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Review Article

COVID-19 Associated Fungal Diseases: Its impact on disease and treatment

Tahsin Tabassum[1], Fahim Ahmed[2], Nasima Begum[2]

[1]School of Community Health and Policy, Morgan State University, Baltimore, MD, USA
[2]Foothill Infectious Disease Medical Group, Claremont, CA, USA

***Corresponding author: Nasima Begum,** Email: begum293@gmail.com

Abstract

Background: In the wake of COVID-19 pandemic, fungal superinfections are on the rise. Individuals with underlying comorbidities such as diabetes mellitus, those receiving corticosteroid therapy, and critically ill patients are at grave risk of developing COVID-19-associated fungal diseases.

Aim: The purpose of this literature review is to provide a detailed analysis of how COVID-19 facilitates the pathogenesis of COVID-19-associated fungal diseases. This review will present current research regarding the risk factors, clinical features, relevant laboratory investigation, diagnosis, and treatment regimen of COVID-19-associated fungal diseases such as COVID-19 Associated Pulmonary Aspergillosis (CAPA), COVID-19 Associated Mucormycosis (CAM), and COVID associated yeast infections.

Methods: This literature review was conducted to analyze the association between SARS-CoV-2 infection and fungal superinfections through the utilization of online research databases such as PubMed and Google Scholar. This literature review revealed and supported the link between COVID-19 and COVID-19 Associated Pulmonary Aspergillosis (CAPA), COVID-19 Associated Mucormycosis (CAM), and COVID-associated yeast infections. This review highlights the epidemiology, mode of transmission, pathogenesis, and clinical management of COVID-19-associated fungal diseases illustrated by contemporary studies.

Results: This literature review revealed and supported the association between SARS-CoV-2 infection and fungal superinfections in critically ill patients, diabetic, and immunocompromised individuals.

Conclusions: COVID-19-associated fungal diseases were seldom reported during the onset of the COVID-19 pandemic. However, with the emergence of novel subvariants of the omicron variant of SARS-CoV-2, COVID-19-associated fungal superinfections could affect the immunocompromised hospitalized patient population across the U.S. and potentially wreak havoc on our hard-pressed healthcare system. Therefore, we need to deepen our understanding of how SARS-CoV-2 is causing secondary fungal diseases and what can be done to alleviate this dire situation.

Keywords: Mucormycosis, COVID-19, Pulmonary Aspergillosis

Introduction

As of today, the world is grappling with an unpredictable battle against SARS-CoV-2 which although started as a viral outbreak in Wuhan, China, has now advanced into a deadly pandemic. At present, the nations affected by this menace are engrossed in research pertaining to epidemiology, mode of transmission, clinical management, prevention of the spread of the virus, and challenges of global health, while crucially significant fungal infections secondary to COVID-19 have been given less momentum in this endeavor [1]. Despite the fact that fungal superinfections were seldom reported during the onset of the COVID-19 pandemic, currently, they are gradually escalating 2. In this article, we aim to shed light on the risk factors, pathogenesis, clinical features, relevant laboratory investigation, diagnosis, and treatment regimen of COVID-19-associated fungal diseases such as COVID-19 Associated Pulmonary Aspergillosis (CAPA), COVID-19 Associated Mucormycosis (CAM), and COVID-19-associated yeast infections.

Methods

Utilizing online databases, research studies beginning in the year 2020-2021 were identified. The only exception was an article published in 2018 that depicted the pulmonary host defense against Rhizopus species regulated by iron restriction inside macrophages. Current research on COVID-19-associated fungal diseases such as COVID-19 Associated Pulmonary Aspergillosis (CAPA), COVID-19 Associated Mucormycosis (CAM), and COVID associated yeast infections was chosen because it pertained to this literature review. For our selection process, we used PubMed and Google Scholar as our primary online databases. A combination of key terms such as COVID-19 pandemic; COVID-19 associated fungal diseases; risk factors of COVID-19 associated fungal diseases; diagnosis of COVID-19 associated fungal diseases, and management of COVID-19 associated fungal diseases was used to retrieve the relevant, peer-reviewed articles for analysis from these two databases. We entered the key terms such as (COVID-19 pandemic) AND (fungal diseases/Broad[filter]) into the selected database's search engines. From our initial hits, we screened twenty-one articles. A thorough analysis and synthesis were done to select appropriate quantitative and qualitative study articles that emphasize the link between SARS-CoV-2 infection and secondary fungal diseases.

Risk factors linked to COVID-19 Associated Fungal Disease

According to Shivakumar et al. (2021), underlying comorbidities such as diabetes mellitus and receiving corticosteroid therapy are considered as common risk factors for COVID-19 associated fungal diseases[3]. Furthermore, hematologic malignancy, and solid organ or stem cell transplant could also predispose to COVID-19-associated fungal diseases [4].

Allaw et al. (2021), propounded that COVID-19 patients with a history of prolonged hospital stay, administration of central venous catheter and Foley catheter, undergoing mechanical ventilation, and receiving broad spectrum antibiotics including piperacillin-tazobactam, carbapenems and ceftolozane-tazobactam later developed secondary fungal infections [5]. Therefore, these attributes should be regarded as risk factors.

Besides, getting Anti-interleukin6 (Anti-IL6) treatment, lung injury, prolonged Intensive Care Unit (ICU) stay, and receiving Extra-Corporeal Membrane Oxygenation (ECMO) therapy could also result in COVID-19 associated fungal diseases [6,7].

COVID-19 Associated Pulmonary Aspergillosis (CAPA)

The development of invasive pulmonary aspergillosis (IPA) in temporal proximity to a prior SARS-CoV-2 infection in a patient is termed as CAPA[8]. The European Confederation for Medical Mycology (ECMM) and the International Society for Human and Animal Mycology (ISHAM) published a consensus CAPA case definition in December 2020[9]. As per ECMM and ISHAM, the patients are classified as proven, probable, and possible CAPA[9]. *Aspergillus* spp. causes co-infections in critically ill patients with

COVID-19 [10]. Most generally *Aspergillus fumigatus* species, and subsequently *Aspergillus flavus* species cause co-infection in COVID-19 patients[10]. Salmanton-García J, et al. (2021), conducted a retrospective study utilizing clinical data of 186 CAPA patients worldwide, who were diagnosed from March 1 to August 31, 2020[11]. As stated by Salmanton-García J, et al. (2021), there is male predominance among the CAPA patients; and the median age is 68 years[11]. Meanwhile, Armstrong-James et al. (2020), stated that the median (interquartile range) age of CAPA cases is 70 (57–75) years [12]. In a multinational study conducted on 592 patients by Prattes et al. (2022), CAPA was remarkably found to be more prevalent among older patients, patients receiving invasive ventilation and patients receiving the drug tocilizumab[13]. According to Salmanton-García J, et al. (2021), the concurrent conditions with CAPA are chronic cardiovascular disease, renal failure, diabetes mellitus, obesity, chronic pulmonary disease, hematologic or oncologic diseases/malignancy, solid tumor, solid organ transplantation, and neutropenia[11]. In their study, Salmanton-García J, et al. (2021), found the incidence of CAPA among COVID-19 patients admitted to Intensive Care Unit (ICU) to be 2.5%-39.1% [11]. The cumulative incidences of CAPA among COVID-19 patients admitted to ICU requiring mechanical ventilation ranged from 1.1%–47.4% [11]. They inferred an overall 6.9% cumulative incidence for CAPA among COVID-19 patients [11]. Lai and Yu J. (2021) stated that the incidence of IPA in COVID-19 ranged from 19.6% to 33.3% [10]. According to Verweij et al. (2021), the prevalence of CAPA varied between 0 and 33% [9].

Respiratory viruses directly cause local air way epithelial damage, thus providing a portal of entry for *Aspergillus* to colonize respiratory tract, invade tissue and blood vessels[8,9]. Furthermore, viral infection impedes ciliary clearance, and therefore leading to immune dysfunction or dysregulation[8]. As a result, patients develop profound immune-suppression, facilitating fungal super infection[8]. As mentioned by Lai and Yu J. (2021), post respiratory viral Th-2 immune response of increasing IL-10 followed by temporary Th1 immune depression predisposes to down-regulation of macrophage responses, and concertedly increase an individual's susceptibility to invasive pulmonary aspergillosis [10].

Clinical features of COVID-19 Associated Pulmonary Aspergillosis (CAPA)

If a COVID-19 patient presents with any of the following clinical findings such as refractory fever for more than 3 days or a new fever after a period of defervescence of longer than 48 hours while receiving appropriate antibiotic therapy, in the absence of any other obvious cause; worsening respiratory status (eg, tachypnoea or increasing oxygen requirements); haemoptysis; and pleural friction rub or chest pain, refractory respiratory failure for more than 5–14 days despite receiving all treatment mentioned in the guidelines, CAPA should be considered[8]. Proven CAPA is termed as pulmonary or tracheobronchial infection[8]. It is confirmed by histopathological or direct microscopic detection, or both, of fungal elements that are morphologically consistent with Aspergillus spp, exhibiting invasive tissues growth and damage[8]. Probable CAPA tracheobronchitis diagnosis requires the presence of trachea-bronchial ulceration, nodule, pseudo-membrane, plaque, or eschar, alone or in combination, on bronchoscopic analysis as well as mycological evidence[8]. Possible pulmonary CAPA can be diagnosed by the observation of pulmonary infiltrate or nodules via chest CT scan, or cavitating infiltrate in combination with mycological evidence (for instance, microscopy, culture, or galactomannan, alone or in combination) collected through non-bronchoscopic lavage[8]. Positive SARS-CoV-2 RT-PCR test result anytime during 2 weeks between hospital admission and ICU admission or positive RT-PCR within 72–96 hours after ICU admission with clinical symptoms that are compatible with COVID-19, who develop respiratory insufficiency requiring intensive care, should be considered at high risk for CAPA [8].

Diagnosis of COVID-19 Associated Pulmonary Aspergillosis (CAPA)

According to Lai and Yu J. (2021), fungus culture and galactomannan test, performed in respiratory specimens aid in early diagnosis of CAPA [10]. Thereby, the desired specimen for elaborating mycological

evidence is respiratory samples[8]. Respiratory specimens are obtained through bronchoscopy and bronchoalveolar lavage. Direct microscopy, fungal culture, PCR that is specific to the *Aspergillus* spp, testing for galactomannan, Aspergillus Galactomannan Lateral Flow Assay (LFA) should be performed in the bronchoalveolar lavage fluid [8]. Here, the Aspergillus LFA is a rapid test done to diagnose invasive pulmonary aspergillosis (IPA) especially in patients with hematologic malignancies[14]. In a multicenter, retrospective study on 296 patients conducted by Jenks et al. (2021), LFA assay demonstrated good diagnostic performance for IPA when performed in bronchoalveolar lavage fluid (BALF) specimens [14]. Hence, bronchoalveolar lavage fluid and lung biopsy samples are the preferred samples to diagnose IPA[8]. Identification of galactomannan in bronchoalveolar lavage fluid is considered to be highly suggestive of IPA[8]. Bronchoalveolar lavage fluid can also be utilized as favored specimen for *Aspergillus* antigen test (via enzyme immunoassay/ELISA) and *Aspergillus* DNA PCR [8].

Evidence of invasive growth of septate fungal hyphae present in tissue culture and tissue microscopy is considered the diagnostic gold standard in proving infection [8]. Besides, direct visualization of the trachea and bronchi can be done via bronchoscopy, which enables identification of patients with aspergillus tracheobronchitis[8]. Bronchoscopy allows for the inspection of lesions such as plaques which aids the diagnosis of IPA [8].

Nonetheless, bronchoscopy has an elevated risk for aerosol generation, nosocomial viral transmission and resultant SARS-CoV-2 infection of health-care workers[11]. Therefore, bronchoscopy and bronchoalveolar lavage fluid samples from COVID-19 patients must be handled with adequate safety precautions[11]. Bronchial aspirate, Non-bronchoalveolar lavage, tracheal aspirate, and sputum are the substitute respiratory sample sources to be considered [11].

Lai and Yu J. (2021), mentioned that the levels of galactomannan in bronchoalveolar lavage (BAL) fluid were always higher than those in serum [10]. Although PCR, galactomannan, and LFA testing performed on serum samples has low sensitivity, but they possess high specificity in case of non-neutropenic patients, including CAPA patients [8].

Furthermore, (1–3)-β-D-glucan is another biomarker for serum screening [8]. Despite (1–3)-β-D-glucan, not being specific for aspergillosis, two consecutive results for serum (1–3)-β-D-glucan might raise the possibility of invasive aspergillosis [8]. Therefore, (1–3)-β-D-glucan might be considered beneficial [8].

CT scan should be considered in those patients without clinical response or with progressive nodular infiltrates[8]. Multiple pulmonary nodules, lung cavitation, and dendritic signs is found in early stage of IPA[8,10]. Peripheral nodule, air crescent, reverse halo sign, nodular consolidation, ground-glass opacities, pleural effusion, and pulmonary cysts are the additional radiographic findings in CAPA patients [10].

Treatment of COVID-19 Associated Pulmonary Aspergillosis (CAPA)

Antifungal drug therapy specifically voriconazole or isavuconazole is indicated in CAPA patients, as stated by Verweij et al. (2021) [9]. Intravenous voriconazole or isavuconazole are considered as first-line treatment option for possible, probable, and proven CAPA patients[8]. Salmanton-García J, et al. (2021), found voriconazole to be associated with decreased death [11].

The loading dose for Voriconazole treatment is 6 mg/kg twice a day for two doses [8]. This is followed by 4 mg/kg twice a day [8]. The loading dose for Daily isavuconazole treatment is 200 mg three times a day for six doses [8]. This is followed by 200 mg once a day, 12–24 h after the last loading dose [8]. Treatment with isavuconazole shares similar clinical activity to voriconazole but has less adverse effects such as hepatotoxicity, neurotoxicity [8]. It also has decreased risk of corrected QT-interval prolongation compared to voriconazole [8]. Besides, drug–drug interactions are generally less profound with isavuconazole than with voriconazole [8]. Therefore, twice in the first week and afterwards weekly therapeutic drug monitoring is recommended in CAPA patients, specifically for voriconazole and posaconazole [8]. Rezafungin is an echinocandin designed to be dosed once weekly [15].

The time limit of 6–12 weeks is considered as optimal duration of therapy [8]. Lung CT imaging is advised for follow-up for the purpose of documenting the resolution of infiltrates before ending of drug therapy [8]. Longer duration of treatment might be required for immunocompromised patients such as those with haematological malignancy or those receiving immunosuppressive therapy[8]. Although liposomal amphotericin B is the cardinal alternative drug for treatment of IPA patients in the ICU; but, it is nephrotoxic and might lead to deterioration of renal function[8]. Vanderbeke et al. (2021), advocate that posaconazole (POS) prophylaxis may deter the development of CAPA in COVID-19 patients[16]. Thereby, prevention of CAPA with the intravenous drug posaconazole (POS), may result in improved overall outcomes among these patients [16].

In critically ill CAPA patients, echinocandins (in combination with an azole) can be used for salvage therapy[8]. Fosmanogepix is an inositol acylase inhibitor or a novel GPI-anchored wall transfer protein 1 (Gwt1) enzyme inhibitor, which is in clinical trials for invasive aspergillosis[8,15]. Ibrexafungerp is an oral, first-in-class, triterpenoid betaglucan inhibitor, which inhibits the 1,3-beta-D-glucan synthase enzyme and acts fungistatically on *Aspergillus* spp; it is also in clinical trials for invasive aspergillosis [8,15]. Olorofim belonging to class Orotomide is a novel dihyroorotate dehydrogenase enzyme inhibitor, which targets pyrimidine synthesis[15]. Opelconazole is a novel triazole optimized for inhalation[15]. According to Hoenigl et al. (2021), new antifungal drugs, such as fosmanogepix, ibrexafungerp, opelconazole, which at present are in late-stage clinical development may surmount current concerns of drug-drug interactions, toxicity, and constraints in administration routes[15]. Fusmanogepix and Olorofim have equivalent efficacy without the adverse effects of toxicity and drug-drug interactions[15]. Rezafungin, ibrexafungerp, and Opelconazole is prepared for inhalation via readily available nebulizers[15]. Consequently, they might prove to be better treatment options for CAPA patients in the future [15].

Discussion

The clinical outcome of CAPA is quite poor. The most common complication of CAPA is acute respiratory distress syndrome (ARDS), in which a patient needs mechanical ventilation[10]. According to the retrospective analysis of 186 CAPA patients conducted by Salmanton-García J, et al. (2021), overall mortality rate was found to be 52.2%, of which most (47.8%) died in less than 6 weeks after the diagnosis of CAPA was made [11]. As per Verweij et al. (2021), mortality of CAPA is approximately 50% [9]. Additionally, a multinational case-control study conducted by Ergün et al. (2021), on 219 critically ill COVID-19 cases, ascertained the mortality rate to be 53.8% in CAPA patients compared to 24.1% in patients without CAPA[17]. They also found that positive serum galactomannan and serum (1,3)-β-d-glucan (BDG), were linked to greater mortality compared to serum biomarker-negative CAPA patients [17]. Since the serum biomarkers, if positive, suggest angioinvasion and a high risk of mortality, hence, they can be utilized for staging CAPA disease progression [17].

Besides CAPA, other significant COVID-19 Associated fungal diseases include COVID-19 Associated Mucormycosis (CAM) and COVID Associated yeast infections such as COVID-19 Associated Candidiasis (CAC). Uncontrolled diabetes mellitus resulting in an increase of Fe2+, high dose or unindicated corticosteroid use, hematologic malignancy, solid organ tumor or receiving stem cell transplant are considered risk factors for COVID-19 Associated Mucormycosis (CAM)[3,4,18]. Since Mucorales use free iron in their biological processes, therefore, raised free iron can be found in COVID-19 Associated Mucormycosis (CAM)[19]. Uncontrolled diabetic patients with COVID-19, who received corticosteroid therapy are at risk of developing complications such as Rhino-orbito-cerebral mucormycosis (ROCM) and Pulmonary mucormycosis (PM) [18]. According to Rudramurthy et al. (2021), management of CAM is comprised of administration of systemic antifungal therapy, surgical resection and debridement of the external infected tissues, and control of underlying disease [18]. Here, injectable liposomal amphotericin B is recommended as the first line of treatment [18]. Besides this, posaconazole and isavuconazole are also deemed to be useful [18]. Notable risk factors of COVID associated yeast infections include subpar infectious disease protocols in emergency department (ED) and critical

care unit such as improper hand washing, inadequate cleaning and disinfection of the patient equipment such as ventilators and central venous catheters[5]. According to Allaw et al. (2021), increased age, receiving broad-spectrum antibiotics such as piperacillin-tazobactam, carbapenems and ceftolozane-tazobactam; use of tocilizumab, steroids, and requiring mechanical ventilation serve as additional risk factors [5].

Rezafungin, Ibrexafungerp, and fosmanogepix are the newer classes of antifungal drugs targeting *Candida* spp including *Candida auris* that are considered future treatment modalities for COVID associated yeast infections [15]. As stated by Hoenigl et al. (2021), the antifungal drug ibrexafungerp inhibits the 1,3-beta-D-glucan synthase enzyme and acts fungicidally on *Candida* spp.[15]. Table 1 illustrates the therapeutic options for COVID-19, COVID-19 with Aspergillosis, COVID-19 with Mucormycosis, and COVID-19 with Candidiasis[8, 9,15,18,21].

Table 1: Therapeutic Management of COVID-19, COVID-19 with Aspergillosis, COVID-19 with Mucormycosis, and COVID-19 with Candidiasis[8,9,15,18,21]

Treatment criteria	COVID-19 +ve	*COVID-19 + Aspergillus +ve*	COVID-19 + Mucormycosis +ve	*COVID-19 + Candia +ve*
Non-hospitalized Adults	Ritonavir-boosted nirmatrelvir (Paxlovid) Remdesivir	-	-	-
Hospitalized Adults requiring supplemental oxygen	Remdesivir Dexamethasone	Voriconazole Isavuconazole Rezafungin	liposomal amphotericin B Posaconazole Isavuconazole	Ibrexafungerp Rezafungin Fosmanogepix
Hospitalized Adults requiring Mechanical Ventilation or Extra-Corporeal Membrane Oxygenation (ECMO)	Dexamethasone For patients who are within 24 hours of admission to the ICU-Dexamethasone Plus, Intravenous Tocilizumab	-	-	-

Conclusion

Since invasive pulmonary aspergillosis (IPA) is tough to diagnose and is coupled with high morbidity and mortality, therefore, we should pay close attention to critically ill COVID-19 patients, for the potential occurrence of pulmonary aspergillosis [10]. In this regard, application of better screening could facilitate early detection and treatment of CAPA in presence of well-established risk factors [11,20]. For this reason, there is a pressing need for the development of a biomarker that is specific for fungal tissue invasion; and can also distinguish between Aspergillus tissue invasion and respiratory tract colonization [9]. This article highlights the requirement of large, multi-center studies, randomized controlled trials to ascertain antifungal prophylaxis efficacy, and uncover the effect of immunomodulation in patients with CAPA [16,20]. In this respect, further research to identify the ideal diagnostic approach, patient management practices, treatment modalities with far less adverse effects, and best possible ways to mitigate the COVID-19 associated fungal disease burden has become utterly crucial.

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Dr. Nasima Begum, MD, graduated from Dhaka medical school in the K40 batch. She completed her internship and residency training at LAC-USC medical center. Subsequently, she completed an Infectious diseases fellowship at LAC -USC medical center in 1997-1998.

She has been in private practice with Foothill Infectious disease Medical Group in Claremont since 1998. She is chair of the infection control department at Kindred Hospital and co-chair of the ASP antibiotic stewardship program at Emanate Health medical center. She is an educator at the western college of osteopathic medicine of the pacific. She is a past President of the BMANA, California chapter. She lives in Orange County with her husband and is a mother of two.