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Inevitable Impact of Steroids and Mucormycosis – A Review

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Authors' contributions

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Review Article

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ABSTRACT

The human population remains in the threat of the Pandemic of COVID 19 till date with one another faces of it. The second wave of the pandemic led population into vain again with yet another danger of the third wave. The use of the steroids for controlling and treatment of the upsurge during the second wave remained a trend. The uncontrolled use of steroids invites the secondary infection mucormycosis also called black fungus which affected the population badly. Mucormycosis is opportunistic infection that acquired immune compromised patients with COVID 19 and steroids in treatment paradigm. Most of the patients with high blood glucose levels and diabetes faced this threat and created pandemic in pandemic again. The reviews focus on the positive and negative both prospects of the steroidal use and how steroids were the leading cause of the blowout of the Black fungus infection.

Keywords: SARS COVID-19; mucormycosis; dexamethasone; diabetes; immune system; steroids.

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1. INTRODUCTION

The world was shaken by the emerging threat with the name of novel corona virus (COVID 19) in the year 2019. The disease became prevalent with its first appearance in the Wuhan(China) in the last months of the December which was the result of the zoonotic transmission [1]. Later with its wide spread it was declared the pandemic which took almost 216 countries its host and was termed as the severe respiratory syndrome coronavirus 2(SARS COV 2). The blowout of the virus was related with the animal perspective because of its genomic identity with bat corona virus. Further studies revealed that SARS COV2 shared almost more than 90% similarity with Pangolin-COV which turned out to be linking host between the bats and humans [2]. The disease manifests itself with clinical signs of cough, fever and laboured breathing in the patients with the infection. Some more clinical extra pulmonary signs included altered olfactory senses, urticarial, erythematous rashes, altered consciousness and certain cerebrovascular changes. The virus targets the respiratory system causing distress with normal physiology and ultimately leading to opacity in the lungs visualised with diagnostic interventions. Due to the compromised immune system patients with the disease were more susceptible to the infections particularly fungal infections moreover unethical use of the steroids also worsened the prevailing situations.Patients suffering with the disease were hospitalised and steroids were also added to the treatment regimen. Steroids were incorporated in the treatment regimen due to their quick response but the availability of the steroids over the counter had a negative effect on the treatment. Steroids like dexamethasone, Hydrocortisone and other Corticosteroids proved to be effective in controlling the situation a while but invited a new threat to encounter in the form of the mucormycosis [3].

Mucormycosis medically also termed as the zygomycosis is a fungal infection with some serious outcomes. The disease is triggered through a cluster of moulds called mucormycetes. The various strains of the fungi family have the potential to cause the infection more potentially Rhizopus Oryzaewas responsible for the wide spectrum of the infection in the human population. The dead decaying organic matter is the home to the fungi and is spread when the host body is exposed to the spores of fungus present in the atmosphere [4]. The clinical manifestations depend on the organs which is being attacked by the fungi. Highest number of the patients were reported in the India due to the associated COVID 19 worldwide. Steroid induced hyperglycaemic conditions, hypoxia, compromised immune system, diabetic ketoacidosis or metabolic alkalosis proved to be the favourable environment for the development and further spread of the fungal infections. Worldwide occurrence rate of the invasive mucormycosis in populations per million in the various continents was estimated as Europe reported from 0.2 cases found in Denmark to Portugal reporting 95 cases, USA reported 3.0 cases, and Canada reported 1.2 cases and Australia about 0.6 cases. India according to studies reported around 140 cases per million populations with the occurring rate between 137,807 cases to 208,177 cases. The mortality rate was estimated occurring to be 65,500 ranging 38.2% per year [5]. Immunosuppression, hyperglycemia, and lymphopenia caused by glucocorticoids predispose to mucormycosis development. The use of larger dosages of steroids (glucocorticoids) or indiscreet use of glucocorticoids in COVID-19 instances without hypoxemia should be avoided. Even in the absence of diabetes mellitus, people with COVID-19 have been found to develop ketones and ketoacidosis [6]. Acidosis can impede phagocytic activity and increase serum-free iron due to proton-mediated displacement of ferrous iron from transferrin, allowing this fungal infection to thrive [7]. Similarly, the widespread use of zinc and iron-containing multivitamins as "immunity boosters" that can lead to elevated free-iron levels should be discouraged.

The aim of the review is to enlighten the effect of the ethical and unethical perspective of steroids use in the COVID19 and how the steroids were part of the mucormycosis yet another threat which proved to be havoc for the human survival.

2. SEVERE ACUTE RESPIRATORY SYNDROME CoV-2 (SARS CoV-2)

Medically the term SARS CoV2 is the native of the Beta genus of the order Nidovirales having Coronaviridae as its family. The virus is covered with positively single stranded RNA helical nuclear capsule [8]. The four main proteins being the part of the deadly virus are Spike protein, membrane protein, envelop protein and nuclear capsule protein, the four being the most crucial part of the twenty different structurally related proteins found in the viral cascade. Several other proteins not associated as structurally are also

part of the virus including RNA dependent RNA polymerase, Papain like protease and corona virus main protease (3CLpro) that are more likely to be the molecular targets of drugs used for the virus [9].

Talking more on the receptor category angiotensin converting enzyme II (ACE II) is key receptor when attachment of the SARS COV2 is considered which is further responsible for its replication in humans [10]. The host cell is targeted by the virus with the help of the receptor binding domain which is part of virus in the form of the spike protein. The interaction of the spike protein with the ACE II receptor induces a conformational change inthe C terminal S2 subunit that is solely responsible for the virus interaction with the membrane. Type II transmembrane serine protease enzyme found in the host cells processes the complex of the S protein ACE II proteolytically. This dispensation cleaves the ACE II and leads to the entry of virus into the cells of host [11]. Two of the polyproteins namely pp1a and pp1ab under the influence of the genomic RNA translation just after the un-coating of the viral cascade is cleaved by the proteolytic activity and leads to the formation of the 15-16 non-structural proteins. The non-structural proteins induce cell membrane rearrangement which ultimately forms double membrane vesicles. The genomic RNA is further transcribed into the sub-genomic RNA which in turn leads to the synthesis of the proteins of virus that is structural and accessory proteins. The virions are released by the secretory pathways as they are associated with the Endoplasmic Reticulum-Golgi Intermediate complex [12]. Other strains of the virus are also prevailing and shares similar genetic and clinical manifestations as that of the native strains [13]. The pathophysiology stands out to be same for the all the strains that is interaction with some of the specific receptors of Angiotensin converting Enzyme category like in case of NL 63 and other strains [14].

The strains may differ with each other in the length of the specific structural and non-structural proteins however on genetic basis they stand out to be almost similar as that of the native and are equally destructive and pathogenic [15].

The schematic representation shows how the virus is entered into the host body and completes its cycle of replication and proven to be really destructive for the human body.

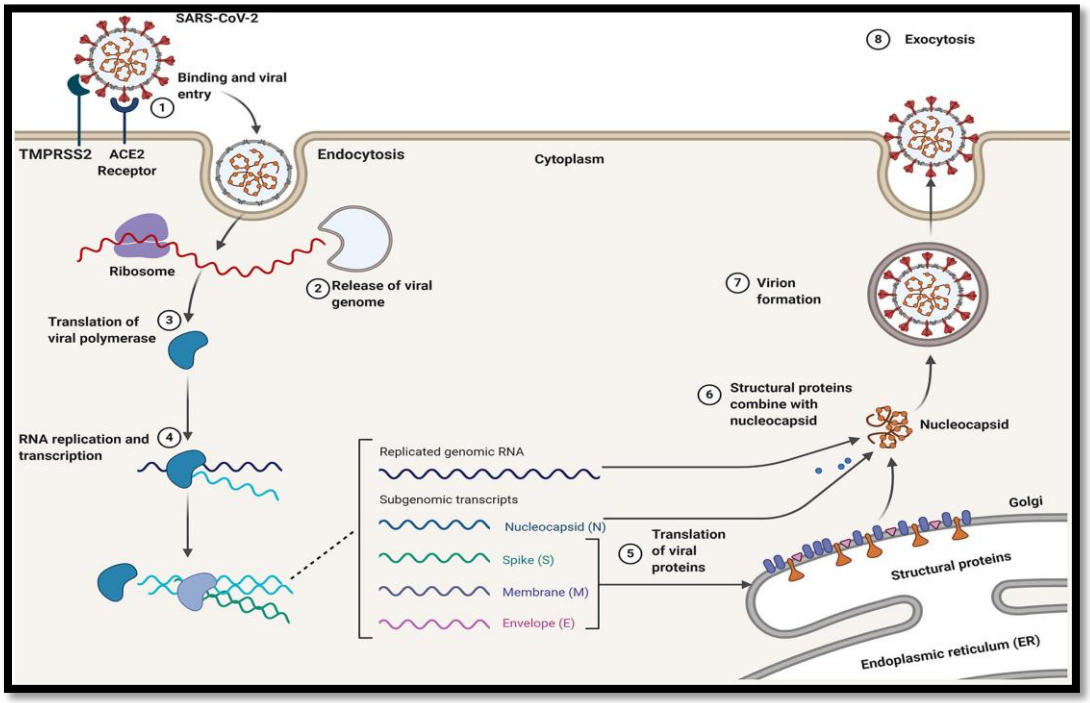

Fig. 1. Infection mechanism and life cycle of SARS-cov-2 in the host cells [15]

3. STEROIDS AS TREATMENT PARADIGM

The studies over the different populations according to the need revealed results that actually depicts how the steroids were to be used and why to not adopt in use. The data was collected for the reduction in the mortality rate by incorporating the steroids within limited use for the treatment of COVID 19 patients. WHO recommended use of the low dose of the dexamethasone around 6mg for ten days for the patients needing oxygen and mechanical aeration which significantly reduced mortality rate. But on the other hand no significant reduction in the mortality rate of the patients not requiring additional supplementation of ventilation and oxygen was seen as the trial was being recorded for around 600 patients of both the categories [16].

The clear situation was that the patients who were hospitalized with severe infection with oxygen level less than 90% and less than 30 breaths per minute showed positive response to the steroidal intake. The results were depicted for the hospitalised patients and significant decline was seen in their mortality rate with the induction of the steroids as the drug of choice.

Further WHO quick evidence evaluation for COVID-19 remedies combine the data obtained from the intensive care unit patients requiring invasive ventilation, high flow of the oxygen through cannula and with patients having symptoms before the trial accomplished. The results clearly stated the reduction in the mortality rate with the judicial and recommended use of the steroids in patients selected for the study. But the exact mechanism behind the steroidal mechanism of action may be through reduction in the cytokines firing and reduction in the ARDS is still in darkness. The Table shows the data of the REMAP- CAP, CODEX and CAPECOVID and their effects. The observations and results of the various studies is the sole for the dosage and duration of the steroid induction in patients. The data reveals here that hydrocortisone should be administered in low doses only. The high doses and over the counter usage of the steroids without any certain adoption of the medical ethics may lead to the fatal results. The dose for the dexamethasone comes out to be 6mg orally or intravenously daily, Hydrocortisone 50mg intravenously every eight hours for 7-8 days of hospitalization under expert supervision only in mild infections [17].

4. STEROIDS AND MUCORMYCOSIS

In the study conducted in the early stages as reported earlier depicted that the judicial use of the steroids reduced the mortality rate in patients with mild symptoms and hospitalized patients. The report leads to the further extension and incorporation of the steroids over the counter medicines in India for the controlling of the COVID-19 patients. This diminished the thin line between ethical and proper use of the steroids as drug of the choice. After which millions of the people which don't have a bit knowledge about its use thought it as the treatment for the COVID 19 started its use without having a bit consideration of its negative and harmful effects [16].

5. CLINICAL TRIALS

5.1 Alternative Study and Secondary Infection

A study conducted by the Jeronimo and his colleagues concluded that the use of the prednisolone in the patients with the COVID 19 patients did not however reduced mortality risk. This proved to be the controversial and it also reported that the methylprednisolone is not sole treatment to avoid mortality in the pandemic [18]. WHO clearly stated that the judicial use of the corticosteroids orally as well as intravenously but the due to the lack of the proper medical information and panic environment the patients who didn't required the use of the drug received it.

Even in the mildest cases of COVID-19, the use of steroids on a regular basis is likely the most important factor leading to the rise in COVID-19–associated mucormycosis in India. Mucormycetes thrive in an environment that includes glucocorticoid-induced hyperglycemia and immunosuppression, as well as COVID-19-induced hyperglycemia, lymphopenia, and immunological dysregulation (leading in decreased T lymphocytes, CD4+ and CD8+ T cells). Due to the widespread usage of large doses of steroids, even in the mildest COVID-19 cases, these issues are exacerbated by their simple over-the-counter availability in India. In addition, current Indian steroid guidelines prescribe methylprednisolone in 0.5–1 mg/kg/day

in mild COVID-19 cases and 1–2 mg/kg/day in severe cases [19].

Moreover, the accepted dose for the corticosteroids like dexamethasone, prednisolone and hydrocortisone was for patients who really need it not for the mass which ultimately lead to the spread of the Mucormycosis. The overdose of the steroids supressed the immune system of the population and increased the risk of the wide spread of the infection throughout India. The potential side effects of the steroids misuse lead variety of the symptoms that gave invitation to the Mucormycosis [20].

Table 1. Randomized trials on corticosteroids use in COVID-19 and their characteristics [17]

Study	CoDEX	Recovery	REMAP-CAP	CAPECOVID
Drug	Dexamethasone	Dexamethasone	Hydrocortisone	Hydrocortisone
Dose	20 mg/day IVfor 5 days and then 10 mg/day IVfor 5 days	6 mg/day OSorIVfor 10 days or until discharge	Two treatments were used: a fixed 7-day course of 50 mg or 100 mg IV hydrocortisone every 6 hours; and a shock-dependent course of 50 mg hydrocortisone every 6 hours when shock was clinically manifest.	Continuous IVinfusion for 8 days (if the patient's respiratory and general status had sufficiently improved) or 14 days: a) For a total of 8 days, take 200 mg/day for four days, then 100 mg/day for two days, then 50 mg/day. b) 200 mg/day till day 7, then 100 mg/day for four days, 50 mg/day for three days, for a total of 14 days.
Respiratory support	Invasive ventilation	ECMO, mechanical ventilation or NIVor oxygen support	HFNOorNIVor invasive ventilation	Invasive ventilation or oxygen through a reservoir mask
Setting	ICU	Not reported	ICU	ICU
Initiation of steroid therapy	Within 48 hours of meeting criteria for moderate to severe ARDS	Not reported	Within 48 h of hospital admission	In 24 hours of the first severity criterion appearing*, or in 48 hours for patients referred from other hospital
Adverse events	Not significant	Two episodes- First one of hyperglycaemia, and gastrointestinal bleeding, and second of psychosis	10 patients (2.6%) who incurred a serious adverse event (severe neuropathy and fungemia)	No serious adverse events were attributed to the study treatment

ECMO: Extracorporeal membrane oxygenation; NIV: non-invasive ventilation; HFNO: high-flow nasal oxygen cannula; ICU: intensive care unit.

**Need for mechanical ventilation with a positive end-expiratory pressure (PEEP) of 5 cmH2O or higher; a PaO2:FiO2 ratio of less than 300 on high-flow oxygen therapy with a FiO2 value of at least 50%; a PaO2:FiO2 ratio of less than 300 for patients receiving oxygen through a reservoir mask*

Table 2. Characteristics of the trials with the steroids [21,22]

	DEXA COVID 19	CoDEX	RECOVERY	CAPECOVID	COVID STEROID	REMAP-CAP	STEROIDS SARI
ClinicalTrials.gov Identifier	NCT04325061	NCT04327401	NCT04381936	NCT02517489	NCT04348305	NCT02735707	NCT04244591
Planned Sample Size	200	250	NA	290	1000	Nab	80
Eligibility criteria	Intubation Mechanical ventilation Moderate to severe ARDS per Berlin criteria[3] Confirmed COVID-19	Intubation Mechanical ventilation Moderate to severe ARDS per Berlin criteria[3] Onset of ARDS <48 before randomization Probable or confirmed COVID-19	Criteria used for this meta-analysis: Intubation Suspected or confirmed COVID-19	Minimal severity Admitted to ICU or intermediate care unit Oxygen (6 L/min) Probable or confirmed COVID-19	Oxygen (10 L/min) Confirmed COVID-19	Admitted to ICU receiving high-flow nasal oxygen with Fio2 >0.4 at >30 L/min, noninvasive or invasive ventilatory support, or receiving vasopressors Probable or confirmed COVID-19	Admitted to ICU with Pao2:Fio2 <200 mm Hg on positive pressure ventilation (invasive or noninvasive) or high-flow nasal canulae >45 L/min Confirmed COVID-19
Corticosteroid							
Drugname	Dexamethasone	Dexamethasone	Dexamethasone	Hydrocortisone	Hydrocortisone	Hydrocortisone	Methylprednisolone
Dosage and administration	20 mg/d intravenously 5d and then 10 mg/d intravenously 5d	20mg/d intravenously S dand then 10 mg/d intravenously 5d	6mg/d orally or intravenously	Continuous intravenous infusion 8d or 14 d (200 mg/d 4 dor 7d; 100 mg/d 2d or 4d; 50 mg/d 2d or 3d)	200 mg/d intravenously 7d (continuous or bolus dosing every 6h)	50 mg intravenously every 6 h x 7 d°	40mg intravenously every 12 h 5 5d
Dose classification	High	High	Low	Low	Low	Low	High
Control intervention	Usual care	Usual care	Usual care	Placebo	Placebo	Usual care	Usual care
Primary outcome	60-d mortality	Ventilator-free days	28-d mortality	21-d treatment failure (death or persistent requirement for mechanical ventilation or high-flow oxygen therapy)	Days alive without life support at 28 d	Composite of hospital mortality and ICU organ support-free days 21 d	Lower lung injury score at d and 14 d

	DEXA COVID 19	CoDEX	RECOVERY	CAPECOVID	COVID STEROID	REMAP-CAP	STEROIDS SARI
Mortality outcome, d	28	28	28	21	28	28	30
Serious adverse event definitions	Secondary infections of pneumonia, sepsis, or other similar Pulmonary embolism	Mortality Infections Insulin use	Cause-specific mortality Ventilation Dialysis Cardiac arrhythmia (in subset) Other that were believed to be related to study treatment	Any Excluded some listed in protocol Excluded expected adverse events related to the patient's disease or comorbidity	New episodes of septic shock (Sepsis-3 criteria) Invasive fungal infection Clinically important gastrointestinal bleeding Anaphylaxis	Per ICH good clinical practice guidelines (events not already captured as trial end point; eg, mortality) When the event may reasonably have accurred because of study participation	Secondary bacterial infections Barotrauma Severe hyperglycemia Gastrointestinal bleeding requiring transfusion Acquired weakness
Location	Spain	Brazil	UK	France	Denmark	Australia, Canada, European Union, New Zealand, UK, US	China
ClinicalTrials.gov Identifier	NCT04325061	NCT04327401	NCT04381936	NCT02517489	NCT04348305	NCT02735707	NCT04244591
Planned Sample Size	200	250	NA	290	1000	Nab	80
Eligibility criteria	Intubation Mechanical ventilation Moderate to severe ARDS per Berlin criteria[3] Confirmed COVID-19	Intubation Mechanical ventilation Moderate to severe ARDS per Berlin criteria[3] Onset of ARDS <48 before randomization Probable or confirmed COVID-19	Criteria used for this meta-analysis: Intubation Suspected or confirmed COVID-19	Minimal severity Admitted to ICU or intermediate care unit Oxygen (6 L/min) Probable or confirmed COVID-19	Oxygen (10 L/min) Confirmed COVID-19	Admitted to ICU receiving high-flow nasal oxygen with Fio2 >0.4 at >30 L/min, noninvasive or invasive ventilatory support, or receiving vasopressors Probable or confirmed COVID-19	Admitted to ICU with Pao2:Fio2 <200 mm Hg on positive pressure ventilation (invasive or noninvasive) or high-flow nasal canulae >45 L/min Confirmed COVID-19
Corticosteroid							
Drugname	Dexamethasone	Dexamethasone	Dexamethasone	Hydrocortisone	Hydrocortisone	Hydrocortisone	Methylprednisolone
Dosage and	20 mg/d	20mg/d intravenously	6mg/d orally or	Continuous	200 mg/d	50 mg	40mg intravenously

	DEXA COVID 19	CoDEX	RECOVERY	CAPECOVID	COVID STEROID	REMAP-CAP	STEROIDS SARI
administration	intravenously 5d and then 10 mg/d intravenously 5d	S dand then 10 mg/d intravenously 5d	intravenously	intravenous infusion 8d or 14 d (200 mg/d 4 dor 7d; 100 mg/d 2d or 4d; 50 mg/d 2d or 3d)	intravenously 7d (continuous or bolus dosing every 6h)	intravenously every 6 h x 7 d°	every 12 h 5 5d
Dose classification	High	High	Low	Low	Low	Low	High
Control intervention	Usual care	Usual care	Usual care	Placebo	Placebo	Usual care	Usual care
Primary outcome	60-d mortality	Ventilator-free days	28-d mortality	21-d treatment failure (death or persistent requirement for mechanical ventilation or high-flow oxygen therapy)	Days alive without life support at 28 d	Composite of hospital mortality and ICU organ support-free days 21 d	Lower lung injury score at d and 14 d
Mortality outcome, d	28	28	28	21	28	28	30
Serious adverse event definitions	Secondary infections of pneumonia, sepsis, or other similar Pulmonary embolism	Mortality Infections Insulin use	Cause-specific mortality Ventilation Dialysis Cardiac arrhythmia (in subset) Other that were believed to be related to study treatment	Any Excluded some listed in protocol Excluded expected adverse events related to the patient's disease or comorbidity	New episodes of septic shock (Sepsis-3 criteria) Invasive fungal infection Clinically important gastrointestinal bleeding Anaphylaxis	Per ICH good clinical practice guidelines (events not already captured as trial end point; eg, mortality) When the event may reasonably have accurred because of study participation	Secondary bacterial infections Barotrauma Severe hyperglycemia Gastrointestinal bleeding requiring transfusion Acquired weakness
Location	Spain	Brazil	UK	France	Denmark	Australia, Canada, European Union, New Zealand, UK, US	China

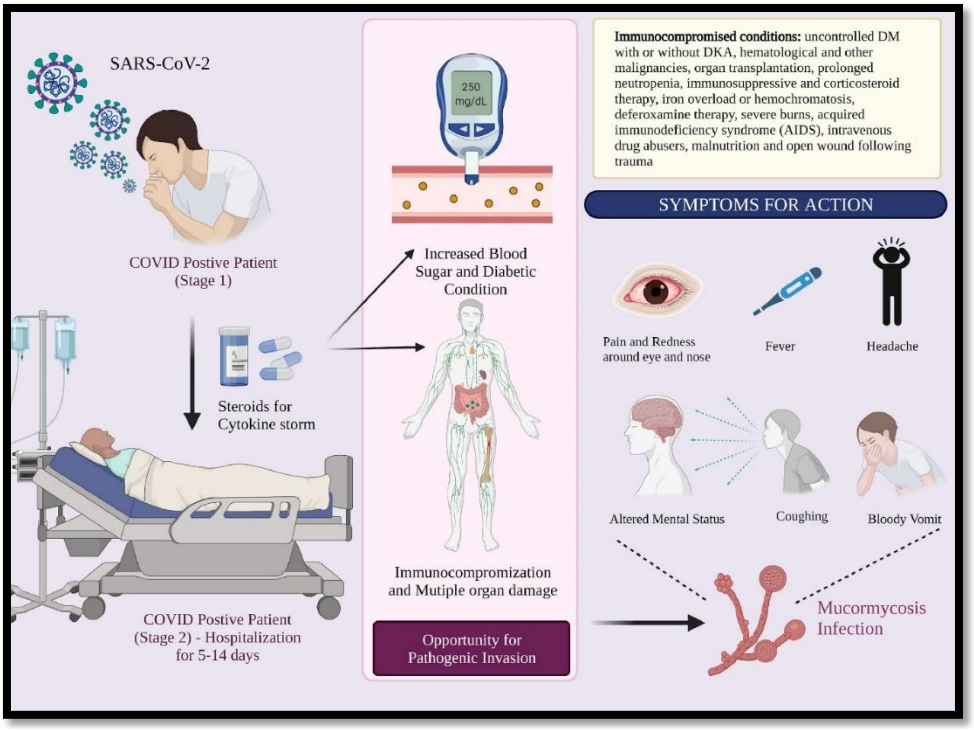

Fig. 2. The representation of the spread of the mucormycosis with steroidal drug

The reason ascertained for the spread of the infection is the compromised immune system of the individuals suffering and recovering from the COVID 19 pandemic. The abusive steroidal intake and its impact over the diabetic patients made individuals more susceptible to other diseases. To avoid a cytokine storm, medical professionals must add steroid medicines in the COVID 19 therapy protocol. However, including these treatments in patients who do not require steroids can weaken their immune system, allowing the fungus to infiltrate.

The patients suffering from diabetes are the first target of the black fungus infection. According to report published by the International Diabetes Federation around 77 million suffer from diabetes and are more prone to the disease of black fungus. The steroids giving rise to the blood glucose levels and weakening immune response pave way for the infection to invade in the patients.

The long stay of the patients in the hospital for the treatment of the patient with severe illness and requirement of the additional interventions like oxygen masks and ventilators made the patients susceptible to the infection. Furthermore, the high dose steroids cause hyperglycaemic conditions along with the diabetes as one of its major cause diabetic ketoacidosis, chronic kidney disease, immunosuppressive medications, weakened immune system due to the COVID 19 were all the way responsible for the mucormycosis to spread widely in the population so rapidly. As result early detection and necessary education regarding the judicial use of the drugs should be taken for the morbidity associated to reduce [23].

6. MUCORMYCOSIS

In an immune compromised host, mucormycosis is an arduous angio-invasive unscrupulous infection. Mucormycosis can manifest itself in a variety of ways, including rhino-orbital-cerebral, pulmonary, disseminated, cutaneous, gastrointestinal, and disseminated forms. The key risk factors for the condition include diabetes, neutropenia, iron overload, malignancy, and organ transplantation.

The most common metabolic illness is diabetes, and it is a risk factor for Severe COVID-19 and Mucormycosis on its own. Superinfection with Mucormycosis in individuals with diabetes who have COVID-19 will result in a worse clinical outcome and a longer hospital stay. The goal of this research is to look at the medical range of Mucormycosis in individuals with COVID-19 and diabetes, as well as their consequences.

In COVID 19 patients on supplemental oxygen, corticosteroids are considered crucial therapy. Though using prednisolone or an equivalent dose of 1 mg/kg for 3 weeks or longer is typically thought to be a risk factor for Mucormycosis, certain case reports have revealed that Mucormycosis can develop after a diminutive usage of steroids. Corticosteroids have a wide range of effects in CAM. First, they can cause immunosuppression by preventing macrophage migration, phagocytosis, and phagolysosome formation. Second, they cause drug-induced hyperglycaemia and deterioration of glycaemic control in diabetic individuals. Furthermore, in countries where it is available over-the-counter, such as India, incorrect and extended steroid use may increase vulnerability to Mucormycosis [24].

Mucormycosis is a zygomycete-related opportunistic fungal infection that is found throughout the environment. Inhalation of spores of Rhizopus oryzae, a conjoint source of rhino-orbital-cerebral infections that extend to the paranasal sinuses and lungs, is the main route of infection. Molds can be found in a variety of places, including soil, plants, manure, and decaying fruits and vegetables.

Mucormycosis is an intermittent but serious and lethal fungal infection that generally distresses those who have weakened immune systems. These fungi are generally non-pathogenic in immune-competent patients, but in patients whose immune systems have been impaired by steroids or additional co-morbidities such as diabetes or solid malignancies, malignant and hematologic diseases can be life-threatening. Additional menace issues for black fungus mortality include organ transplantation and high levels of iron in the blood.

The immune system in covid-19 patients, particularly those who require oxygen support, may become weakened as a result of an inflammatory storm or the use of steroids. This could lead to opportunistic infections such as mucormycosis. The clinical signs associated with the infection include discoloration of the tongue and nose, pyrexia, reduced vision, redness in the eyes, headache, cough, black lesions in mouth, dyspnoea, pain in chest and vomiting.Clinical suspicion and histological investigation are frequently used to make a diagnosis [25].

Rendering to current reports from India, the number of individuals dying from black fungus is constantly rising, and specialists are calling it a "pandemic within a COVID-19 pandemic." In India, the second wave of Covid-19 saw more cases than the first wave, with higher fatality percentage.Reduced oxygen levels, trouble breathing, and other respiratory tract-related disorders like pneumonia and Acute Respiratory Distress Syndrome were the most common sequelae of mucormycosis in the second wave. In India, patients who have had long-term oxygen sympathetic therapy are further likely to contract mucormycosis.Any clinical suspicion of fungus should be evaluated, and antifungal therapy should be given as soon as possible [26].

7. DIABETES AND MUCORMYCOSIS

In India, diabetes is the most common co-morbidity in Mucormycosis, accounting for 73.5 percent of cases [27]. In western countries, however, diabetes is linked to 17% of Mucormycosis cases [28] Mucormycosis is seen in about 1.6 instances per 1000 diabetic people. Poorly controlled type II diabetes is the most prevalent risk factor for mucormycosis in diabetic patients, accounting for 44–88 percent of cases, primarily from south India and North India, with half of them having ketoacidosis. Type I diabetes (10–15 percent) and Type II diabetes have been detected in some situations. [29,30,31].

The specific predisposition of diabetic patients to mucormycosis is due to a number of variables. For starters, diabetes and ketoacidosis cause phagocytic cells to malfunction [32]. Both neutrophils and macrophages show diminished chemotaxis and incorrect killing by both oxidative and non-oxidative routes in these settings, however the exact mechanisms underlying this are unknown. Second, patients with diabetic ketoacidosis have an acidic serum pH and large amounts of free iron, which is a major nutritional component in Mucorales susceptibility.

Table 3. Mucormycosis clinical indicators in COVID-19 patients

Type	Pathogenesis	Clinical Manifestation	Risk Factors
Rhino-Cerebral Mucormycosis	Sinuses are invaded by spores, also through cribriform plates, and cavernous sinus.	Infects the sinuses and spreads to the brain. Destroys maxillary-facial structures and causes ptosis, apoptosis, and permanent vision loss	Patients suffering with diabetes in uncontrolled conditions and kidney transplanted patients.
Pulmonary Mucormycosis	Fungal infection also spread through blood flow	Dyspnoea due to bronchial airway destruction, the lungs invaded through trachea, and a reverse halo sign on CT scan.	Cancer patients and immunosuppressive medication in the post transplantation
Gastrointestinal Mucormycosis	Spores Enter the GIT through inhalation	Fever, bowel, and per rectal bleed	Constant use of broad-spectrum antibiotics, malnutrition, and neutropenia.
Cutaneous Mucormycosis	Through site of trauma or thermal burns direct inoculation in skin	Black discolouration and lesions on the skin.	Trauma of skin through surgery or burns
Disseminated Mucormycosis	Through bloodstream infection spreads to the other parts of the body	Generallydistresses the brain, but also other organs such as the spleen, heart, and skin.	Overloaded Iron , neutropenia immune system suppressed

8. MEDICAL ETHICS COMPROMISED

Treatment with corticosteroids and mortality in COVID-19 appears to follow a U-shaped pattern, [33] with treatment initiated too early (viral replication phase) or too late (advanced illness with multi-organ failure) being related with the worst prognosis. Fear of contracting this new and dangerous virus has led to self-prescription and medication abuse. Corticosteroids are currently being abused and misused in COVID-19 due to an unfounded notion that if taken early enough, these medications can arrest the disease's natural progression. Patients with non-severe COVID-19, defined as the lack of any symptoms of severe or critical COVID-19, should not be treated with corticosteroids, according to the WHO (conditional recommendation, based on low certainty evidence) [34]. Outside of the prescribed conditions, corticosteroids can have a significant impact on a patient's outcome. The Recovery trial's reported by Horby [33] in his literature findings were consistent with the possibility of corticosteroid treatment causing harm in individuals who did not require breathing support. Recent research has also linked the usage of corticosteroids in COVID-19 patients to an increased risk of acquiring pulmonary aspergillosis and mucormycosis [35,36].

9. DISCUSSION AND CONCLUSION

The biggest challenges for the survival of the human population came into existence in the form of the SARS COVID 19 which is still being a cause of concern. The pilot studies and various detailed researches reported by the various researchers and hospital data gave the view of the situation and give rise to a big question of the judicial use of the treatment regimens. The studies are the sole source of the incorporation of the steroids in the treatment regimen and various drug candidates suited for the situation to be controlled. Meanwhile, where the steroids proved to be effective in certain scenario of controlling the patient conditions where the oxygen saturation level was less than 90 % and less than 30 breaths per minute and certain fixed doses of the steroids like dexamethasone, hydrocortisone proved to be the drug of choice

[9]. But the unethical prospect still came into picture as the lack of the awareness and medical negligence the scenario turned out to be worse. As the steroids were drug of choice for the hospitalized patients requiring additional accessory medical interventions but the treatment was adopted as preventive measure and over the counter availability of the steroids added more concern to the situation of pandemic. The uncontrolled use of the steroids by the unsuited candidates not only created shortage of the medicine for the eligible patients but also invited another threat to encounter in the form of the secondary infections. To combat with the scenario of pandemic the patients receiving high doses of steroids for reducing the lungs inflammation to cease the cytokine firing where exposed to the threat of the secondary infection called mucormycosis. Mucormycosis also called as Black Fungus was the result of the high dose steroid therapy as steroids while reducing the inflammation reduced white blood cells count and T- cells response to an invasion. The extreme use of the high dose steroids, oxygen masks and ventilators made patients more susceptible to the mucormycosis. Mucormycosis is an intermittent and invasive fungal illness that mostly distresses persons who are immunocompromised. Even if additional factors should be addressed, the immunosuppressive effects of steroids, which are commonly recommended in COVID-19 patients, may be a predisposing factor for unscrupulous infections. Due to a serious COVID-19 infection, a middle-aged man with no major prior medical history was admitted to the hospital. As part of his treatment, he was given a large dose of steroids. He has a headache and a fever five days after being discharged and was eventually diagnosed with orbital mucormycosis [37].

Corticosteroids have a strong anti-inflammatory impact and are thought to play a role in treating COVID-19 infection immunologic sequelae such as cytokine storm, lung inflammation, fever, and aberrant laboratory indicators of inflammation [38,39]. Corticosteroid medication has been linked to greater influenza fatality rates and nosocomial infections, as well as delayed virus clearance for SARS-CoV and MERS-CoV, according to observational studies; however, data on SARS-CoV-2 is limited. Steroids have also been linked to a higher risk of superinfection, which includes bacterial, mycobacterial, and fungal infections [40-42]. The most common clinical form in IAM was pulmonary mucormycosis (7/8 [87.5 percent]), whereas the most common clinical form in CAM was rhinoorbitocerebral mucormycosis (ROCM) (2/7 [28.6 percent]). Despite the fact that 7 (46.7 percent) studies did not give characteristics of the fungal agent causing mucormycosis, Rhizopus species was the most commonly encountered pathogen causing pneumonia-associated mucormycosis (4/15, 26.7 percent). Around 66.7% of individuals with pneumonia receiving steroids were major risk factor for the development of the mucormycosis. In 5/7 (71.4%) and 5/8 (62.5%) of instances, patients with CAM and IAM, respectively, received steroids as an adjuvant treatment for viral pneumonia or underlying medical issues [43].
Additionally, the steroids also shoot high blood glucose levels and patients with diabetic [44,45] ketoacidosis provided best way for the mucorales to enter the host body and spread vastly. The cessation of the immune system by the steroids and unhygienic medical treatment collectively lead to wide spread of the mucormycosis[46] in India. The cases reported in India were not only the result of the unethical medical use of the drugs but also medical negligence during the pandemic period. The situation has not ended even for now as new face of the virus is rising with more susceptibility and fast rate spread with omicron as its name and need of the hour is to follow the medical suggestions and regimens in a judicial way to prevent world not to be in a situation before acquired. The proclivity of hypercortisolaemic individuals for life-threatening mucormycosis is due to steroids pleiotropic effects on immunity. However, determining the exact prevalence and associated mortality of such illnesses is difficult. As more information becomes available, a better understanding of steroids specific role in mucormycosis pathophysiology may lead to earlier detection and treatment. Because mucormycosis severity is linked to steroid treatment intensity, every attempt should be made to employ the lowest steroid dose for the shortest duration possible, taking into account host characteristics.

Even though medicinal treatment might be valuable in the treatment of COVID-19, clinical monitoring and respiratory support techniques should take precedence. Furthermore, the corticosteroid research raises new questions: the best timing, drug kind and dosage, immunological target, drug interactions, the threshold of disease to consider, and the patient to choose. Moreover, recent data and researches over the steroids and their impacts will definitely

aid the treatment regimen and judicial judgement regarding the use of the same.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable**.**

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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