

Mucormycosis complicates India's COVID-19 Pandemic: A Review

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Abstract: COVID-19 or SARS-COV-2 becomes the universal deadly health alarm from December 2019 to till date with the global cases record of 180,777,842 as well as India's cases record of 30,134,455 till 25th June, 2021. As the country's health system tries to recover from corona crisis, another fungal threat comes in existence known as Mucormycosis or Black fungus Infection, especially affecting the Asian continents like India with the presents recorded updates of more than 10,000 infected cases. Mucormycosis is opportunity seeking fungal infection mainly affects immunocompromised population such as diabetic ketoacidosis patients and those whose immunity has been already hijacked via SARS-CoV-2 virus, creates the fungal entry roadmap from various routes like inhalation, ingestion or inoculation to rule over the body. In the present review, we enlightened the Covid-19 tuned mucormycosis Indian epidemic figures, causative aspects, molecular studies or pharmacological and non-pharmacological approaches. In addition we would also like to talk about the role of human body's immune system and how to reconstruct our immunity both at physical and non-physical (molecular) level as a defending wall towards affection of this infection.

Keywords: Mucormycosis, immunocompromised, opportunity seeking, Pharmacological & Non-Pharmacological.

Introduction:

Globally, a biological war like scenario in the form of Corona Virus Disease-19 (COVID-19) carried out from Dec, 2019 (Wuhan, China) till date in both developed and underdeveloped nations. Countries like New Zealand, Tanzania, Vatican, Fiji, Montenegro etc are already becomes mask free or corona free [1]. However, some developing countries such as India, the second highest populated country in the world after china facing the cruelty of second wave of COVID-19 with the advance expectation and preparation of third wave. But this time embodiment of fungal invaders like Black Fungus, White Fungus or Yellow Fungus in ongoing SARS-CoV-2 infection complicates the current pandemic situation of India [2]. This review mainly highlighted the Black fungus associated complication of India. Mold categorized infection with its 85 years of pathogenic ancestry or Mucormycosis is a very familiar invasive fungal infections (IFI) characterised by tissue infraction and necrosis [3] belonging to the subphylum Mucoromycotina, order Mucorales [4, 5, 6, 7].

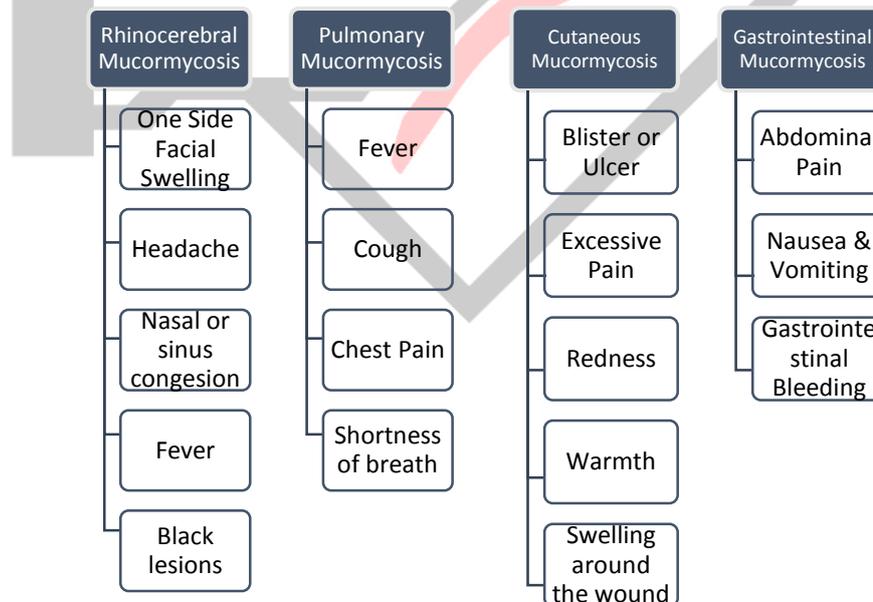


Figure 1: Sign & Symptoms as per Anatomical codification

Mucorales are extreme thermo defenders fast-growing omnipresent microbes commonly found in soil, dust, on fruits and decaying vegetation [8, 9]. *Rhizopus oryzae*, commonly isolated mold species of mucormycosis in India [5, 6, 10] associated with high fatality

rate (>50%) [11, 12]. Anatomical demarcations becomes the backbone for clinical codification of mucormycosis includes rhino-orbital-cerebral (ROCM), pulmonary, gastrointestinal, cutaneous, renal and disseminated mucormycosis [10, 13]. Immunocompromised population such as Diabetic Mellitus Ketoacidosis (DMK) patient in India are more prone to develop black fungus infection. Some other associated risk factors are other forms of metabolic acidosis, long term use of corticosteroids, any transplantation procedure, trauma and burns, neutropenia, and malignant hematologic disorders etc [5, 14]. Mucormycosis is not a contagious infections, so that it ruled over the body via inhalation, ingestion, or inoculation route [15]. The symptomatic profile of mucormycosis **Figure 1** depends upon its anatomical codification [6, 9, 16] but as per Centre of Drug Control and Prevention (CDC) the major symptom are facial deformity, headache, facial pain, nasal congestion, black crust in upper area of nose, swelling in cheeks and eye, toothache etc which are detected or diagnosed by various clinical and molecular methodologies such as clinical studies, histopathological studies etc [17, 18, 19]. In the present review, we discuss the universal as well as Indian epidemic figures, multiple etiological contributing factors, pathogenicity, and pharmacological and non-pharmacological approaches in COVID-19 associated mucormycoses infection in India. In addition we would like to talk about the role of human body's immune system and how to reconstruct our immunity both at physical and non-physical (molecular) level as a defending wall towards affection of this infection

Global Epidemic Perspective:

The Severe Acute Respiratory Syndrome-Corona Virus-2 (SARS-CoV-2) virus has become the creator of multiple other new diseases [20] and one of the rapidly spreading black fungus infection in post-COVID recoveries patients is the bigger example [21]. The incidences of mucormycosis or black fungus is commonly observed in immunocompromised patients [10,22] such as those who are receiving steroids from a long time, hospitalized and on oxygen support or ventilator, heaving poor hospital hygiene or have been taking medication for other illness such as diabetes **Figure 2**.

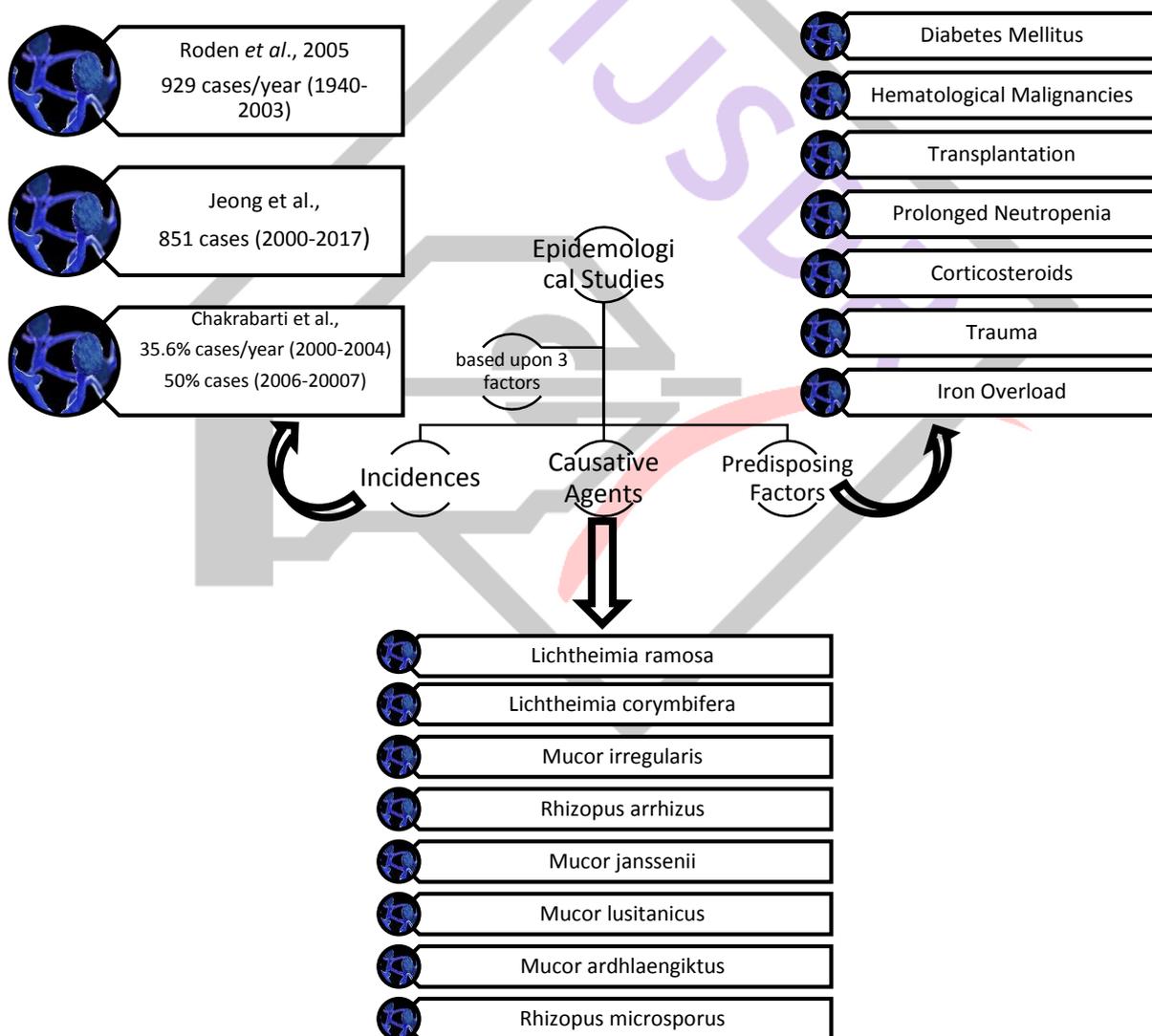


Figure 2: Major contributing factors in the universal epidemiology of Black Fungus.

Today mucormycosis cases are relay from everywhere but with the epidemiological variations worldwide. The pronicity of the fungal infection is remain uncommon, but in developed nations, it is mostly seen in patients with hematological malignancies (HM).

However, in developing nations, specifically in Indian community, diabetes mellitus (DM) or trauma patients are more prone to it [23].

Black Fungus Tuned India's Epidemic Figures:

In 2021 among Asian continents, India sees an increase in mold infection cases [24] partly because many people already grapple with SARS-CoV-2 infection, therefore, these pandemic conditions create a roadmap for the easy spreadability of fungal infection **Figure 3** [25]. Numerous yearly studies had been carried out like Southern India (Tamilnadu) stands with the annual incidence of 18.4 cases per year (2005–2015) [26]. Again during the year 2016-2019 Tamilnadu reported 9.5 cases per year [27], along with it multicenter study throughout India reported 465 cases from 12 centers over 21 months; means annual incidence of 22 cases per year with an average of 38.8 cases from each contributing centre [28]. India's reported death rate due to different clinical forms of mucormycosis includes ROCM (31–49%), pulmonary (61–77%), cutaneous (23–57%), gastrointestinal (67–94%), and disseminated (62–79%) has been almost similar to the global data [10, 13]. The latest black fungus tuned COVID-19 associated report of some state of India till 17 may, 2021 is shown by media reports [29].

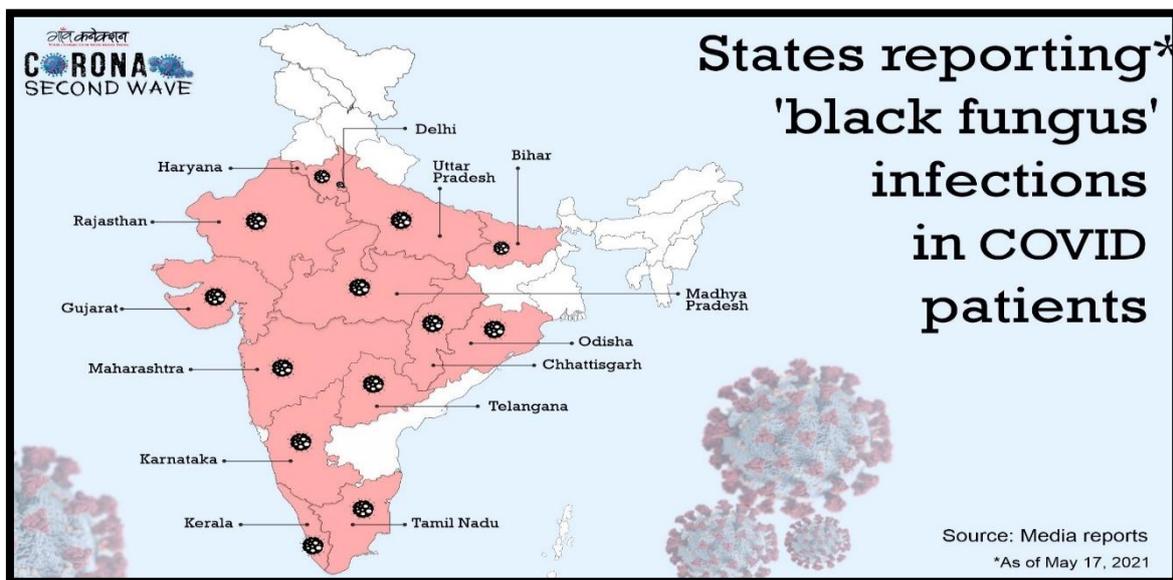


Figure 3: Black Fungus cases in India till 17 May, 2021.

Pathogenesis/Symptoms/Diagnosis:

Mucorales spores via inhalational or inoculated routes generates very vigorous inflammatory response in healthy human [4]. The spore's journey inside the nasopharyngeal route for establish inflammatory network has also not very easy, because for that they must smartly escape killing by immunological defenders such as resident mononuclear and polymorph nuclear phagocytes [5]. This results in the germination of hyphae, the angioinvasive stage of fungal infection, which eventually disperse to other organs [30]. In mucormycosis, glucocorticoids listed among strong etiological contender known to impair the defending immunity drives of our immune system like ingestion, macrophage migration and phagolysosome fusion [31, 32]. Therefore, patients on long term, heavy - dose steroids treatment may have chances to get mucormycoses infection [33]. Previous studies reported that, diabetic ketoacidosis (pH 7.3–6.8) patients have upraised free iron concentration in the serum which supports in the mucorales growth and nourishment [34, 35]. Therefore, Iron overload and mucormycosis is the another important logical area of interest [14, 30, 36, 37]. The symptoms of mucormycosis depend on where in the body the fungus is growing [6, 9], which are detected or diagnosed by various clinical and molecular methods such as clinical studies, histopathological studies etc **Figure 4** [17, 18].

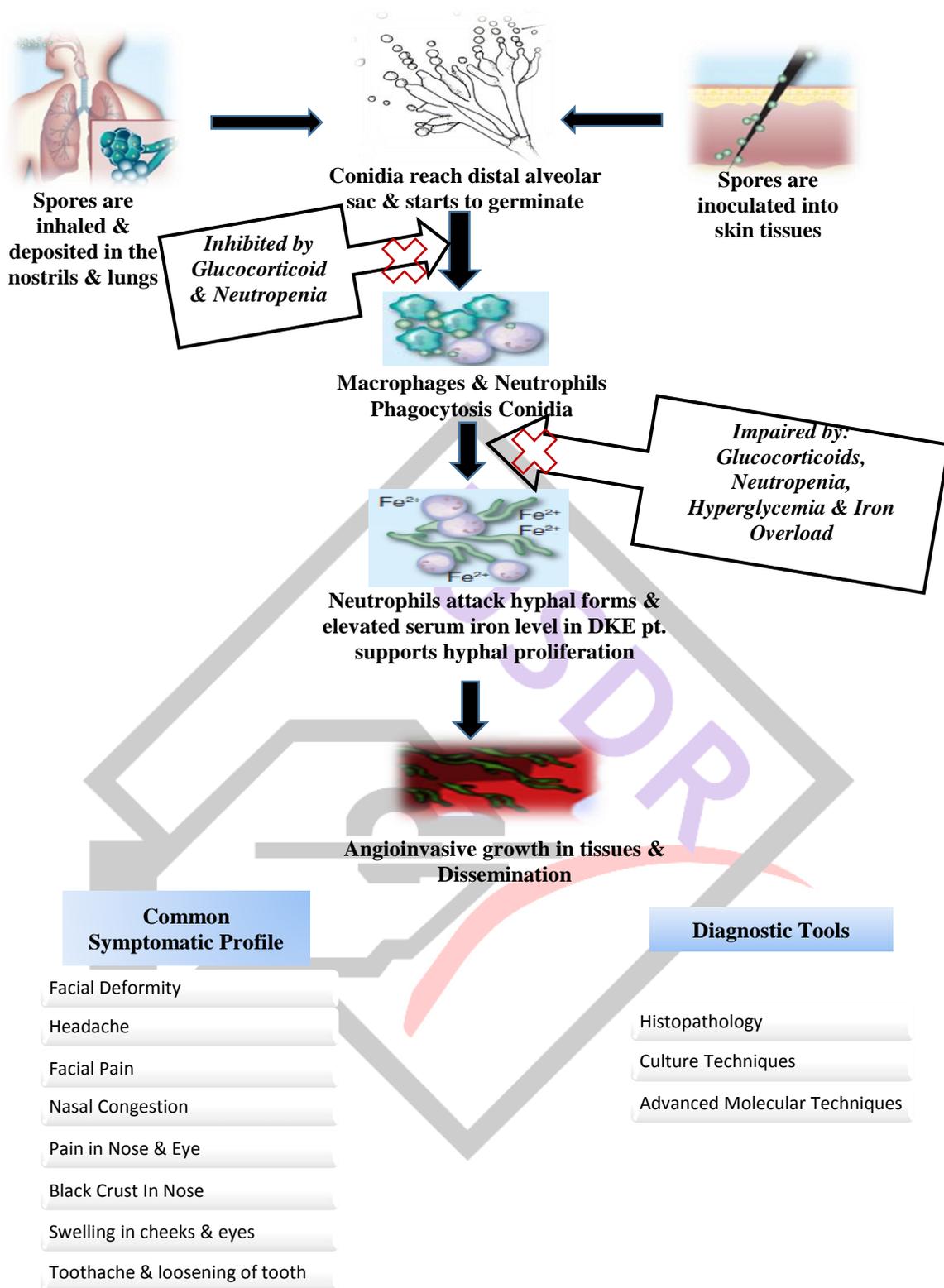


Figure 4: Pathogenesis of Mucormycosis or Black Fungus

Treatment Regimen:

Therapeutic perspective of mucormycosis during this pandemic has been based on the Pharmacological & Non-Pharmacological approaches as mentioned by the global health organization.

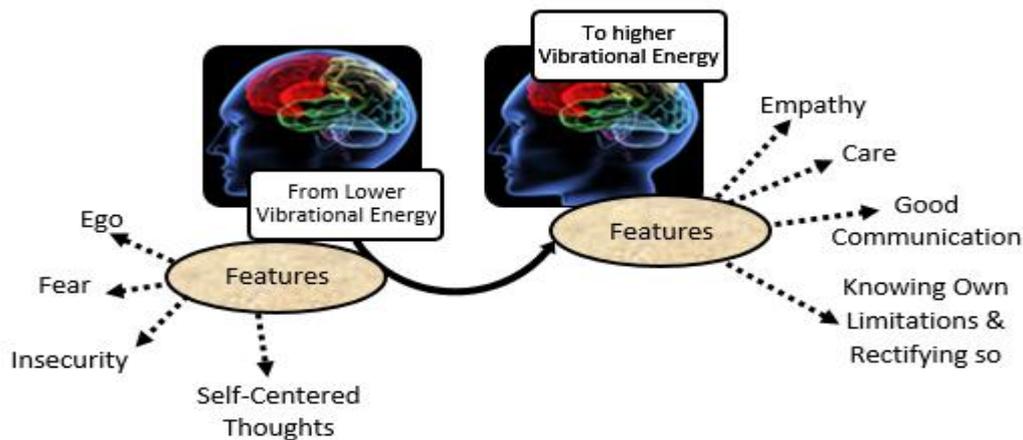
Pharmacological Approaches:

As per Indian Council of Medical Research (ICMR) guidelines [38] four keystone therapy's has been used for managing mucormycosis which includes timely identification and diagnosis of fungal infection followed by immediate administration of a lipid amphotericin B (liposomal AMB) alone or in combinations with Anti-Mucorales, surgical procedures specifically for rhino cerebral or skin conditions and expeditious reversal of principal factors responsible for fungal infection if possible [39].

- **Antifungal Treatment:** Generally polyene based Amphotericin B (AMB), is the first line of defence against mucormycosis [40, 41, 42] subsequently followed by posaconazole and isavuconazole, if needed [43, 44, 45, 46]. On a pharmacological platform AMB lipid formulations (liposomal AMB) [47] or AMB lipid complexes are one step ahead than AMB-deoxycholate [48, 49], but still stand with some major complications like nephrotoxicity and infusion reactions. As we all know that the liposomal drug delivery system is the target based, therefore enhances the treatment cost and becomes a substantial drawback in handling mucormycosis in India [28, 50].
- **Salvage Therapy:** Salvage therapy or Rescue therapy is preferred when any infirmity doesn't respond to standard treatment regimen [51]. For mucormycosis patients who becomes intolerant to polyene therapy, the posaconazole or deferasirox are the better salvage options [52, 53]. In comparative studies Posaconazole appears to be quite safe and effective as compare to deferasirox despite dosing for months to years [54, 55]. In salvage therapy, deferasirox regular dose monitoring i.e. 20 mg/kg/d for 2–4 weeks has been very important for avoiding any kind of renal and hepatic complications because its pre-clinical studies give some evidences about deferasirox toxicity, if its uses beyond 4 weeks [56, 57].
- **Surgical Management:** In skin and sinus mold conditions the immediate surgical removal of mucormycosis lesions has been recommended due to the aggressive nature of the infection [40, 41, 58, 59], even though, some cases of sinus mold infection associated with radical debridement includes enucleation of the eye. As per retrospective studies, patients who had received surgical treatment along with systemic antifungal therapy had grater chances of survival [60, 61, 62]. In case of pulmonary mucormycosis, the surgical treatment benefits are less well accepted. Lobectomy may be the option in mild to moderate category patients with unifocal disease [60, 63], however, for severe category patients sometimes pneumonectomy has been recommended [64]. Meanwhile, the surgical procedure outputs has been not yet cleared in patients suffering with the multifocal disease or disseminated infection [65].
- **Adjunctive therapies for mucormycosis:** We all are very familiar to this fact, that the treatment options regarding mold infection are very limited. Therefore, the adjunctive or supplemental therapies focused on the restoration of a host immune functions against the fungal infection [66] via the administration of granulocyte-macrophage growth factor and IFN- γ . Hyperbaric oxygen plays a very impressive role in the treatment of diabetic patients with rhinocerebral or cutaneous infection [67] via improving neutrophil oxidative killing and in this way might speed up wound healing [68].

Non-Pharmacological Approaches:

- **Technology tuned Awareness Programmes:** COVID-19 has also been known as techno-medico tuned pandemic, because we live on a technology based medical, academic or professional supports from 2020 to till date [69, 70]. During this pandemic time, technology based medical awareness programmes becomes the life time non-pharmacological achievements for various contagious or non-contagious diseases. Today all health organizations like World Health Organization (WHO), ICMR, CDC etc update their health related bulletin or guidelines with digitalization using android technology, tele-communication [71] etc. Let's take the brief outlook on ICMR based mucormycosis preventive guidelines: 1).for prevent mucormycosis condition in Covid-19 patients, there will be a better control of the sugar levels with or without steroids, 2). Use of clean or sterile water for humidifiers during the oxygen therapy, 3). Use masks if you are visiting dusty construction sites, wear shoes, long trousers, long sleeve shirts and gloves while handling soil (gardening), moss or manure, 4). Maintain personal hygiene includes oral hygiene, skin care etc [72, 73].
- **Human Nature & Psychology-Remodeling:** Pandemics doesn't means any physical trauma or immunity weakness, beside this, they also effects on one invisible factor of human body i.e. psychological ability or human behaviour [74]. A strong perception of human psychology and behaviour during an epidemic situations becomes a key factor for various recommendations in a manner that would enhance the use of guidelines [75]. In this way, we might limits the hazardous health consequences of pandemic like crucial situations on community level. All low-vibrational activities and behaviour give rise to low self-esteem **Figure 5**. To counteract that people generally try to put others down and dis-obey healthy rules and regulation. Therefore, this type of gesture may help in preserving one's ego but not the society at large.



Conclusion & Future Framework:

As India continues to achieve stability over the existing situation, another imminent threat has emerged as a challenge to India in the form of coronavirus disease-associated mucormycosis and kept India's health care system is on the brink of collapse. The incidence of mucormycosis has risen more rapidly during the second wave compared with the first wave of COVID-19 in India. The ICMR released guidelines for the screening, diagnosis and management of mucormycosis in patients with COVID-19. The most common causes attributed to the rise of mucormycosis in COVID-19 patients are uncontrolled diabetes, excessive use of corticosteroids for immunosuppression and long-term stays in the intensive care unit. Understanding the mechanisms of innate host responses to Mucormycetes infection is important, as the patient's immune status appears to be the most significant factor for a favorable prognosis for mucormycosis. Therefore early diagnosis, antifungal therapy, and prevention steps can be used to cure the infection and for getting this target the Ministry also needs to step up to monitor and analyse the situation; to disseminate information, education and communication materials for the general public and to undertake essential measures for preventing a further rise in the number of mucormycosis cases in patients with COVID-19 and mortality. Moreover, the population explosion is also one of the key factor for improper hygiene, lack of awareness and non-utilization of preventive measure, even though too much urbanization leads to destruction of natural habitants on the planet give rise to diverse ill- health scenarios. However, revolution in 5th generation (5G) technology threatens us towards several diseases including cancer, cell-death, etc. Could it ever be a probable cause for viral mutation and pandemic threat? All these could be our probable area of future action for improvement.

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