergillus, and fungi of the order Mucorales have been documented to pose a serious burden to the healthcare system. To enhance clinical results, early identification and proper antifungal medication are necessary; nevertheless, the developing trend in drug resistance highlights the need for new therapeutic agents. This article's goal is to provide an overview of current understanding of COVID-19-associated mycoses, treatment options, and most recent developments in the development of antifungal drugs, with a focus on peptides with antifungal action.

Introduction

Given that they pose a nearly one-billion-person global hazard to human health, fungi diseases continue to be a serious medical concern. The prevalence of invasive fungal infections has been steadily rising for a number of reasons, including the use of immunosuppressive medications during cancer treatment or organ transplantation, an increase in the use of contemporary medical devices like catheters and implants, and the use of broad-spectrum antibiotics. The 2019 Coronavirus Disease (COVID-19) Pandemic made matters worse because it makes it more challenging to get an accurate diagnosis and predisposes patients to additional, fatal fungal infections in intensive care units. The management of COVID-19 is made more challenging by the concomitant respiratory symptoms. Lymphopenia, leukopenia, and systemic hyperinflammatory response, combined with a prolonged hospital stay and perhaps requiring mechanical ventilation, encourage the growth of fungus in COVID-19 patients. Additionally, the (WHO) COVID-19 treatment guidelines advise against prescribing broad-spectrum antibiotics based solely on symptoms to address potential bacterial co-infections (WHO, 2021). Most significant fungal illnesses are caused by the main pathogenic species Candida, Aspergillus, Mucorales, and Cryptococcus. Despite the unacceptably high mortality rate

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linked with fungal healthcare-related invasive infections, the actual number of deaths is probably underestimated because of inadequate epidemiological data and misdiagnosis. Antifungal drugs are widely used as a result of the high clinical mortality and financial burden caused by invasive fungal infections. Prophylaxis and antifungal therapies are crucial to lowering the comorbidities and fatalities brought on by fungus infections. However, under the strain of selective pharmaceuticals, the effectiveness of few systemic antifungal medications has changed, giving rise to species with less predictable antifungal susceptibility. Some fungal species are prone to microbial resistance, which can be either secondary (acquired resistance in an otherwise susceptible strain as a result of medication exposure) or intrinsic (strains are naturally less susceptible to a given antifungal agent). Triazole-resistant Aspergillus fumigatus is the most notable species that has recently emerged and is thought to be a serious threat to public health. The hunt for safer alternatives with lower toxicity, enhanced pharmacodynamics and pharmacokinetics, and increased specificity has been sparked by the limited spectrum activity and cross-resistance caused by similar mechanisms of action across medications.

Aspergillosis

Aspergillus spp. are common environmental moulds that produce spores that can be inhaled and cause illness. Due to the conidia's relatively tiny size and ability to deeply penetrate the alveolar space, A. fumigatus is the most prevalent etiological agent globally. Immunocompetent people' lungs are usually cleared of Aspergillus spores by neutrophils and macrophages, which are cellular elements of the innate immune system. However, in those with impaired immune systems, Aspergillus spp. can result in a range of clinical symptoms. After exposure to environmental spores by inhalation or inoculation, an infection may form, triggering allergic reactions or infectious disorders that may spread from the respiratory system to become widespread or invasive. According to reports, critically sick individuals frequently develop invasive pulmonary aspergillosis (IPA), which has a high morbidity and fatality rate. Hospitalized patients who get corticosteroid medication, antibiotics, or have hematologic malignancies are more likely to develop IPA. Influenza and other respiratory viral illnesses have also been linked to IPA. Critically ill patients run the risk of developing secondary infections with Aspergillus spp. due to immunopathological similarities between severe influenza and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pneumonia (such as cytokine storm syndrome, epithelial damage within the airways, and lymphopenia). Since COVID-19 patients in ICUs typically exhibit less-specific radiological indicators of infection in the presence of acute respiratory distress syndrome, the identification of COVID-19-associated pulmonary aspergillosis (CAPA) is challenging. The diagnosis of CAPA mostly relies on indirect fungal biomarkers (galactomannan and 1,3-D-glucan), culture-based approaches, and direct microscopic indication of fungal features that are unique to Aspergillus spp. Established CAPA categories include confirmed, likely, and possible based on sample validity and diagnostic evidence. Although serum -D-glucan and serum galactomannan both have poor sensitivity and specificity, and upper respiratory samples frequently are unable to

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distinguish between Aspergillus colonization and invasive disease, the presence of galactomannan in lower respiratory samples, such as bronchoalveolar lavage, is strongly suggestive of CAPA. Although the majority of experts considered bronchoscopy with bronchoalveolar lavage to be an effective method for detecting CAPA, bronchoscopy is not frequently carried out in many institutions in order to lower the danger of Covid-19 transmission due to aerosolization produced during this sampling method. Due to the fact that it has frequently been challenging to demonstrate the association between IPA and COVID-19, the majority of reported cases were therefore labelled as probable or possible CAPA. Since the incidence of CAPA post-mortem was somewhat lower than anticipated based on clinical findings, a comprehensive examination of autopsy series including histological investigations of COVID-19 decedents has further illustrated the difficulties with CAPA diagnosis.

Additional risk factors are frequently related to the care of severe COVID-19 patients. Studies with prospective and retrospective cohorts of COVID-19 patients admitted to intensive care units revealed a connection between the administration of high doses of corticosteroids and co-infection with Aspergillus. In addition, anti-interleukin-6 (IL-6) receptor therapy, like tocilizumab therapy, which is frequently used to treat COVID-19, seems to potentially confer higher risk for developing CAPA because 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. The importance of worldwide awareness and early diagnosis is shown by the incidences of CAPA, COVID-19, which increased the likelihood of developing an IPA, and CAPA, which was strongly associated with a higher mortality rate (up to 50%). VOR or isavuconazole are the first-line antifungal medications advised for CAPA by the European Confederation of Medical Mycology (ECMM) and International Society for Human and Animal Mycology (ISHAM). However, a number of adverse consequences of VOR therapy are well-known (for example, hepatic problems and gastrointestinal disturbances). Remdesivir, a medication frequently used in the treatment of COVID-19, and VOR both interact with other medications due to the cytochrome P450 enzyme CYP3A4's involvement in their metabolism. Due to VOR's unpredictable metabolism and the fact that both sub-therapeutic and hazardous amounts have been found in individuals who are severely unwell, plasma concentration monitoring is necessary. Its limited use in ICU patients was caused by its limited therapeutic window, toxicity, and medication interactions. Isavuconazole has a superior pharmacokinetic profile and is less toxic than VOR, but it also acts as a substrate for CYP3A4, which lowers its effectiveness. The alternate treatment is liposomal amphotericin B, with the exception of those who have renal impairment caused by COVID-19. Posaconazole and echinocandins are two other second-line medications. Echinocandins must be used as a last resort or in conjunction with other medications.

Mucor mycosis

Mucorales, an order of filamentous fungi, are the source of the Angio invasive fungal illness known as Mucor mycosis. After aspergillosis and candidiasis, it is the third most frequent fungal

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infection, accounting for 9% of all invasive mycosis in immunocompromised patients. Even with adequate treatment, the disease has a high fatality rate (reaching 40–80%) and a rapidly progressing nature. The pathogens that cause Mucor mycosis are Rhizopus species, Mucor species, Lichteimia species, Rhizomucor species, Cunninghamella species, Apophysomyces species, and Saksenaea species. In recent years and during the COVID-19 pandemic, the prevalence of Mucor mycosis has gradually increased, particularly in India. In the second wave of COVID-19, which was designated an outbreak in May 2021, India experienced a sharp rise in cases of COVID-19-associated Mucor mycosis (CAM), which caused the healthcare system to crumble in the midst of the pandemic. However, Mucor mycosis cases among individuals with COVID-19 or those who are recovering from it have been rising globally. Mucorales are widespread in nature and can be found in the soil and on decomposing organic waste. Fungal spores, which are always present in the air, can cause infection when they are breathed or when they are injected into damaged mucous membranes or wounds. Regardless of the route of invasion, hyphal development causes invasion of blood vessels, leading to thrombosis and gradual necrosis, which destroys soft tissue and bones. Six unique clinical manifestations—rhino-orbital-cerebral, pulmonary, gastrointestinal, cutaneous, disseminated, and rare infection—could be seen in susceptible hosts. The most prevalent type of Mucor mycosis is rhino-orbital-cerebral, with Rhizopus spp. being the most common etiological pathogen. Uncontrolled diabetic mellitus with ketoacidosis, neutropenia, haematological malignancy, stem cell and solid organ transplantations, iron chelation therapy with deferoxamine, and corticosteroid use are the main risk factors for the development of Mucor mycosis. Most COVID-19 patients had hyperglycemia, low oxygen levels, high iron levels, an acidic environment, and impaired phagocytic activity, all of which promote the growth of fungus, notably Mucorales, which rely on free iron levels in the serum for their pathogenesis. The non-specific clinical and radiological signs of pulmonary and disseminated Mucor mycosis could be confused with symptoms of COVID-19, making a diagnosis difficult. Furthermore, the results of imaging procedures or serological testing from sputum and BAL samples are illuminating, thus CAM can easily be mistaken for CAPA, the most common mould infection in patients with COVID-19-associated acute respiratory distress syndrome. The gold standard for disease diagnosis is thought to be histological evaluation of paraffin-embedded tissue samples. Mucorales species contain aseptate hyphae that are wide, ribbon-like, and branch at right angles. Polymerase chain reaction (PCR) is a new molecular diagnostic tool that may provide an alternate method for quick diagnosis and early medication initiation. Controlling the underlying condition or risk factor, surgically removing necrotic infected tissue, and administering appropriate antifungal medication are crucial therapeutic tenets for Mucor mycosis. In order to successfully manage Mucor mycosis, surgery must be performed before the illness spreads to other organs and tissues. When paired with early, appropriate systemic antifungal therapy, surgery is associated with noticeably better clinical outcomes. Due to the difficulties in making the right diagnosis, patients are typically treated

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empirically for Mucor mycosis. Due to Mucorales' inherent resistance to the majority of antifungal medications, there are few effective treatment choices available, which results in therapeutic failure. Since lipid formulations of amphotericin B have less nephrotoxicity than other formulations, they are especially advantageous when given in high daily doses in case of orbital-cerebral involvement and are strongly advised as first-line treatment for serious life-threatening Mucor mycosis. For people with reduced renal function, posaconazole and isavuconazole have become standard second-line or salvage therapies. Echinocandins and VOR are ineffective. In severe cases of Mucor mycosis, other preventative measures (such combination therapy) should be taken.

Biologically Active Peptides as Potential Therapeutic Agents for Fungi

The need for novel medicines with enhanced safety profiles and broad-spectrum antimicrobial efficacy has been driven by the narrow spectrum of activity, side effects, drug-drug interactions, and high emergence of resistance of currently utilized antifungals. To overcome these obstacles, novel antifungals are now being researched, with a focus on toxicity reduction, pharmacodynamic and pharmacokinetic optimization, formulation enhancement, and increased specificity. Rezafungin, tetrazoles, and ibrexafungerp are some examples of innovations that have concentrated on medicines with new structures for established targets or on the establishment of completely new targets. Despite current efforts, antifungal drug resistance remained a significant issue; therefore, it is indisputable that different therapeutic techniques should be introduced. One of the possible therapeutic methods could involve combining conventional antifungals with quorum-sensing molecules (like farnesol or tyrosol) or non-antifungal medicines. Antimicrobial peptides (AMPs) are one of the other potential antimicrobial possibilities grabbing researchers' interest. The host defense peptides known as AMPs are crucial to the innate immune response. The 15–50 amino acids that make up AMPs are primarily cationic at physiological pH, and their amphipathic shape makes it easier for them to interact with the negatively charged membrane of microorganisms, which can result in membrane insertion, cell rupture, and membrane destabilization. Because AMPs exhibit a swift and dramatic effect on the slowly evolving fungal cell membrane, resistance to them is less likely to develop.

Future perspective

As a result of COVID-19, secondary fungal infections are a major cause for concern as the mortality rate in ICUs, particularly in patients with underlying conditions, rises due to delayed diagnosis brought on by similar symptoms of infections and the difficulties of identification techniques and treatment. Along with candidiasis, aspergillosis, and Mucor mycosis, COVID-19 patients are increasingly reporting fungaemia caused by Cryptococcus and Trichosporon species. Medical practices are challenged by the need to quickly and accurately identify fungal pathogens and adopt stringent infection control measures, which understates the prevalence of fungal co-infection in COVID-19 patients. Corticosteroid, immunosuppressant, and broad-spectrum antibiotic dosage and duration should all be carefully examined. Corticosteroid, immunosuppressant, and broad-spectrum

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antibiotic dosage and duration should all be carefully examined. The survival rate of hospitalized COVID-19 patients with fungal co-infections may be increased with prompt diagnosis and appropriate antifungal management; however, the therapeutic options currently available are limited, and the emergence of resistant or MDR fungal species compels us to look for new alternatives to combat nosocomial drug-resistant infections in hospital settings. Because of their variety and broad-spectrum activity, AMPs become excellent candidates for the creation of brand-new antimycotics. Commercial applications of AMPs are hampered by their poor pharmacological characteristics, toxicity, and high cost of large-scale manufacture.

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