

Systematic Review

Pervasiveness and Consequence of Co-Infection and Superinfection with SARS-CoV and Mucormycosis (Black Fungus): A Systematic Review

Soumendrar Darbar ^{1,*}, Sangita Agarwal ^{2,*}, Srimoyee Saha ³¹ Research and Development Division, Dey's Medical Stores (Mfg.) Ltd., 62, Bondel Road, Kolkata-700019, West Bengal, India² Department of Applied Science, RCC Institute of Information Technology, Canal South Road, Beliaghata, Kolkata-700015, India.³ Faculty of Science, Jadavpur University, 188, Raja S C Mallick Road, Kolkata-700032, West Bengal, India

*Correspondence: dr.soumendraradarbar@deysmedical.com; mailsangvee@gmail.com

Abstract: Mucormycosis or black fungus although a rare fungal infection but has potential to be lethal and thus requires immediate treatment. The immune system is weakened due to SARS-CoV-2 and the body becomes susceptible and vulnerable to other infections as people are immune compromised. The immune system becomes weakened due to COVID-19 treatment especially in patients who are taking steroids making the body prone to attack by black fungus. As the black fungus cases are increasing in India, the country is facing shortage in medicaments in face of dual crisis. An epidemic of black fungus is sweeping India in the wake of a severe surge in COVID-19 cases. Experts are of the opinion that the cause is a combination of factors. These factors might include contaminated oxygen equipment and use of steroid drugs to treat certain COVID-19 patients.

Keywords: Black fungus; SARS-CoV-2; fungal infections; Immune response; India

How to cite this paper: Darbar, S., Agarwal, S., & Saha, S. (2021). Pervasiveness and Consequence of Co-Infection and Superinfection with SARS-CoV and Mucormycosis (Black Fungus): A Systematic Review. *Global Journal of Epidemiology and Infectious Disease*, 1(1), 1-11. Retrieved from <https://www.scipublications.com/journal/index.php/gjeid/article/view/69>

Received: July 2, 2021**Accepted:** August 11, 2021**Published:** August 12, 2021

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1. Introduction

The SARS-CoV-2 outbreak has been responsible for the health crisis all across the globe and has changed our perceptiveness. This biological disaster has impacted both physical and mental health along with the economic stability. Till date for management of COVID-19, no direct specific pharmacological antiviral therapeutic medication is available [1]. This deadly viral infection has taken many lives throughout the globe and it is still continuing its outrage by mutating its form. The need of the hour is to develop effective and novel therapeutic medications to prevent and control the coronavirus infection. After being infected by the coronavirus the immune response is compromised and makes it difficult for the body to fight back against infection [2,3]. Various type of supportive medications are very effective to boost immune power. The role of vitamins and micronutrients including zinc, iron, selenium, magnesium, and copper in boosting the human immune system has been well established [4,5]. One of the strategies to combat the onslaught of the pandemic worldwide is mass vaccination. The Government of India has encouraged development of vaccines in multiple ways [6]. Covaxin which has been developed by Bharat Biotech in collaboration with the Indian Council of Medical Research (ICMR) and the National Institute of Virology (NIV), Pune showed efficacy of 81% according to report. Vaccination gives hope to eradicate the deadly virus permanently [7].

Mucormycosis, widely known as "Black fungus" is a diseased condition which is caused by pervasively developing moulds in dead and decaying soil and vegetation. The infected site develops necrotic black tissues and hence is named as "Black fungus" [8]. This condition has been observed synonymously among Covid-19 patients in various

states all over the India. It is first observed in skin and also in the respiratory and nervous system by targeting the lungs and brain respectively [9]. The deadly fungus infections have been detected in Delhi, Rajasthan, Karnataka, Uttarakhand, Telangana, Madhya Pradesh, Chhattisgarh, Andhra Pradesh, Haryana, West Bengal, Uttar Pradesh and Bihar, among others. Infection is drastically increased in West Bengal. Recently 54 black fungal cases have been detected in West Bengal.

As reported by number of super speciality health providers all over India, the tissues of nose and cheeks of patients become blackened or discoloured, black lesions develop inside their mouth and vision is also blurred [10,11]. Weakened immune system, too much steroid consumption, voriconazole therapy and diabetes also put patients at greater risk of infection (Figure 1). Some doctors are of the opinion that the state of black fungus developed during home treatment of COVID patients during quarantine and when no care was taken of bringing blood sugar levels under control [12].

In India up to May 27, 2021 more than 12,000 cases of the fungus have been reported as per statement of Health ministry. This potentially fatal fungal infection is likely increasing due to the surge of people with COVID-19. Fighting the coronavirus can leave people's immune systems compromised or weakened, which means they may have a higher chance of developing mucormycosis [13]. This infection is being seen in people with health issues (like COVID-19) or those who are on medications which reduce the disease fighting ability of the immune system. It commonly affects the sinuses or lungs after the fungal spores are inhaled from the air. The associated symptoms of sinus and brain mucormycosis comprise of congestion in the nasal cavity, swelling of the face, and headache [14,15]. If the infection reaches the lungs, then fever, cough and shortness of breath is observed in patients. The Indian Council of Medical Research (ICMR) has issued an advisory on the diagnosis and treatment of the disease.

2. Causes of mucormycosis (Black fungus)

Black fungus infection is a very rare infection and is caused when a person is exposed to mucormould. These moulds generally originate in decaying fruits and vegetables, soil, manure and plants. At times it is present in air and in nose and mucus according to the subject experts. The infection can affect the sinuses, brain and lungs. If not treated on time, it can be life-threatening. It's even dangerous for people suffering from diabetes, cancer or HIV/AIDS. The use of steroids which are used as last resort in life-saving treatment in case of moderate to serious COVID are primarily responsible for triggering Mucormycosis. Though steroids help in reducing inflammation in the lungs, it lowers the overall immune response and remarkably escalates the sugar levels in both Covid-19 patients who are diabetic or non-diabetic. This becomes a big challenge in patients who are hyperglycemic and managing the sugar level during corona virus infection becomes difficult. [16]. Scientific reports confirm the occurrence of two types of Mucormycosis namely Rhino-Orbito-Cerebral Mucormycosis (ROCM) and pulmonary mucormycosis (PM) in Covid-19 patients who have recovered or discharged or infected.

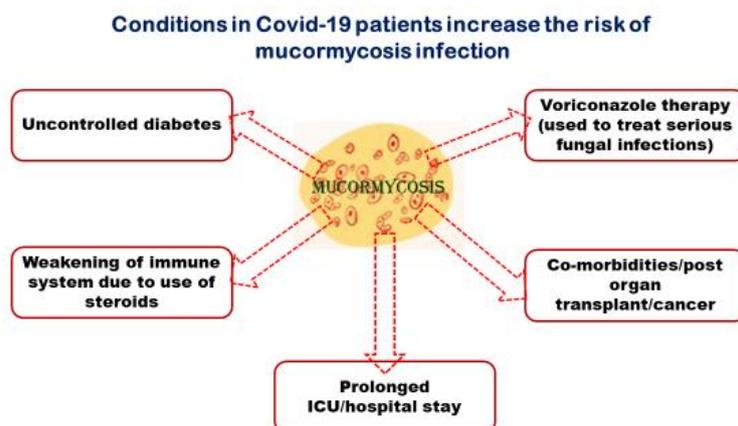


Figure 1. Conditions in Covid-19 patients increase the risk of mucormycosis infection

3. Spread of the fungus

Black fungus does not spread from animals to humans and is not infectious or communicable. Mostly the fungal spores are present in air and when inhaled they are attacked and destroyed by normal body's defense mechanism which is the immune system. In cases of persons who are immunocompromised, since the immunity is weak thus the moulds survive and cause infection. The risk of catching the COVID-19 virus from the feces of an infected person appears to be low.

There is some evidence that the COVID-19 virus may lead to intestinal infection and be present in feces. Approximately 2–10% of cases of confirmed COVID-19 disease presented with diarrhea [17], and two studies detected COVID-19 viral RNA fragments in the fecal matter of COVID-19.

People who fall into the following categories are more likely to develop black fungus:

- Uncontrolled diabetes, diabetic ketoacidosis, and diabetics taking steroids or tocilizumab.
- Patients taking immunosuppressant or receiving anticancer treatment, as well as those suffering from a chronic debilitating illness
- Patients taking high doses of steroids or tocilizumab for an extended period
- Cases of COVID-19 Severity
- Patients on oxygen who required nasal prongs, a mask, or a ventilator support

4. Some Common Symptoms of Black Fungus Infection

- **Sinus and respiratory:** This type of symptom is most common and the cavities which are involved include sinus, oral and nasal and might extend to the eyes.
- **Skin Infections:** The burnt skin or cut or scratches exposes the inner tissues to the black fungus. This results in reddening, swelling, blistering, blackening of the skin tissue and tenderness of the skin.
- **Brain Infection:** The black fungus infection promulgated to brain can affect the mental state of the person or lead to coma.
- **Ocular infection:** The black fungus infection when propagates to eyes can result in reddening and swelling of the eyes. The infection can cause eye pain; vision could be blurred and leading to blindness. In some instances, to stop the spread of infection, the eyes are required to be removed.
- **Gastrointestinal Infection:** The black fungus infection reaching the gastrointestinal tract can cause vomiting and nausea along with pain in the abdomen and gastrointestinal bleeding.

The common symptoms those are commonly observed are stated in [Table 1](#) and [Figure 2](#).

Table1: Various common Symptoms of Black Fungus

Sl. No.	Symptoms of Black Fungus
1.	Sinusitis – nasal blockade or congestion, nasal discharge (blackish/bloody)
2.	Local pain on the cheek bone, one-sided facial pain, numbness or swelling
3.	Blackish discoloration over bridge of nose/palate
4.	Loosening of teeth, jaw involvement
5.	Blurred or double vision with pain
6.	Thrombosis, necrosis, skin lesion
7.	Chest pain, pleural effusion, worsening of respiratory symptoms

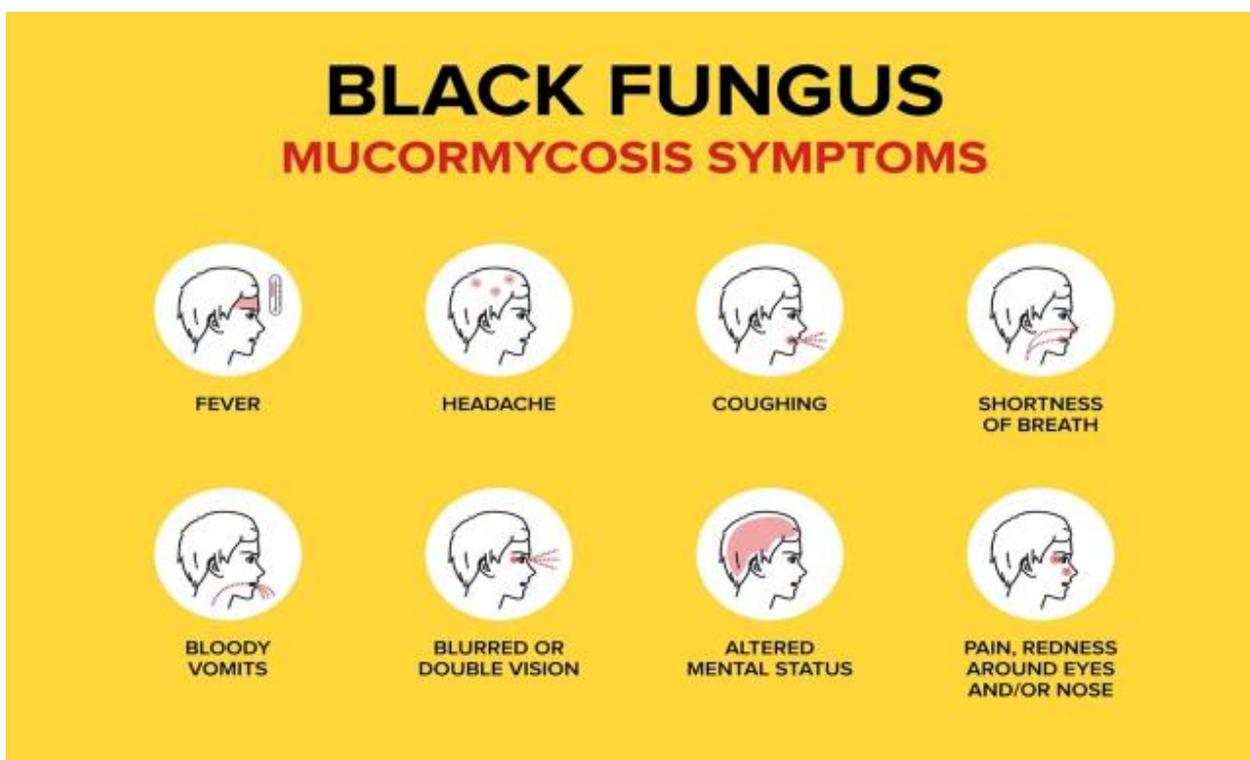


Figure 2. Certain symptoms of Black fungus

5. Covid-19 associated Mucormycosis (Black fungus)

The black fungus infection has become more rampant because of the simultaneous outbreak of Covid-19 outbreak and this infection has become quite frequent in Covid-19 patients throughout India. When infection occurs, the patient’s skin is not only affected but the brain or lungs are also susceptible to infection and many such cases has been reported in Covid-19 patients. As the black fungus infection cases are rising, the government of India has directed all states to report all cases confirmed and even suspected to the Integrated Disease Surveillance Programme. Once the COVID-19 disease occurs, the virus takes over the host machinery, it alters the internal environment and inadvertently the supportive medical treatment are somehow promoting fungal development ([Figure 3](#)). The airway mucosa and blood vessels are also impacted by COVID-19 [[18](#)] and the increase in essential mineral Iron enables the fungus to grow. The broad-spectrum antibiot-

ics which are used as supportive treatment do not discriminate between harmful or beneficial bacteria and thus killing even the beneficial ones. Aspergillosis is prevented by using antifungal like Voriconazole but mucor persists and survives. Moreover, the long-term use of ventilators reduces the body's immunity. Long-term ventilation decreases immunity, and there is prognosis that the humidifier water used in the ventilators is responsible for the transfer of the fungus [19].

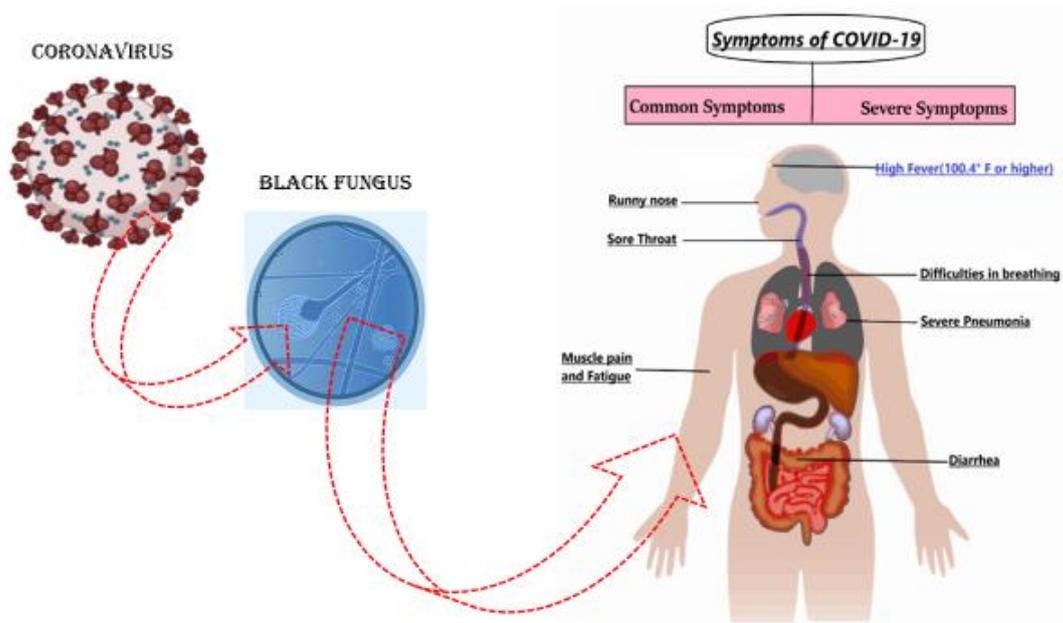


Figure 3. Covid-19 outbreak and the spread of black fungus infection.

6. Spreading of Black fungus in India

India has witnessed greater number of mucormycosis cases because of various factors. India is deemed as the diabetic capital of the world and presently India has estimated 77 million diabetics. Before the COVID-19 pandemic happened and in spite of a large population who were diabetic, the number of cases of mucormycosis were relatively low, but its prevalence was rising. There has been a sharp increase in mucormycosis cases since the beginning of the COVID-19 pandemic [20].

The weakened immune system because of corona virus infection makes the body susceptible to secondary infections, putting the individuals who are recovering from COVID-19 at risk of developing mucormycosis. The virus by way of its replication process, suppresses the immune system and thus the immune system is unable to fight other fungi or bacteria. As for example HIV infection leads to long-term immunity suppression but some viruses subdue the immunity for shorter duration which might be for few days or weeks during its presence. When steroids are used to treat COVID-19 patients they suppress the body's immune response which is responsible for increasing mucormycosis infection rates [21].

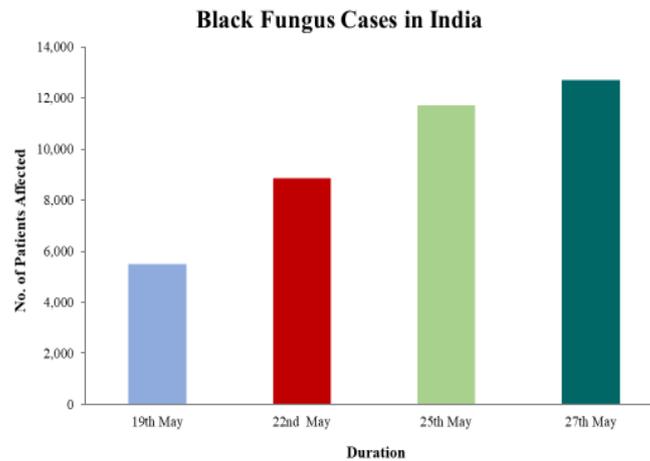


Figure 4. Number of Black fungus cases in India in May 2021

According to expert opinion the steroids are playing pivotal role in the spread of mucormycosis as they are suppressing the body's normal immune responses and allow the invasion by the fungus. Additionally, patients on oxygen support having severe COVID-19 causes the drying of the nasal cavity which is instrumental in increased risk of infection. The state of Rajasthan was the first state in the country to declare a mucormycosis epidemic on May 19, 2021. In another report from the city of Surat, 8 out of 40 COVID-19 survivors who developed mucormycosis in the eye lost their eyesight. More than 1500 cases of mucormycosis, have been reported from the state of Maharashtra which resulted in 8 deaths [22]. Figure 4 shows the number of cases of Black Fungus in Month of May 2021 in India. Table 2 highlights the black fungal cases and death due to COVID-19 during the second wave in India in 2021.

Table 2. Number of black fungal cases and death due to surge of COVID-19 and its second wave in India in 2021

Sl. No.	States	Number of Cases	Number of Death
1.	Maharashtra	1510	90
2.	Gujarat	1500	-
3.	Telangana	700	-
4.	Madhya Pradesh	573	2
5.	Karnataka	250	-
6.	Delhi	200	-
7.	Haryana	190	14
8.	Uttar Pradesh	160	8
9.	Rajasthan	100	-
10.	Chhattisgarh	77	2
11.	Bihar	56	1
12.	Uttarakhand	46	2
13.	Jharkhand	30	4
14.	Odisha	10	1
15.	Tami Nadu	9	-
16.	Kerala	9	-
17.	Goa	8	1
18.	West Bengal	4	1
19.	Punjab	2	-

20.	Assam	1	1
21.	Himachal Pradesh	1	-

7. Treatment of Black fungus

Amphotericin-B injection is the prime treatment for the treatment of this fungal infection. The injection is an antifungal medicine. If infected, the patient has to be kept under the strict supervision of eye surgeons, ENT specialists and neurosurgeons as the infection affects different parts of the body simultaneously [23].

Safety of the patient is of paramount importance and to save life in case of severe mucormycosis the infected tissues need to be surgically removed when need arises. Thereby, if the eye is affected people have lost their eyesight and in some extreme case even the upper jaw. The patients might even require an intravenous anti-fungal procedure spanning four to six weeks.

Treatment protocol are as follows:

1. The treatment of Mucormycosis needs to be immediate and aggressive. The concern is because of the fact time is very crucial to control the infection and if essential time is lost even in a presumptive diagnosis, irreversible damages are caused to the tissues of the patient.
2. Generally, all patients with the infection require medical treatment and or surgery.
3. Experts reckon that since it spreads very fast, to save lives of patient aggressive surgical debridement of the infected area is essential.
4. The role of medications in treatment of mucormycosis is vital. The objective is twin that needs to be fulfilled simultaneously: treatment with antifungal drugs to stop or slow the spread of infection and medicines to treat debilitating underlying diseases.
5. The usual choice is Amphotericin B (initially intravenous) for antifungal therapy.
6. Posaconazole or isavuconazole can treat mucormycosis.
7. Patients may even require an intravenous antifungal procedure lasting 4 -6 weeks.
8. The control of underlying diseases like diabetes need to be in optimum in patients and should be taken care.
9. The steroid treatment needs to be stopped immediately as steroids or drugs like deferoxamine (Desferal; used to remove excess iron from the body) can increase the survival of fungi in the body.
10. Additionally, some patients may require surgeries and the antifungal treatment need to be continued for an extended period (weeks to months) depending on the severity of the disease.

8. Prevention of Black fungus

The people having some health issues or dependent on medications owing to which there is reduction in the resistance offered by the body to combat pathogens are quite prone to Black fungus (mucormycosis) infection. The patient's immunity during and after COVID-19 treatment becomes low making them vulnerable to mucormycosis. If the patient is diabetic and develops COVID-19 disease than the chances of getting black fungal infection is increased [24,25].

Here are a list of dos and don'ts (Table 3) as per the Indian Council of Medical Research (ICMR) guidelines:

Table 3. Dos and Don'ts to reduce the risk of Black fungus infection

Dos	Don'ts
Control high blood sugar levels	Do not overlook the symptoms of black fungus
Monitoring blood sugar level regularly post-recovery	Do not take blocked nose lightly mainly after getting recovered from COVID-19
Use clean, sterile water in the humidifier for oxygen therapy	Do not think twice about getting done any investigation if suggested by the doctor
Use steroids and antifungal medicines only when prescribed by the doctor	

Preventive measures to be followed (Figure 5):

1. The humidifier should be regularly cleaned and replaced when Oxygen Concentrators are used.
2. The bottle containing humidifier bottle needs to be sterilized using normal saline and should be regularly refilled.
3. The face masks also need to be disinfected regularly and replaced on regular basis.
4. The person who are on steroids are required to monitor their blood glucose levels.
5. Mortified Oxygen should be used during the COVID-19 treatment.
6. The practice of good hygiene should be inculcated and also keeping the surrounding clean.
7. The daily routine of brushing and gargling can be very useful.
8. The importance of wearing mask should be advocated and practiced and the chances of getting reinfection should also be kept in mind even if the person has recovered from COVID-19.
9. Regular monitoring of blood glucose levels is mandated in diabetics and should manage to keep diabetes under control.
10. The monitoring of patients is also crucial post COVID-19 infection and the use of steroids need to be reduced and drugs used for immunomodulation should be stopped.

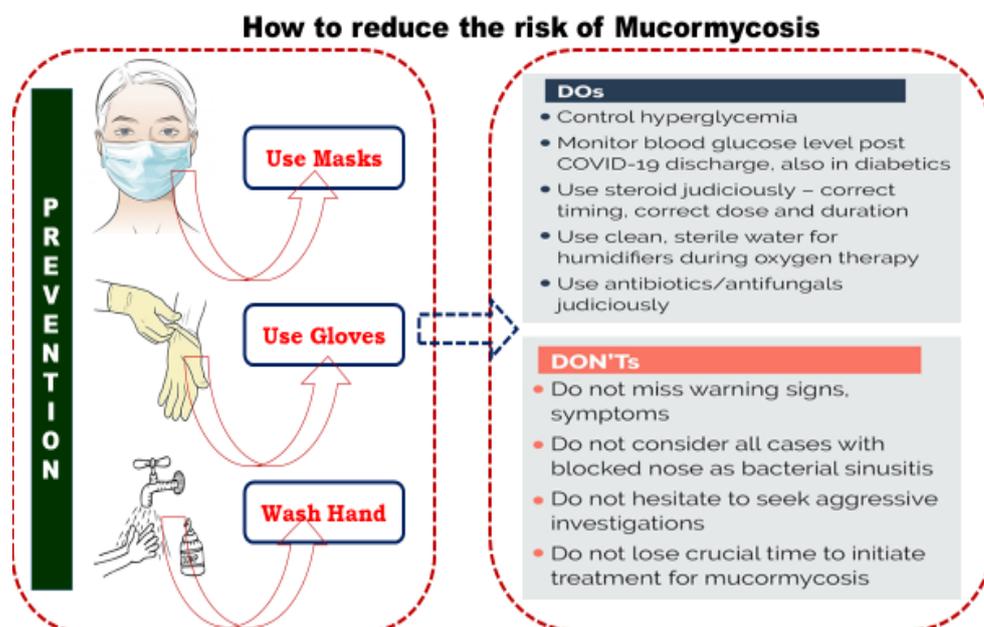


Figure 5. Prevention of Black fungus infection during COVID-19 infection

Prevention of Black fungus by using Methylene Blue

Methylene Blue (MB) has been used as an antiseptic to heal wounds for ages. Methylene Blue was initially used as an antimalarial drug and it has anti-fungal activity as it has the mechanism of redox reduction in mitochondria [26]. Currently Methylene Blue was prescribed to COVID-19 patients in sub-lingual and nebulized forms during the first wave by some doctors. Since it is quite cheap and inexpensive, cost, it was also thought to be a viable regime for developing countries like India in the treatment of symptomatic patients and as a prophylactic drug for the vulnerable population. For the treatment of methemoglobinemia, MB has been approved drug and it is fast-acting with strong anti-fibrotic action. COVID-19 patients show resemblance to methemoglobinemia. Silent hypoxia is caused by COVID-19 in many cases where there are no clinical symptoms of dyspnoea but patients have low oxygen saturation (SpO₂). This leads to severe cytokine storm and causing irreversible phase of respiratory distress in the patients. Given the similarities in the clinical presentations, doctors started using it. However, they stopped prescribing MB for COVID-19 treatment in absence of clinical trials and data proving the effectiveness of MB in the treatment of Covid-19. Recent clinical research stated that Methylene Blue has the mechanism to destroy mitochondria of fungus and therefore can help us in controlling mucormycosis or Black Fungus [27].

9. Conclusion

Fungal infections can be devastating. Mucormycosis is adding to the burden of suffering in a country already in a deep Covid-19 crisis. COVID patients those have diabetes, obesity, kidney problem, cardiac symptoms and neural complication are prone with this deadly black fungus. Commonly used drugs such as Tocilizumab and steroids and will lower the immunity of patients and use of such drugs without the supervision of a doctor will make the patient vulnerable to Covid-associated mucormycosis (CAM), loosely described as black fungal infection. It is associated with high morbidity and treatment costs. Rampant self-medication by COVID-19 patients at home without any expert supervision has become a major concern as they become vulnerable to black fungus. Proper medication and right treatment can control this dual infection.

Conflict of Interest

The authors have no conflict of interest.

Acknowledgement

The authors are thankful to Mr. Gautam Dey, M.D. and Mr. Ranajit Dey, Jt. M.D. for facilities and encouragement during this investigation. They are also thankful to Dr. Atiskumar Chattopadhyay, Principal Secretary, Faculty Council of Science, Jadavpur University for his valuable suggestions and encouragement to conduct & completion of the work. They are also thankful to the Management of RCCIIT for their cooperation.

Author Contributions

All authors made a significant contribution to conduct the review, whether that is in the conception, literature review, drafting, preparation of data, acquisition of data, and interpretation. After critically reviewing the article, the authors gave final approval of the version to be published; have agreed on the journal to which the essay has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they do not have any financial involvement. This also includes honoraria, expert testimony, employment, ownership of stocks or options, patents or grants received or pending, or royalties.

Peer-review

External peer-review was done through double-blind method.

Data and materials availability

All data associated with this study are present in the paper.

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