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Short Communication

Increase of Airway Fungal Co-Infections in Covid-19 Hospitalized Patients: A Brief Report

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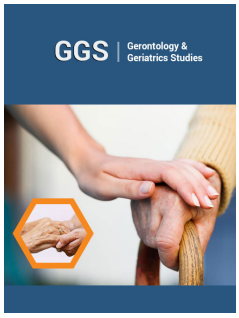
ISSN: 2578-0093



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Submission: January 03, 2022
Published: January 19, 2022

Volume 7 - Issue 4

How to cite this article: Efthymia Iliana Matthaiou. Increase of Airway Fungal Co-Infections in Covid-19 Hospitalized Patients: A Brief Report. Gerontol & Geriatric stud. 7(4). GGS. 000666. 2022. DOI: 10.31031/GGS.2022.07.000666

Abstract

The human-to-human transmitted disease, coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread worldwide and affected more than 270 million people, leading to more than 5 million deaths. COVID-19 patients with Acute Respiratory Distress Syndrome(ARDS) are often admitted to Intensive Care Units (ICUs), frequently receive corticosteroids, broad-spectrum antibiotics and immunomodulatory agents. An increase of secondary fungal infections has been described in these patients, which are frequently associated with poor patient outcomes. The incidence of these infections varies from country to county. Additionally, a variety of fungal species have been reported around the globe. In this report we will discuss various aspects of COVID-19 associated fungal infections focusing on risk factors, treatments and current challenges.

Keywords: COVID-19; SARS-CoV-2; Co-infection; Aspergillosis; Mucormycosis

Short Communication

Infectious diseases plagued humanity throughout history, the most recent Coronavirus Disease 2019 (COVID-19) pandemic had a severe impact in the world and revealed the vulnerability of the modern society to the airway infections. Respiratory fungal infections can be life-threatening and usually affect immunosuppressed patients, such as HIV/AIDS and cancer patients who undergo chemotherapy, as well as those patients who receive immunosuppressive therapy such as patients that receive transplants or patients with autoimmune diseases. *Aspergillus*, *Cryptococcus*, *Pneumocystis*, *Rhizopus*, *Mucor* and endemic fungi are major pulmonary fungal pathogens that can cause invasive disease. Recent studies have estimated that globally, fungal infections kill more than 1.7 million people per year, which is higher to the mortality due to tuberculosis (1.5 million) and about four-times more than malaria (405.000) [1]. Alarmingly, these numbers are continuously on the rise with a number of social and medical developments during the past decades that have abetted the spread of fungal infections. Moreover, the long-term therapeutic application and prophylactic use of antifungal drugs in high-risk patients have promoted the emergence of (multi)drug-resistant fungi. Thus, invasive fungal diseases are very difficult to treat, and their associated mortality remains very high depending on the pathogen and the patient population, making them an emerging issue worldwide.

Fungal and viral co-infections have been reported throughout the years with Severe Acute Respiratory Syndrome (SARS) and Influenza. *Aspergillus* species was the prevalent fungus found in these patients. Data published on SARS in 2003, reported the incidence of fungal infection in SARS patients was 14.8-27%, which was even higher in severely ill ones, up to 21.9-33%, meanwhile, fungal infection was the main cause of death for SARS patients,

accounting for 25-73.7% in all causes of death [2]. Furthermore, studies in global epidemiology of influenza reported that the mortality rate of influenza and invasive aspergillosis co-infection is 51% almost double compared to patients without invasive aspergillosis (28%) [2]. Since February 2020 more than 700 manuscripts have been published on COVID-19 and fungal co-infections. These co-infections seem to be affecting mostly patients in the ICUs. COVID-19 clinical manifestations include hypoxia, immunosuppression, hyperferritinemia, hyperglycemia secondary to diabetes mellitus and prolonged hospitalizations [3].

These create a favorable environment for opportunistic fungal pathogens to infect hosts with COVID-19. According to the literature, fungal coinfections in COVID-19 infected patients were most commonly caused by *Aspergillus*, *Candida species*, *Cryptococcus neoformans*, and fungi of the *Mucorales order* (*Rhizopus spp.*, *Lichtheimia spp.*, and *Mucor spp.*), with *Aspergillus* being the most prevalent pathogen in COVID-19 co-infections worldwide and Mucorales order fungi were markedly skewed towards low- and middle-income countries [1,3,4]. The incidence rates of COVID-19 associated aspergillosis (CAPA) reached up to 35% in the United States and European countries while in some countries like Japan the incidence rate of CAPA in critical COVID-19 cases was extremely low (0.54%). COVID-19 Associated Mucormycosis (CAM) reported incidences were high in Bangladesh, India, Iraq, Nepal and Pakistan with an over 50% mortality rate [3]. In the literature COVID-19 associated fungal infections seem to mostly affect non-immunocompromised patients (75%) with severe Acute Respiratory Distress Syndrome (ARDS) receiving corticosteroids in the ICUs [4].

Despite the ranging incidences the mortality rate in these co-infections remain high (over 50%) so it is important to understand the underlying risk factors that leads to these infections. The current knowledge of the risk factors for secondary pulmonary infections in SARS-CoV-2 is continuously evolving but remains poorly understood, it remains unclear if critically ill patients are at greater likelihood of development fungal co-infections. COVID-19 infection triggers both the innate and adaptive immune responses, including recruitment of macrophages and monocytes, release of cytokines, and prime adaptive T- and B-cell in an effort to resolve underlying inflammation. Within a week from COVID-19 infection an increase in the inflammatory mediators (interleukin (IL)-2, IL-6, IL-8, IL-10, tumor necrosis factor (TNF)-α, interferon (IFN)-γ) and a decrease in the lymphocyte count (specifically T-cells) is observed [1,3,5-7]. This immune dysregulation has been reported to a greater degree in critically ill COVID-19 patients. This well-documented lymphocytopenia-induced immunosuppression could explain to some degree the time that the secondary pulmonary infections occur (typically 9 days upon ICU admission) [2,8]. In addition to the viral-associated immunosuppression, COVID-19 critically ill patients are often given steroids in the first few days preceding or after ICU admission for a variety of reasons including COPD exacerbation or complications such as sepsis. However, corticosteroid treatment has additive immunosuppressive effects. Particularly, corticosteroids regulate adaptive immunity by inhibiting lymphocyte activation and promoting lymphocyte apoptosis. At high concentrations, glucocorticoids also inhibit the production of B cells and T cells. In COVID-19 cases corticosteroid treatments were reported to cause decrease of IL-6 in the plasma, which could explain the susceptibility of these patients to fungal infections [6]. On the other hand, corticosteroid treatment leads to hyperglycemia, a well-known risk factor for fungal infections. Hyperglycemia can inhibit immune responses via several mechanisms, including glycosylation of complement proteins leading to impaired function, impaired binding of oligosaccharides by C-type leptin, impaired opsonophagocytosis, and decreased production of IL-10, TNF-a, and IFN-γ [3]. COVID-19 patients with hyperglycemia were reported to have nearly double the risk of fungal coinfection compared to patients with normal blood glucose levels.

Patients with COVID-19 present with hypoxia and hypoxic tissue injury. Hypoxemia is also common in patients with COVID-19 infection. It has been reported that COVID-19 infection has an impact on the vascular system and blood's coagulation properties, damaging the respiratory epithelium, injuring vascular walls and causing blood clots to form in both large and microscopic blood vessels [3,5]. This COVID-19 associated capillary damage could interfere with tissue oxygenation and result in the clinical development of hypoxia. The COVID-19 associated airway tissue injury aids the fungal invasion, while hypoxia has been linked to the fungal pathogenesis. Particularly, opportunistic fungi like *Aspergillus* can sense environmental oxygen levels, adapt and thrive in hypoxic conditions. Furthermore, in animal models, hypoxia was associated with fungal virulence. On the other hand, this COVID-19 associated vascular injury leads to elevated iron levels in the airways [3,4]. In addition, high-ferritin levels have been correlated with severe COVID-19 infections. Increased levels of iron are known to moderate the immune response through phagocytosis impairment; while iron is essential for fungal growth and has been linked to fungal virulence and invasiveness. This could explain to some extend the COVID-19 patient susceptibility to fungal co-infections. Additionally, since ferritin levels are also known to be elevated in diabetic patients, which may partially explain the increased propensity for severe inflammatory reactions and death seen in hyperglycemic COVID-19 patients [1-5,9]. Over and above that, high incidence of people with untreated diabetes is usually found in low-income countries, this could elucidate the increase of COVID-19 associated fungal infections in these countries compared to the developed countries.

Finally, COVID-19 patients in admitted in the ICU are receiving mechanical ventilation. Mechanical ventilation leads to an increased rate of micro aspiration of contaminated oropharyngeal secretions and gastric contents, which increases the chances of introduction of pathogenic fungi. A study that analyzed 197 critically ill COVID-19 patients that were under mechanical ventilation in the ICU, reported that 68% of these patients had positive respiratory fungal cultures. Despite the dramatic increase in positive fungal

cultures only a small percentage of these patients seem to develop life-threatening invasive fungal disease. Among these positive fungal cultures Candida is the most frequently detected fungus (75.4%), while *Aspergillus* the leading cause invasive pulmonary fungal infections is not detected as frequently [2,3,5,7-9]. Even if mechanical ventilation increases the risk of exposure to pathologic fungi, COVID-associated fungal infection seems to be dependent on the fungal species.

As discussed above, a combination of risk factors seems to be responsible for the increased occurrence of COVID-19 associated fungal infections. Despite the recent medical advances, the mortality rate in these patients is high. This could be attributed to two factors

(i) lack of accurate and timely diagnosis and

(ii) Insufficiency of effective treatments. The most common diagnostic methods for fungal species are Bronchoalveolar Fluid (BALF) and tracheal aspirate cultures, screening for the fungal biomarker Galactomannan (GM) in BALF, tracheal aspirate, and serum specimens.

Aspergillus specific detection assays include the *Aspergillus* PCR, serum (1→3)-β-D-Glucan (BDG), the *Aspergillus* galactomannan Lateral Flow Assay (LFA), and the *Aspergillus*-specific Lateral-Flow Device (LFD) test [2,5,8,9]. BALF and tracheal aspirate cultures and the GM screening from BALF appear to be the most reliable diagnostic methods. However, bronchoscopy is a high-risk procedure since it can potentially aerosolize the SARS-CoV-2 virus and pose a risk to both patients and hospital personnel. Thus, diagnostic methods using blood samples are considered safer and more optimal. Furthermore, for timely diagnosis a more frequent screening (twice weekly) could be beneficial for COVID-19 patients and has been implemented in many centers. Unfortunately, the sensitivity of the blood sample detection methods is low and not specific. We are in need of novel, safe, sensitive, and fungal species-specific diagnostic methods to detect fungal co-infections in patients with COVID-19. Early diagnosis would trigger early anti-fungal treatment and possibly result in better patient outcomes. Voriconazole is the recommended first-line therapy for invasive pulmonary aspergillosis.

Besides voriconazole's narrow therapeutic window, this drug side-effects include neuro- and hepato-toxicity [2,5,8,9]. Also, since voriconazole is being metabolized via CYP2C19, CYP2C9, and CYP3A4, interaction with other drugs is inevitable and limits its usage in the ICU. New classes of anti-fungal drugs are under development and seem promising to use in the ICU since they have been reported to have less drug-drug interactions and toxicity. If the identified increase of COVID-19 associated fungal infections will be confirmed by larger studies then fungal prophylactic treatments might be employed for COVID-19 patients admitted in the ICU. Moreover, given the potential role of free iron in severe COVID-19, iron chelation could be a potential therapy for hospitalized COVID-19 patients, as iron chelators are effective in reducing free iron levels and possess direct antiviral properties that decrease viral binding and entry via host cell receptors. However, safety and tissue delivery issues need to be addressed for this type of treatments.

To this day, our understanding of the true impact of fungal co-infections remains limited. Healthcare professionals should be aware of risk factors and the possibility of secondary infections associated with them in treating COVID-19 patients. Autopsies of COVID-19 fatalities would likely increase and prove the clinical relevance of COVID-19 associated fungal infections. Immunosuppression, epithelial cell damage, hypoxia, tissue iron- and blood sugar levels-increase, and mechanical ventilation are the identified risk factors that could lead to life-threatening fungal disease in COVID-19 patients. Invasive fungal co-infections are associated with poor patient outcomes in COVID-19, but the incidence of these co-infections will likely continue to vary between different ICU settings. Key goals are to improve COVID-19 patient outcomes by avoiding misdiagnosis and by initiation of early and targeted antifungal treatment.

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