COVID

Review

Effect of Indoor Bioaerosols (Fungal) Exposure on the Health of Post-COVID-19 Patients and Possible Mitigation Strategies

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Abstract: Bioaerosols are present everywhere around us, either on surfaces or in the air. Depending on their nature, these bioaerosols have positive or negative impacts on our bodies. Our immune system always creates a balance in our health system in response to these bioaerosols. If our body's immune system is compromised for a while, it could have many severe health complications. A good example is in patients who recovered from COVID-19 during the COVID-19 pandemic. During treatment, many drugs like dexamethasone, tocilizumob, itolizumab, and steroids were extensively used that suppressed the immune system, resulting in many fungal infections. In this review, we summarise the various studies carried out throughout the globe regarding fungal infection, including Mucormycetes (black fungus), *Candida* spp., *Aspergillus fumigatus*, and *pneumocystis jirovecii*. The patient disease history and treatment details were also examined so as to develop the risk of mortality. Populations with other pre-existing diseases such as diabetes and asthma are more vulnerable to infection. These infections spread at a very high rate and have a high risk of mortality in patients who have recovered from COVID-19. Earnest attention is needed regarding the treatment procedure of COVID-19 patients and for the follow-up of recovered patients. Here, we suggest some treatment methods that will help prevent infection in patients who have recovered from COVID-19 or in immunosuppressed bodies.

Keywords: black fungus; bioaerosols; immune system; health effect; fungal infection; COVID-19

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1. Introduction

Since the pandemic started in Wuhan, China, it has covered the entire world [1]. Humanity faced the bitter experience of this pandemic in the form of loss of life and society and economic loss. It is still happening now and the population that suffered from this pandemic also faces adverse post COVID-19 effects. Because of the higher use of steroids and other medications, immunity decreases to some extent, which causes other health-related issues in different forms [2]. This leads to increased coinfections caused by the interaction of COVID-19 with other microbes, such as bacteria, viruses, fungi, and some allergens [3]. According to the reported data, fungal spores known to be present in air or dust particles can cause severe disease in patients who have recovered from COVID-19 due to corticosteroids [4]. A study conducted in Italy regarding lung infection as a result of COVID-19 found 28 participants (80%) showed colonization through fungi or *Pseudomona aeruginosa*. This study also suggested that fungi are the main contributors to mortality in immunocompromised bodies; on the other hand, in the case of non-COVID-19 patients, only 20% were affected by fungal infection. Rhinosinusitis mucormycosis (a fungal) infection due to treatment with corticosteroids in patients after complete recovery from COVID-19 has also been reported worldwide [5]. Fungal infection symptoms include headache, face swelling and numbness, periorbital edema, and erythema. Heaney et al. [4] reported on the interaction of *Coccidioides* spp. and COVID-19, resulting in respiratory infection due to the inhalation of *Coccidioides* fungal spores present in dusty environments.

It is well known that we cannot isolate microbes from our surroundings in particulate or in other forms. However, we can minimize these microbes through certain treatments or we can decrease exposure to these microbes using some protectors. Microbes are also carriers of COVID-19 in the form of droplets, as has been reported in some studies [6]. Because of their very fine size (in the range of some nm), they are controlled through the use of face masks with small-sized pores to prevent inhalation, thus causing some breathing problems [7].

Studies have suggested that indoor bioaerosols, mainly fungal bioaerosols, are responsible for many health-related infections [8]. Additionally, overcrowding, unhygienic conditions, and poor ventilation enhance the spread of respiratory disease such as COVID-19 [9]. *Mucormycetes* (black fungus), *Candida auris*, *Aspergillus fumigatus*, *Pneumocystis pneumonia*, *Cryptococcal neoformans*, *Coccidioides* spp., etc., are some of the few examples of this. In our review, we aim to emphasize more of the expected diseases associated with bioaerosols, mainly fungal infections. In addition, we suggest precautionary measures to control these types of bioaerosols that would be helpful in the follow-up of patients who have recovered from COVID-19. This might reduce mortality due to COVID-19-associated disease and help with policymaking and for infrastructures necessary in situations such as pandemics.

2. Datasets and Findings

Datasets were collected from the different peer-reviewed journals available on Scopus, ResearchGate, Google Scholar, PubMed, and Web of Science. In addition, we assessed reports that are available on the state health department and government health agencies' websites of different countries and states. We retrieved the details of COVID-19 patients and associated diseases during this pandemic from different international and national agencies reported worldwide. We identified the different articles related to these issues and used citing with backward citations. We examined the patient history, simultaneously associated diseases, patient accommodation, and drugs used for treatment, as shown in Table 1.

Table 1. Database and findings related to fungal infected COVID-19 patients.

	Study Location	Type of Fungus	Initial Common Symptom	Disease History	Status of Patients	Final Remark	References
1	U.S.	*Candida auris*	Respiratory problems	Resistant to amphotericin b	83.3% mortality	Resistant to amphotericin b	[10]
2	India	*Mucormycetes*	Vomiting, coughing, and breathlessness	History of hypertension and asthma	Expired on day 26	Mucous membranes became dry and the palate turned to brown, dry-like secretions	[11]
3	France	*A. fumigatus*	Invasive pulmonary aspergillosis (IPA), chronic pulmonary aspergillosis (CAPA), allergic bronchopulmonary aspergillosis (ABPA), chronic rhinosinusitis, fungal asthma, and aspergillus bronchitis	Immunosuppression, hematopoietic transplantation, and structural lung damage were observed in those who receive systemic corticosteroids. Chronic obstructive pulmonary diseases (COPD)		Putative invasive pulmonary aspergillosis was very high (30%)	[10]
4	Denmark	*A. fumigatus*		Hypertension and asthma	Multiorgan failure results in death 41 days post hospitalization	Died with multiorgan failure	[12]
5		*A. fumigatus*		Prior smoker prior non-regular smoker	Large intracranial hemorrhage while on ECMO, 34 days post hospitalization	Death occurred as a result of a large intracranial hemorrhage	[12]
6	Egypt	*Mucormycetes*		* Uncontrolled diabetes melli, # diabetic, and hypertensive, along with a previous history of operated colon cancer and chronic kidney impairment	* Death reached 25%, and the case reported deaths were of the cutaneous and rhino-cerebral types	* Patient died, # patient was discharged by their own choice against the hospital's will	[13]
7	Italy	*Candida albicans*	Acute hypoxemic respiratory failure		Besides respiratory symptoms, thrombosis and pulmonary embolism	Fungal and *Pseudomona. aeruginosa* colonization were observed in severe COVID-19 patients	[14]
8	India	*Mucormycetes*	Nasal blockage, facial and periorbital swelling, and blackening of middle turbinate with thick dirty nasal discharge	A post coronary artery bypass grafting patient with well-controlled diabetes mellitus	The patient developed myocarditis with cardiac arrhythmia and died	After microbiological confirmation of caifs, liposomal amphotericin b was given (total dose of 3050 mg)	[15]

Table 1. *Cont.*

	Study Location	Type of Fungus	Initial Common Symptom	Disease History	Status of Patients	Final Remark	References
9		*Mucormycetes*	COVID-pneumonia, uncontrolled diabetes mellitus, and deranged kidney functions	Diabetes mellitus and deranged kidney functions	Died	Liposomal Amphotericin B	[15]
10		*Mucormycetes*	COVID-pneumonia, septicemia, shock, renal failure, and altered sensorium	Diabetes mellitus, renal failure, and peptic ulcer	Died	Antifungal agents not given	[15]
11	Germany	*A. fumigatus*			Foru died expired, one alive	2 patients received voriconazole, 1 patient used isavuconazole and 2 patients were given caspofungin followed by voriconazole	[16]
12	France	*A. fumigatus*			Two died	One patient was given voriconazole and to the other one caspofungin	[17]
13	Belgium	*A. fumigatus*			Three died, three alive	Four patients were given voriconazole and two others had voriconazole plus isavuconazole	[18]
14	Netherlands	*A. fumigatus*			Four died, two alive	Five patients were given voriconazole plus anidulafungin and one patient's treatment was done with liposomal amphotericin B	[19]
15	Italy	*A. fumigatus*	Pneumonia related with a confirmed diagnosis of SARS-CoV-2 infection	History of diabetes, hypertension, hyperthyroidism, atrial fibrillation, and obesity	Died	Liposomal amphotericin B	[20]

* first case, # second case.

2.1. Immunosuppression and Coinfection in COVID-19 Patients

There have been doubts related to the use of immunosuppressants whether decreased or increased the risk of infection in COVID-19 patients [21]. Recent studies have shown that immunosuppressants have a greater health risk at a higher dose, but they still used when treating high-risk COVID-19 patients [22]. In COVID-19 infection, persistent lymphopenia is induced significantly, which is responsible for the increase in generating other infections [23]. In a laboratory test of different patients, for COVID-19, 85% showed lymphopenia, indicating a significantly lower T lymphocyte concentration [24]. It is well known that lymphocytes are a significant contributor to balancing immune homeostasis; the lower concentration of lymphocytes in COVID-19 patients induced fungal infection [25].

Many factors have also been linked with the spread of fungal infection, such as long-term use of antibiotics, vitamins, zinc, and steroids [26,27]. In addition, long-term use of low-quality medical equipment and contaminated oxygen storage increase the risk of fungal infection. In addition, fungal bioaerosols are present in the air inhaled via the respiratory tract, and because the lung tissues and the alveoli-interstitial lesion have already been damaged, these fungal bioaerosols have adverse effects. Mucormycosis is one of the most common coinfections that has been reported worldwide in COVID-19 patients [22].

2.2. Fungal Coinfected COVID-19 Patients

The first reported COVID-19 infection caused by fungal was Aspergillosis, with *A. fumigatus* known to be the most common species causing COVID-19-associated pulmonary aspergillosis (CAPA). Candidasis and mucormycosis are the most common fungal infections, with *Rhizopus* spp. reported to be the most common species. Influenza-associated pulmonary aspergillosis is extensively recognized; hence, severe forms of COVID-19 pneumonia are likely to have similar consequences [28]. COVID-19-infected patients are more prone to secondary infection as a result of fungi. Data obtained from Wuhan, China, show that 3 out of 9 patients and 6 out of 17 patients caught secondary fungal infections [29,30].

2.2.1. Mucormycosis

Mucormycosis is a type of fungal infection from Mucormycetes, and it belongs to the family of moulds found in the soil and dust and acts as a decomposer [31]. Mucormycetes infections are often found in COVID-19 patients receiving treatment through high doses of immunosuppressant and diabetic ketoacid [32]. It usually develops post-hospitalization within 10 to 14 days, and the infection reaches the body of a patient through the bloodstream. This infection mainly affects the area of the neck, head, central nervous system, and gastrointestinal tract, as well as other organs. This fungal growth affects the bone marrow and damages the endothelial lining, leading to vascular insufficiency and bone narcosis. The tendency of narcosis depends on exposure to fungal bioaerosols through inhalation, ingestion, or direct contact. This fungal growth in the bone marrow results in fungal osteomyelitis, and it is more adverse than bacterial-associated osteomyelitis [33].

Out of all of the reported mucormycosis diseases (black fungus), India accounted for 42.3%, then the United States (16.9%), followed by Iraq, Bangladesh, Iran, and Paraguay, with one case each from Brazil, Mexico, Italy, the United Kingdom, China, France, Uruguay, Turkey, and Austria [34]. In the reported data total, 102 mucormycosis patients linked to COVID-19 have been documented from India. Males (69.6%) were more likely than females (19.6%) to have mucormycosis, and the majority of the patients had active COVID-19 (70.5%). The popular treatment for COVID-19 was steroid therapy (68.6%), followed by remdesivir (10.7%). Patients who suffered from mucormycosis had sino-nasal necrosis (72.5%), orbital necrosis (24.5%), central nervous system necrosis (18.6%), and maxillary necrosis (13.7%). The death rate reported was 23.5%, and the rate of recovery was reported to be 2.9%. Patients suffering from diabetes mellitus are more common in India than in other nations, and the widespread consumption of steroids along with the presence of COVID-19 creates a suitable environment for mucormycosis fungus infection to thrive [35].

As reported by the Centre for Disease Control and Prevention (CDS), USA, Mucormycosis infection can be categorized based on the infected organ infection, for example, rhinocerebral mucormycosis in the sinus and brain, pulmonary mucormycosis in the lung, gastrointestinal mucormycosis in the intestine and guts, cutaneous mucormycosis in the skin, and disseminated mucormycosis in patients with other medical conditions. The foundations for the successful management of mucormycosis include the early identification and limitation of hyperglycemia, liposomal amphotericin B, and, in some cases, surgery may be required.

2.2.2. Candidiasis

Patients suffering from acute respiratory distress syndrome (ARDS) and COVID-19 are prone to yeast fungal infections due to impaired immune system functioning. Invasive candidiasis as a result of the *Candida* genus species, with *Candida albicans* abundant species, is a highly concerning infection that could lead to high mortality rates [36]. During COVID-19 in New York City, USA, *Candida* spp. was the most abundant fungi that was detected in the bloodstream of patients using central venous catheters [37]. Based on the data reported from Iran, *C. albicans*, followed by other species, were isolated from the oral lesion of COVID-19-positive patients suffering from oropharyngeal candidiasis [38]. Immunocompromised individuals and COVID-19 hospitalized patients showed a high morbidity and mortality due to the multidrug-resistant nosocomial pathogen *Candida auris* (mainly responsible for respiratory problems). If COVID-19-negative patients have difficulty breathing, they could be considered as being infected with *Candida auris*, and for COVID-19-positive patients, infection increases the risks during recovery [39].

One study reported that mortality was observed in about 83.3% of cases due to fungal infection, even though appropriate fungal therapy was used. Thoma et al. [40] found 17 reports in which patient mortality was reported as being generally caused by *Candida auris* or carbapenem-resistant *Acinetobacter baumannii in* 35% (68/193) of cases. In Columbia 2020, 94% (379/404) of cases were clinical cases, of which 225 were bloodstream infection (BSI) and 154 were non-BSI, and out of 404, 121 severe cases of COVID-19 as a consequence of *Candida auris* were reported, making it the predominant species (42%), and followed by *C. tropicalis* [41,42]. The first known case of fluconazole-resistant *Candida auris meningitis* was reported in a pediatric patient in Iran, which is a genotype that typically belongd in South Asia (Clade I). There is more concern regarding *Candida auris* meningitis cases, because the number of cases with *Cauris meningitis* has continuously been increasing in the United Kingdom, India, and Iran [43]. Some factors, such as a compromised immune system, deficiency of iron and zinc, and nosocomial and iatrogenic transmissions, result in patients being prone to infection from candidiasis during COVID-19 treatment [44]. One of the significant findings was that all of the patient samples were resistant to amphotericin B [10].

2.2.3. Aspergillus fumigatus

Aspergillus fumigatus is a type of fungus widely present in indoor and outdoor environments. In humans, these effects are invasive pulmonary aspergillosis, among others. Invasive pulmonary aspergillosis is found most in the vulnerable immunosuppressant body, such as a body undergoing hematopoietic transplantation and those who received corticosteroids with lung damage [17]. COVID-19-related pulmonary aspergillosis was reported in 8 out of 239 ICU patients receiving corticosteroids who already had (75% of patients) severe acute respiratory distress syndrome (ARDS) [45]. Corticosteroid treatment, viral infections, and lymphopenia are all risk factors for invasive aspergillosis [46]. Aspergillosis-related COVID-19 patients were not diagnosed upon admission to hospitals, which a supports the theory of "community aspergillosis", which occurs outside the hospital, maybe from home (pandemic period) which is the main suspected location of infection [47]. There was an occurrence of 19.4% presumed aspergillosis in our cohort of 31 ICU patients, which indicates that the development of invasive pulmonary aspergillosis

(IPA) is higher for patients suffering from COVID-19 infection [16]. The occurrence of IPA in COVID-19 patients was found to be 19.6 to 33.3% [48]. The combined effect of *A. fumigatus* and a Mucorales species, which is responsible for generating fungal infection, which is a secondary type of infection, is rare in immunocompromised patients with SARS-CoV-2 infection [49].

2.2.4. Pneumocystis Pneumonia

Pneumocystis pneumonia has the same symptoms as in COVID-19 diseases, and when it is associated with the *P. jirovecii,* it contributes to severe infection in immunosuppressed patients [50]. It is a very common opportunistic fungal infection in acquired immunodeficiency syndrome (AIDS) patients and is responsible for other immunodeficiency conditions patients [51]. One study on non-immunosuppressed COVID-19 patients indicated that *P. jirovecii* was found in critically ill patients in a proportion of 10/108 (9.8%). It is very difficult to differentiate between COVID-19 and pneumocystis based on symptoms; for this, a sputum culture, CT scan of the chest, and RT-PCR are recommended for diagnosis [52].

2.2.5. Cryptococcal Disease (*C. neoformans*)

C. neoformans has a very adverse consequences on the immunocompromised COVID-19- infected patient bodies. This fungal infection is lethal, and some studies have reported that patients infected with this have a higher risk of mortality, generally within 30 days (approx.) [53]. It is also responsible for meningoencephalitis in immunocompromised patients, but is less apparent in immunocompetent people [53]. *C. neoformans* infection is usually found among immunocompromised patients [54]; however, meningoencephalitis is the formation of cryptococcosis in HIV patients [55]. In the immunocompetent body, this infection has also been seen far less in internal organ (basically in the lungs) observations [56].

2.2.6. Coccidioidomycosis

Coccidioides spp. is a soil-dwelling fungus mostly spread in the environment through the air as a result of wind. It has been found that the risk of coinfection with coccidioidomycosis is most prominent among construction and agricultural workers, incarcerated persons, Black and Latino populations, and persons living in high-dust areas [4]. A hot and arid environment favours the spread of these fungal spores. The epidemic of coccidioidomycosis is ongoing in the desert region in the southwest of the United States. Both COVID-19 and chronic pulmonary coccidioidomycosis have similar symptoms of fever, dry cough, dyspnea, myalgia, and headache, as seen in a 48-year-old Hispanic male [57].

2.3. Control Mechanism for Fungal Spores

2.3.1. Non-Thermal Inactivation of Fungal Spores

These methods are well known because of the fungal spores' resistance to different physical and chemical methods. The use of physical methods such as heat treatment leads to energy losses, and chemical methods produce secondary waste, which needs to be treated again. These novel non-thermal methods include the treatment of fungal spores using irradiation (UV, gamma, and pulse light), atmospheric pressure air plasma, and ozonation [58,59]. Non-thermal methods generally rupture the cell wall, cell membranes, and DNA strands of the fungal spores, thereby completely inhibiting the multiplication of these spores throughout the environment [59–61].

2.3.2. Ozone Treatment

Ozone is a reactive oxygen species, and at very small concentrations it has a strong oxidizing capability. Ozone shows its antimicrobial and germicidal properties through the interaction of ozone molecules with the microbe's cellular structure, which hinders their growth, thereby attacking the cellular component's double bond or ring structure. Ozone treatment has been found to be efficient against many viruses, including viruses with a similar morphology to SARS-CoV-2 [62,63]. Houdson et al. [64] investigated the inactivation of 13 different fungal species with a potable ozone generator and found a 3log10 CFU reduction at an exposure of 35 ppm of ozone for a time interval of 20 min. A very small concentration of ozone is effective against many microbes. This treatment can easily be produced using different ozone generators. Although it is toxic, it has a half-life of 20 min and is dissociated back into O_2. Ozone gas has been reported in numerous literature as being safe for disinfecting many food items [65,66].

2.3.3. Non-Thermal Plasma (NTP)

This method is popular for heat-sensitive food materials to treat spores of different bacteria and fungi. They are very cost-effective against these microbes and inactivate them to 10 log10 CFU within 10 min of application [67,68]. Plasma is the fourth state of matter (ionized gas). Ionized gases, such reactive oxygen, nitrogen, charged species, and electrons, are produced from ambient air or specific gases at an atmospheric or lower than atmospheric pressure through the application of high voltage electric current and radiation in range of the UV, visible, and infrared region [68–70]. Radiofrequency power, microwave power, direct current, or alternating current are used for plasma discharge using different techniques such as direct barrier discharge, corona discharge, and plasma jet [70,71]. NTP is an effective method against many spores and is popular in the pharmaceutical, food industry, and agriculture. Julak et al. [72] observed the inactivation of Alternaria sp., *Aspergillus oryzae* using corona discharge plasma (9 KV, 300 µA, filtered air) and Byssochlamys nivea, *Cladosporium sphaerospermum* using dielectric barrier discharge plasma (high voltage, air) within 10 to 40 min of application. Veerana et al. [70] reviewed the application of the plasma method in detail for the inactivation of many fungal spores such as *A. niger* and *Penicillium citrinum* using dielectric barrier discharge plasma (3 kV at 230 Hz), *C. albicans* using linear micro discharge plasma jet, *Fusarium oxysporum* using Dielectric barrier discharge plasma (0.75 KV, 80 mA, air), etc.

2.3.4. HEPA Vacuuming

Vacuum cleaning enabled with high-efficiency particulate air filters is called heap vacuuming. This technique is gaining popularity due to its cleaning efficacy of at least 99.97% for dust, pollen, mould, airborne particles, and bacteria with a size of 0.3 microns (µm) [73–75]. These filters trap the particles within them and do not dispose of them. Cheong et al. [74] observed the removal of *Penicillium* and *Cladosporium*, and yeast species successfully using this technique. Nowadays, many hospitals and aircraft are installed with heap filters for controlling fungal spores.

2.3.5. UV Radiation

UV radiation is a well-known method for controlling bacteria, fungi, and viruses. It controls fungi in the indoor environment, and is generally employed through source, air cleaning, and ventilation control. It requires the installation of a UV source with air handling units (AHU). Some UV lamps are used as a source of UV radiation. Many studies have reported the germicidal effect of UV lamps installed with AHU [76,77]. Germicidal UV radiation disrupts the DNA of microbes. In many studies, they have been reported to be very effective against bacteria, viruses, and many spores of fungi in the wavelength range of 220 to 280 nm [76,78].

2.3.6. Treatment with Fungicides

Many chemical fungicides, such as glutaraldehyde and cresol, are reported as phenol-based derivatives. Their application is restricted in many places because they are classified as carcinogens. For decades, chemical fungicidal treatment has been replaced with plant-based extracts that produce aromas, such as tea tree oil, Cinnamaldehyde, etc. [73,75,79]. In an experiment comparing the different antimicrobial properties of seaweed extract and tea tree oil, only tree oil reduced the fruit rot significantly by 31% (approximately), anthracnose by 60–88%, and leather rot by 71–72% [80]. Tea tree oil is also a proved antifungal agent for removing *Botrytis cinerea* [81]. Plant-based extracts are safer than chemical fungicides and are widely accepted.

2.4. Discussion and Conclusions

In the above review, we conclude how fungal bioaerosols have adverse effects on immunocompromised bodies. Also, this has a high risk of mortality in the body where the steroids and other drugs were taken during the treatment. there is a high risk of mortality when steroids and cytokines are used during treatment. Here, it could be speculated that over-activation of the immune system could cause misfunction in the regulation of defence mechanisms against other pathogens, resulting in the spread of coinfections. Patients with other disease histories such as diabetes and respiratory problems are at high risk. So, it is very important to tackle this serious infection at an early stage; for this, immunocompromised patients need to be monitored at regular intervals. Patients need to live in a microbe-free environment until they are completely cured. To create a microbe-free environment, we suggest techniques such as ozonation, UV treatment, non-thermal plasma, and installing HEPA vacuuming. Before these techniques are implemented, it must be ensured they are not directly exposed to the patients. Many fungicides are also used to control infection; some fungicides, such as tea tree oil, are very useful in comparison to many chemical fungicides.

Our results are based on different studies performed across the globe on a variety of populations. This study emphasizes the importance of bioaerosol studies regarding the exposure site of post-COVID-19 patients. This study will help to establish the treatment protocol of COVID-19-infected patients and also for patients recovered from COVID-19. Additionally, it will help with developing the infrastructure of hospitals and for upgrading medical equipment. Along with all of the above, it will also help policymakers improve the health and hygiene sector.

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