

Relation between long term steroid use and black fungus in COVID patients.

A project report submitted to the Department of Pharmacy, Daffodil International University for the Partial Fulfillment of the Requirements for the degree of Bachelor of Pharmacy.



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APPROVAL

This project A review on “**Relation between long term steroid use and black fungus in COVID patients**”

Submitted to the Department of Pharmacy, Faculty of Allied Health Science, Daffodil International University, has been accepted as satisfactory for the partial fulfillment of the requirements for the degree of Bachelor of Pharmacy and approved as to its style and contents.

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This is to certify that the results of investigation of this project works are original & have not been submitted before in this university. This entire project work has been accepted satisfactory requirements for Bachelor of Pharmacy.

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DECLARATION

I with this, declare that I do this project Department of Pharmacy, Faculty of Allied Health Science, Daffodil International University, and reasonably meet the requirements of a Bachelor of Pharmacy degree. I declare that this project is entirely my creation. I further certify that the implementations in this project are unique and have never been submitted to any degree program at this university.

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May Allah help us all to contribute our self for the wellbeing of human kind.

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Abstract:

The article describes the relationship between long term steroid use and black fungus in COVID patients. COVID-19 is an acute respiratory illness in humans caused by corona virus. The Rapid progression of the COVID- 19 pandemic has become a global concern. As we know that COVID-19 is a respiratory illness, here black fungus or mucormycosis is related with COVID-19. Because black fungus or mucormycosis is a very rare but dangerous, fungal infection which affects the sinuses, brain and the lungs and can be life threatening in diabetic patients and severely immune compromised individuals. Doctors believe that, mucormycosis, which has an overall mortality rate of 50% may be being triggered by the use of steroids, a lifesaving treatment for severe and critically ill COVID-19 patients. Steroid reduce inflammation in the lungs for COVID-19.

Chapter-1

Introduction

Introduction :

1.1 Definition of COVID-19 :

Infections in both birds and mammals are caused by a group of related viruses called as coronaviruses. Humans are susceptible to both mild and deadly respiratory tract infections brought on by coronaviruses . The coronavirus that creates COVID-19 in humans causes an acute respiratory illness. The virus was originally known as the new coronavirus for 2019 (2019- n CoV), and it has also been termed the 2019 human coronavirus (HCoV- 19 or hCoV-19) [1].

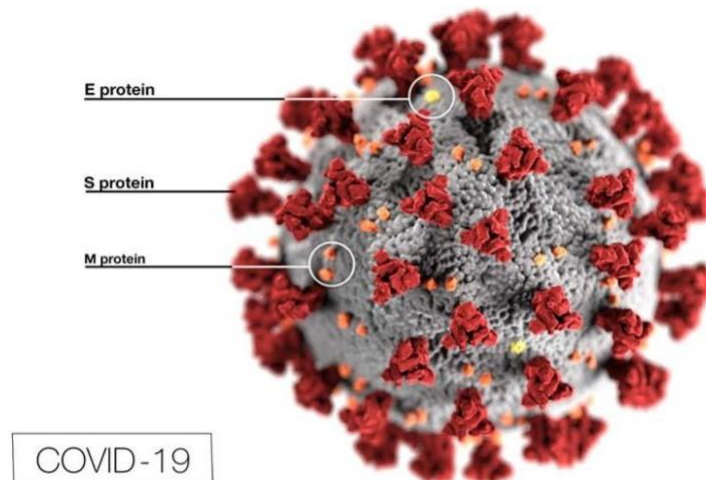


Figure 1.1 : COVID-19

1.2 History:

When the World Health Organization (WHO) learned about On December 31, 2019, there were cases of influenza in Hubei, China, with no confirmed etiology. the first confirmed cases of COVID-19 were noted. A novel coronavirus, currently known as 2019-nCoV, was determined to be the cause of these illnesses by the Chinese government on January 7 .

On January 30, 2020, many weeks after the epidemic of COVID-19 began to spread quickly, the WHO labeled it a situation affecting a global priority in public health. No formal name was given to the novel coronavirus. COVID-19, through February 11th of the following month. Nine days later, the US Center for Prevention and Control of Diseases (CDC) reported the country's first COVID-19 death. It was the individual [2].

1.3 Declaring COVID-19 a pandemic :

Governmental agencies, the general public, and experts in global health had no idea how COVID-19 might spread or first impact ordinary life. On March 1st, 2020, the UN released \$15 million to support the global COVID-19 response. The COVID-19 occurrences topped 100,000 on March 7 after a week. On March 11, a few days later, the WHO declared COVID-19 to be an epidemic. Almost suddenly, COVID-19 moved from being a significant problem that seemed to affect only China to a potential catastrophe for world health .

After the adoption of novel means to confine the virus, the scenario in Wuhan had at this point been defused.

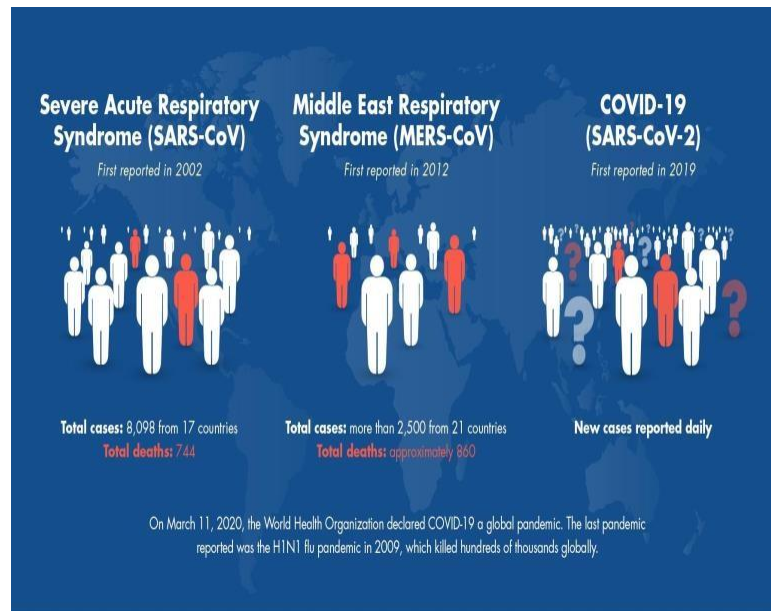


Figure 1.3 : Pandemic steps

China initially reported hundreds of fresh cases each day, but by March that number had dropped to dozens. On the other hand, instances in Europe were increasing quickly every day, with Italy reporting an astonishing 250 death in the 24 hours between March 12 and 13. As a result, the WHO determined that Europe became the pandemic's epicenter on March 13. The US issued a declaration of emergency on the same day [3] .



1.4 Symptoms

Different people are affected by COVID-19 in various ways. The majority of infected individuals will experience mild to moderate sickness and recover without being hospitalized [4].

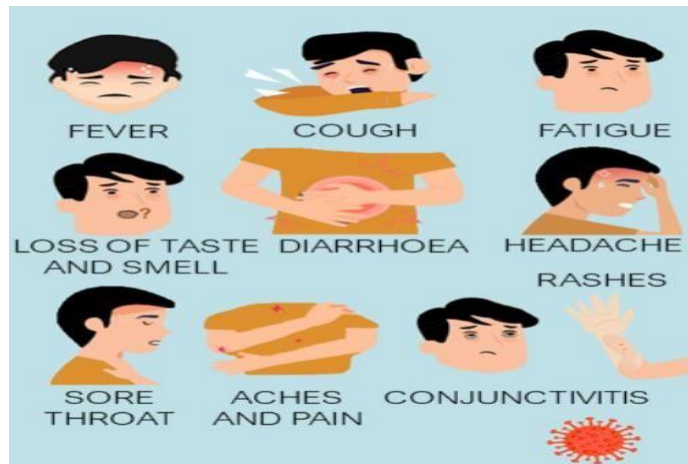


Figure 1.4 : Symptoms of COVID-19

Most common symptoms:

- Fever
- Cough
- Tiredness
- A loss of flavor or odor Less

common symptoms:

- sore throat
- headache
- aches and pains
- diarrhoea
- a rash on skin, or discolouration of fingers or toes
- red or irritated eyes

Serious symptoms:

- difficulty breathing or shortness of breath
- loss of speech or mobility, or confusion

1.2.1 Definition of Black Fungus :

Micormycosis is a very uncommon infection. exposure to plants, soil, and the subsp fungus, which is usually present.



Figure 1.2.1 : Black Fungus

rotting fruits, veggies, dung, and animal waste. It is pervasive and can be found in the air, the soil, healthy people's mucous, and even their noses. A potentially fatal fungal infection known as micormycosis has been seen in an increasing number in 2019 (COVID-19) people with the coronavirus illness, notably in India .

1.2.2 History:

Friedrich Küchenmeister may have recorded the first instance of mucormycosis in 1855. In 1876, Fürbringer published the first description of the lung condition. Rhizopus and Lichtheimia were the subsequent names for Subsp corymbifera and Mucor rhizopodiformis, respectively. were the two species reported by Lichtheim in 1884 along with the development of the disease in rabbits .

Three patients with significant sinus, brain, and ocular involvement from 1943 were documented to have this connection with poorly controlled diabetes [5].

1.2.3 Naming of Black Fungus:

After describing a case with systemic symptoms affecting the sinuses, brain, and digestive system, Arnold Paltauf first used the word "mycosis mucorina" in 1885, which led to the term "mucormycosis" becoming well-known. As a result of revisions to the categorization of the kingdom Fungi, the terms "zygomycosis" and "mucormycosis" are frequently used interchangeably . Mucorales, Entomophthorales, and other organisms belonged to the old phylum Zygomycota. Infections brought on by Mucorales-order fungus are known as mucormycosis.

1.2.4 Steroid:

The body naturally creates hormone-like chemicals, but steroids are synthetic copies of such substances. In order to reduce inflammation, steroids are created to function similarly to these hormones.

Other names for them include corticosteroids. Steroids work by decreasing inflammation and immune system activity. During the inflammatory process, white blood cells and other components in the body can combat infection and foreign substances like bacteria and viruses . When taken in quantities higher than any of those your body produces, steroids reduce redness and swelling (inflammation). This may help with inflammatory conditions including asthma and eczema. Moreover, steroids impair the brain's normal defense versus disease and infection, the immune system [6] .

1.3.1 Objectives :

Global pandemic COVID-19, produced by SARS-CoV-2, was brought on by unchecked viral multiplication and a ferocious host immunological response. Due to an increase in diseased epithelium cells and cell debris, ARDS typically starts to manifest after the second week. With COVID-19, the antimicrobial immune response results in the virus's eradication at the risk of lung damage. Massive vascular inflammatory, disseminated coagulation, shock, and hypotension follow, all of which result in multiorgan failure and death. To avert this calamity, corticosteroid intervention has been considered. Black fungus (mucormycosis), a rare fungal infection brought on by exposure to a fungus known as mucormycete, has emerged as a result of the COVID-19 pandemic. The origin, virulence factors, prevalence, diagnosis, and management in COVID-19/mucormycosis coinfections in COVID-19-associated has these patients will be the main topics of this review. Soil, dumps, old building a wall, or other infection-causing agents are the main sources of infection. The goals of the study are :

- To know about the COVID-19 virus and black fungus.
- To find out the risk, treatment and Symptoms COVID -19 and black fungus.
- Effect and management of steroid use in COVID -19 patients .
- Find out the relation between steroid use in COVID and black fungus affected patients.

1.3.2 Methodology

Introduction

The examination is preceded with a literature study. For this study, 23 or so publications are reviewed.

Research Design

This exploration was planned through Google scholar and many other websites to find literature. For referencing Mendeley software was used.

Method of Data Analysis

After gathering a variety of data, each piece was examined for accuracy and internal coherence to rule out any missing or inconsistent pieces, and those were then deleted. Information research was carried out using Microsoft's dominant updated version. All data was gathered between 1984 and 2022.

Ethical Considerations

The investigation's participants were spoken to and given verbal approval for the information gathering procedure. The study participants were informed that they might withdraw from the study at any time during the data collection procedure, and the respondents' identities were kept a secret. The Department of Pharmacy funded the study.

Chapter-2

Pharmacology and Rule of Steroid

2.1 Pharmacology of Steroid :

The glucocorticoid receptor and/or the mineralocorticoid receptor are both agonists by corticosteroids. Certain corticosteroids may also have progestogenic activity and cause sex-related adverse effects in addition to their corticosteroid activity .

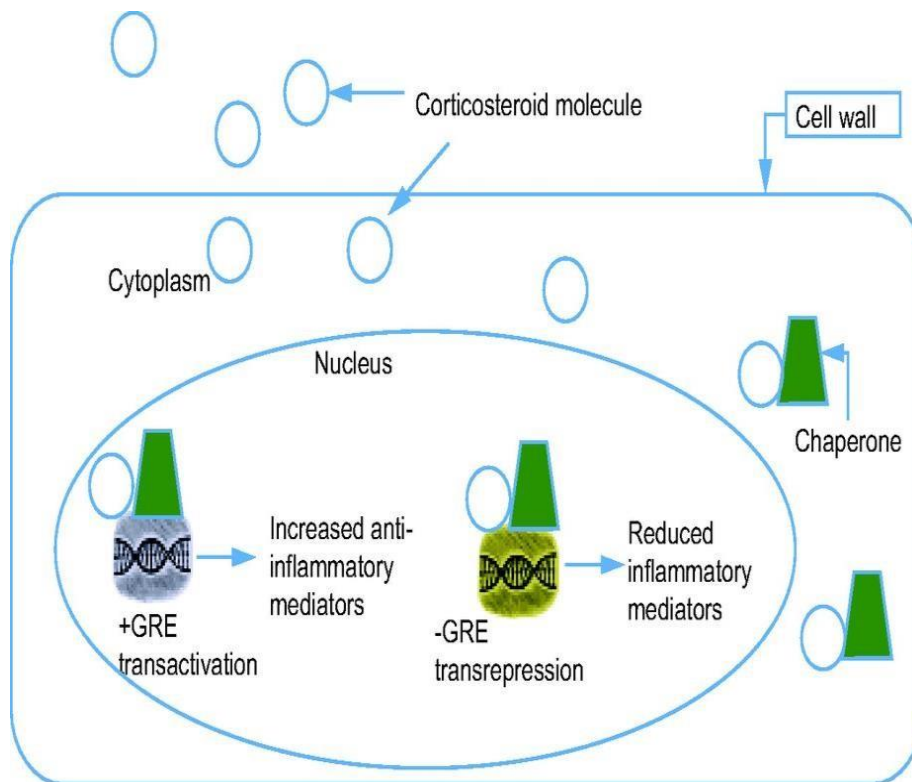


Figure 2.1 : Pharmacology of Steroid

2.2 Risks:

By weakening the immune system, corticosteroids can have significant negative effects on the body. When other therapies fail or a quick response is needed, doctors frequently turn to corticosteroids .

Corticosteroid use can result in blood sugar increases, which are hazardous for those with diabetes.

Corticosteroids could be harmful in people with:

- diabetes
- depression
- obesity
- substance use disorder
- glaucoma or cataracts
- ulcers
- a recent heart attack or heart failure
- high blood pressure
- liver problems
- epilepsy
- ongoing infections
- large wounds

Some drugs' efficacy can be decreased by corticosteroids, while others can become more potent. People should inform a doctor before using corticosteroids if they are taking any drugs to treat the following:

- excessive blood clotting
- seizures

- diabetes
- HIV

A number of vaccines, such as those for the diseases, mumps, and tuberculosis, might negatively interact with corticosteroids. Other vaccines, including those for the flu or bronchitis, may not work as well if a person already is taking an excessive dosage of a corticosteroid. Along with NSAIDs like ibuprofen, the usage of corticosteroids is also potentially dangerous (Advil) [7].

2.3 Role of steroids in the management of COVID-19 :

Anti-inflammatory medications known as steroids have been utilized to treat a range of clinical conditions, including rheumatologic, autoimmune, inflammatory, and various lung disorders. Corticosteroids are helpful in a variety of pulmonary problems, including asthma, chronic obstructive pulmonary disease (COPD), laryngotracheobronchitis, acute respiratory distress, severe pneumonia, and interstitial lung disorders syndrome, since they block the inflammatory cascade. In this case study, we'll describe a COVID-19 patient who was given remdesivir, antibiotics, and steroids. Steroids' involvement in the Patients with COVID-19 will be treated also be covered.

Corticosteroids are hormones that the adrenal cortex naturally produces. They have a role in a number of physiological processes, including the control of inflammation, stress response, immune metabolism of carbohydrates and proteins in response. Corticosteroids are therefore essential for treating autoimmune, allergy, neoplastic, and several inflammatory illnesses. The pathophysiology and clinical consequences of COVID-19-related serious acute respiratory syndrome are significantly influenced by viral evasion of the immune system's cells as well as the cytokine storm. Interleukin dysregulation and the infiltration of inflammatory microglia result in lung inflammation and severe consequences, such as syndrome of acute respiratory distress, respiratory failure, sepsis, inter failure, and death. Particularly in cases of severe pneumonia and advanced stages of cancer, corticosteroids have potent anti-inflammatory and anti-fibrotic actions that may contribute to their ability to reduce pulmonary inflammation .

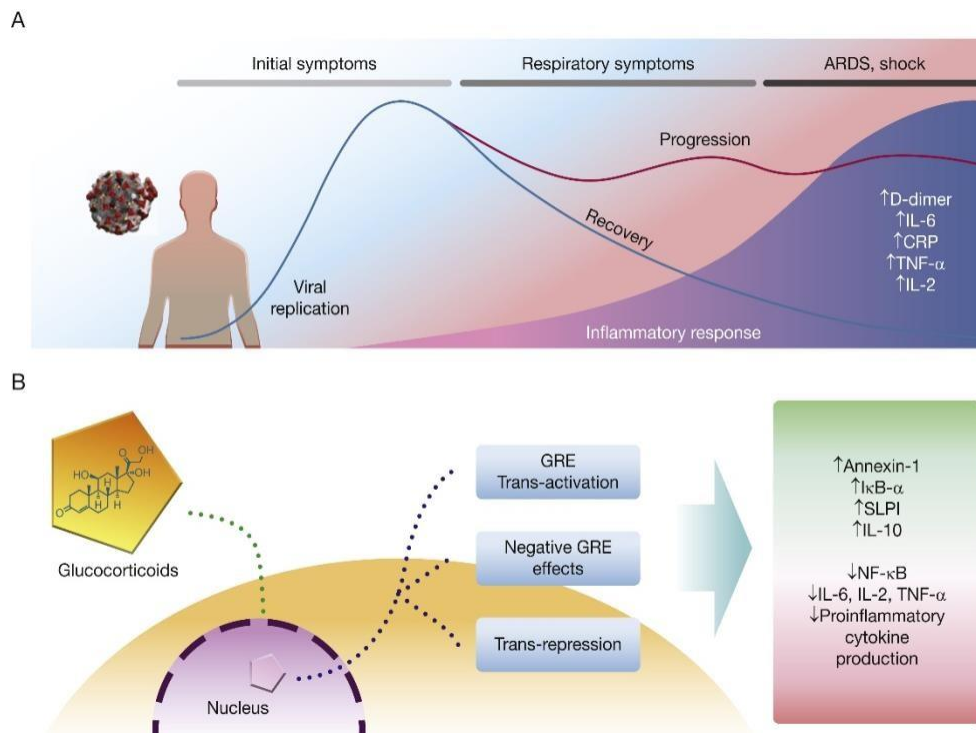


Figure 2.3 : Steroids in the management of COVID-19.

The pathophysiology and clinical consequences of COVID-19-related serious acute respiratory syndrome are significantly influenced by viral evasion of the immune cells and the cytokines storm. severe consequences of lung inflammation, such as syndrome of acute respiratory distress, pulmonary edema, sepsis, multi-organ inability, and death are caused by cytokine dysregulation and the invasion of inflammatory myeloid cells. The anti-inflammatory and anti-fibrotic properties of corticosteroids suggest that they may have a function in lowering pulmonary inflammation, particularly in cases of severe pneumonia and advanced COVID-19 disease. Nevertheless, corticosteroid use may reduce immune response, hasten pathogen removal, and promote viral multiplication. Additionally, because corticosteroids may continue to have a downregulating effect on the transcription of proinflammatory cytokines, they may prevent a full-blown pneumonia-related pulmonary & systemic inflammation repair and cytokine response [8].

2.4 The frequency and results of corticosteroid treatment in COVID-19 infected patients

When compared to patients who did not get corticosteroids, the proportion of COVID-19 patients who did was much lower. Since corticosteroids slowed viral clearance and did not significantly increase survival in subjects with severe acute respiratory syndrome coronavirus 2 infections, they should only be administered with the utmost caution when treating COVID-19 .

2.5 Antiviral effects of steroid in COVID patients :

Dexamethasone administration. Dexamethasone as a result By March 2021, the outcomes of a number of COVID-19 medicinal agents, such as antiviral medications, steroids, and anti-inflammatories, have been established . Clinically effective treatments for COVID-19 include dexamethasone and tocilizumab, a monoclonal antibody against the interleukin-6 receptor. In the open-label Randomized Assessment of COVID-19 Treatment (RECOVERY) experiment, dexamethasone's effects were reported. Dexamethasone use decreased 28-day mortality among COVID-19 patients who received either invasive mechanical ventilation or non-invasive supplementary oxygen in COVID-19 hospitalized patients . Dexamethasone administered within 7 days of COVID-19 initiation, however, was not included in the RECOVERY trial outcomes as having any obvious impact. As a result, it is uncertain when to administer medications, particularly antiviral ones, and the most [9]

2.6 Timing of using Steroids to treat COVID :

Recovery experiments have shown that steroids are helpful, but it's important to know when to provide them. If you take it before your saturation level of oxygen (O₂) starts to fall, it's risky. In COVID patients, early steroid usage was linked to higher mortality than early cessation. It is futile to administer steroids on day one. They are only beneficial when oxygen saturation is declining as a result of moderate to severe illness .

Steroid use increases the virus' capacity to proliferate early in the infection, according to researchers. On the other hand, overusing steroids in minor conditions might lead to a potentially fatal viral pneumonia. Steroids should also be avoided for the first five days of the infection .

2.7 Corticosteroid use frequency and outcomes in COVID-19-infected patients

According to immunological research, people with COVID-19 have increased cytokine levels and chemokines than healthy individuals . The production of too many pro-inflammatory cytokines can lead to ARDS, multiple organ dysfunction, and mortality in these patients. Corticosteroids frequently inhibit the immune system, therefore giving them to COVID-19 patients may ease their severe clinical symptoms and lower mortality. Moreover, corticosteroids are the primary anti-inflammatory medication for coronavirus pneumonia (such as SARS and MERS, caused by SARS-CoV and MERS-CoV, which is identical to SARS-CoV-2) and many clinical trials have reported the efficacy of corticosteroids in the treatment of these disorders. The aforementioned data suggests that corticosteroid medication could be advantageous for COVID-19 patients. Additionally, certain clinical investigations revealed that corticosteroid treatment [10].

In patients hospitalized with severe COVID-19 pneumonia at Wuhan Union Hospital, long-term corticosteroids were compared to a control medication and shown to significantly improve clinical chest computerized tomography (CT) findings and symptoms . Also, the researchers discovered that giving methylprednisolone to 201 people diagnosed with COVID-19 pneumonia in a cohort trial dramatically reduced the risk of death. Also, in order to stop inflammation and lessen exudation, different prednisolone doses and therapy regimens are suggested for normal (with rising factors for severe COVID-19), seriously ill, and critically ill people with COVID-19 pneumonia . According to China's "Diagnosis and Treatment Protocol for COVID-19 (Trial Seventh Edition)" . These results appear to support the use of corticosteroids in the management of COVID-19.

Chapter-3

Symptoms of Black Fungus Prevention and Treatment

3.1 COVID-19 associated Black Fungus:

Mucormycosis cases are on the rise due to the COVID-19, increase pandemic. Since the majority of cases are temporally connected to COVID-19, the condition is known as COVID-19-associated mucormycosis (CAM). The goal of the current systematic review was to give an up-to-date summary of the CAM literature that has previously been published. Until May 14, 2021, the databases of PubMed, Scopus, and Google Scholar were thoroughly searched using the necessary keywords to locate case reports and case series relating to mucormycosis in COVID-19 patients. The pertinent information that was retrieved covered patient outcomes, comorbidity profiles, glucocorticoid use, demographics, and clinical categories of mucormycosis. Using information gathered from 99 CAM patients, we found 30 case reports or case series[11].

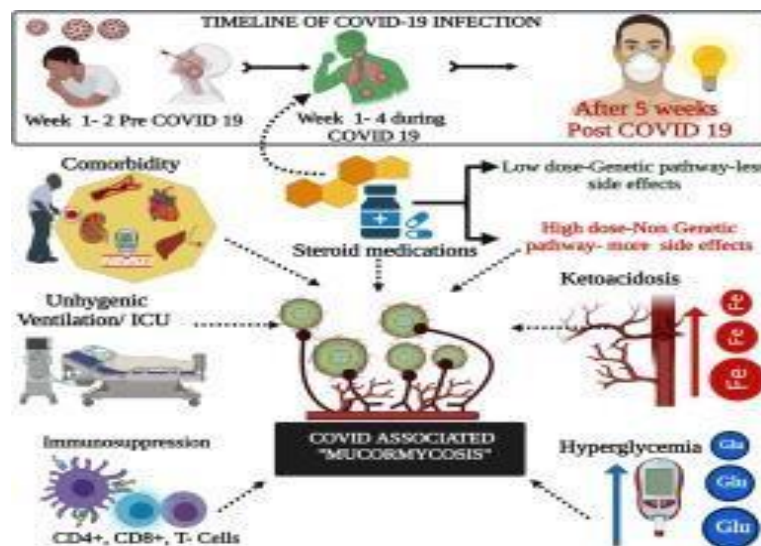


Figure 3.1 : Black Fungus effect on COVID -19 patient.

India accounted for the majority of cases (72%). 85% of the patients had diabetes mellitus, and 78% of them were men. When mucormycosis developed, 37% of individuals had a history of COVID-19.

following a brief recuperation. The median duration between the diagnosis of the COVID-19 of Came was 15 days when the first sign of a has these infection was detected . In 85% of cases, the usage of glucocorticoids was disclosed. The most prevalent type (42%) was rhino-orbital mucormycosis, which was Rhino-orbito-cerebral mucormycosis is next. (24%).

A 10% prevalence of there was pulmonary mucormycosis found in 10 cases. The death rate was 34%, and adjunct surgery was used in 81% of patients . This was related with superior clinical results (p.001) despite the mortality rate. CAM is a developing issue that requires heightened COVID-19 patients should be vigilant, especially if they have a past of COVID-19 patients should be alert, especially if they've got a history of being COVID-19 patients [12].

3.2 Why is Black Fungus Occurring in Covid-19 Patients:

The fungus that causes mucormycosis generally affects persons who have immune system compromises, such Covid-19. In essence, people are more likely to get Black Fungus if they use medications that have the potential to lessen the immune system's capacity to fight against infection . When it comes to Covid-19, the virus chooses an immune system that is already compromised as a host since the body is more open to infection. Thus, those who are recuperating from Covid-19 are more likely to get Black Fungus or Mucormycosis .

3.3 Who Gets Affected by Black Fungus :

No of their age, everyone can get the virus. While most people will come into touch with this fungi at some stage of their lives, those with weakened immune systems are more susceptible to its effects. If you are taking medication for a specific ailment and medications that weaken your immune system, you are a potential target of Black Fungus [13].

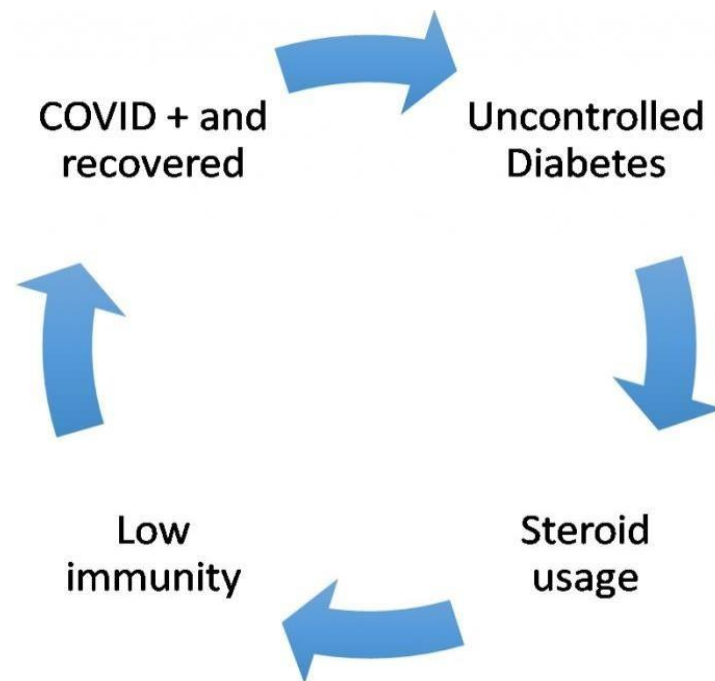


Figure 3.3 : People have risk of black fungus

Mucormycosis infection risk is increased by the following medical conditions:

- Covid-19
- AIDS or HIV
- Diabetes
- Stem cell transplant
- Organ transplant
- Cancer
- Injected drug use
- Long-term steroid use
- Bad health from poor nutrition

- High levels of iron in your body
- Low birth weight or premature birth
- Uneven levels of acids in your body

This condition is considerably more likely to impact those who have COVID and one or more of the comorbidities listed above [14].

3.4 Types of Mucormycosis or Black fungus:

- **Rhinocerebral** Mucormycosis is a sinus infection that has the potential to migrate to the brain. The two groups of patients who are most susceptible to this type of mucormycosis are those with diabetic ketoacidosis and kidney transplant recipients.
- **Pulmonary** (lung) The most prevalent form of mucormycosis affects cancer patients, transplant recipients, and persons who have received stem cell or organ transplants .

Types of Mucormycosis

- 1** Cutaneous mucormycosis (skin)
- 2** Rhinocerebral mucormycosis (sinus and brain)
- 3** Pulmonary mucormycosis (lung)
- 4** Gastrointestinal mucormycosis
- 5** Disseminated mucormycosis



Figure 3.4 : Types of Mucormycosis

- **Gastrointestinal mucormycosis** : is more frequent in younger kids than in adults, especially in premature and low birthweight infants under one month of age who have undergone surgery, received antibiotics, or taken drugs that reduce the body's capacity to fight infection. 9-10 .
- **Cutaneous (skin) mucormycosis**: occurs following the fungi's entry into the body through a skin breach (for example, after surgery, a burn, or other type of skin trauma). When a person's immune system is healthy, this type of mucormycosis is the most prevalent.
- **Disseminated mucormycosis** : occurs when the illness travels to another area of the body through the bloodstream. The infection typically impacts the brain, but it can also harm the spleen, liver, and skin, among other organs[15].

3.5 Symptoms of Black Fungus:

Mucormycosis symptoms will depend on where in your body the fungi are germinating[16].

Respiratory-related black fungus symptoms:

- Shortness of breath
- Sinus or nasal pain and congestion
- Chest pain
- Headache
- Fever
- Cough
- Swelling on one side of the face .

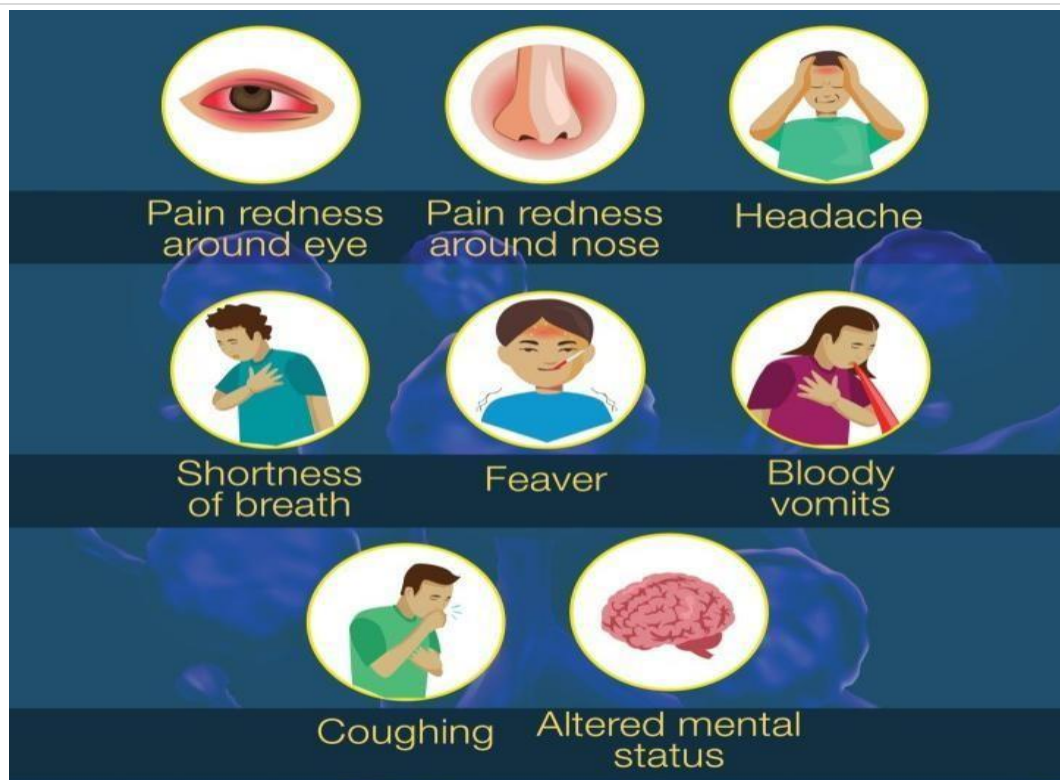


Figure 3.5 : Symptoms of Black Fungus

Skin-related black fungus symptoms:

- Ulcers
- Blisters
- Tenderness, swelling, redness
- Blackened skin tissue

Black lesions on the inside of the mouth or bridge of your nose
 Gastrointestinal - related black fungus symptoms:

- Diarrhea
- Blood in your stool
- Gastrointestinal bleeding
- Nausea and vomiting
- Belly pain

3.6 Prevention of Black Fungus :

To ensure the avoidance of Mucormycosis, there are a couple of things to remember.

- When you are in locations with a lot of mud and dust, constantly wear a face mask. Avoid visiting construction and excavation areas .

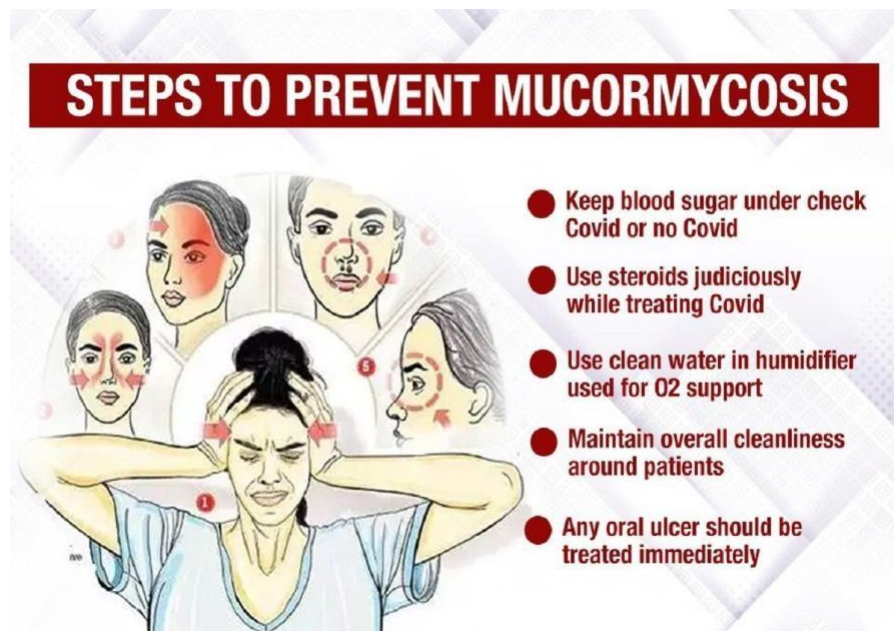


Figure 3.6 : Prevention of Black Fungus

- Activities like horticulture and yard maintenance that require coming into contact with composts, soil, and dust should be avoided by people with compromised immune systems.
- Avoid contaminated water, and restore your home's water-damaged sections [17].

3.7 Treatment of Black Fungus

Black Fungus treatment usually includes antifungal medications.

- Unless the fungus is completely eradicated, medications including Posaconazole, Isavuconazole, and Posaconazole can inhibit the fungus' growth and control the illness .
- In extreme circumstances, surgery is performed to remove contaminated or dead tissues. When
- surgery includes removing components of the eyes and nose, it might result in long-term harm to the mind and body[18] .

3.8 Common Misconception about Black Fungus:

Recently a lot of misconceptions and misunderstandings have cropped up about fungal infection. Let us understand those in more detail:

Myth 1: Human-To-Human Transmission Is Possible

First off, the infection spreads by fungal spores that are already existing in the environment rather than through human contact. Every day, people come into contact with these spores. In general, it is extremely uncommon in healthy people, but certain risk factors, such as diabetes, cancer, a weakened immune system, and HIV, can raise the likelihood of contracting an infection .

Myth 2: This Fungal Infection Cannot Be Treated

Moreover, the degeneration of healthy tissues contributes to the discoloration of skin around the eyes, nose, jaw, and face. Infected areas have a reduction in blood flow, which leads to necrosis or dead material and, ultimately, black lesions .

We must be aware that this infection can be treated with the antifungal medication amphotericin B and, if necessary, surgical debridement. To lessen the severity of infection, the professionals strive to treat the underlying reasons, such as regulating blood sugar levels, cutting back on steroid use, and so forth.

Additionally, wearing a mask in dusty areas, avoiding exposure to the garden soil or vegetable compost during outdoor activities in the high-risk category can work well as preventive measures [19,20].

3.9 Raw Vegetables And Onion Peels Transmit The Fungal Infection

This fungus infection is not propagated or transmitted by raw veggies or onion peels, nor is it brought on by ingesting raw fruits and vegetables . When receiving oxygen therapy or other support-based therapies for COVID, it is important to be aware of the current circumstances and, if possible, maintain oral hygiene by sanitizing the oxygen cylinder, changing the water frequently, or sanitizing humidifiers. We can educate ourselves and protect ourselves from both fungal illnesses and the associated myths by practicing general awareness, maintaining good hygiene, and having a thorough grasp of the black fungus [21].

Chapter-4

Approved Medicines

4.1 Approved medicines for treating COVID-19

The following medications have been authorized for use in treating COVID-19 by Australia's Therapeutic Goods Administration (TGA), which oversees the country's pharmaceutical and medical device industries[22,23].

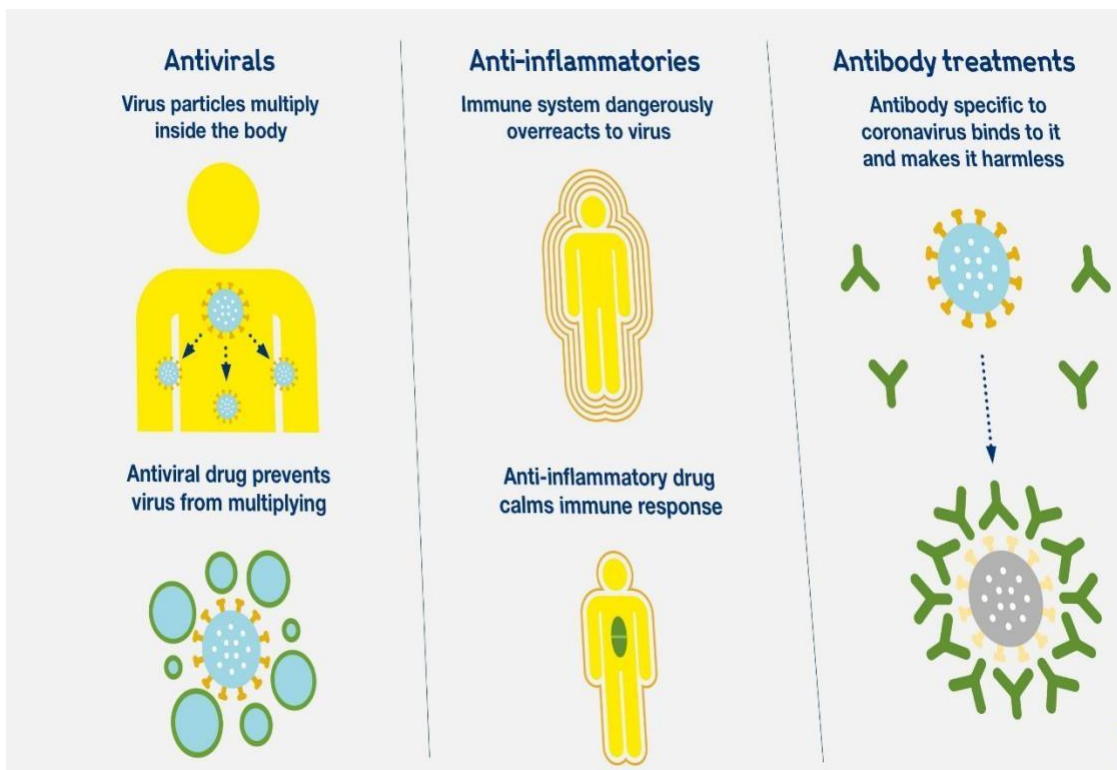


Figure 4.1 : Medicines for treating COVID-19

Antiviral treatments

Antiviral medications prevent the COVID-19-causing SARS-CoV-2 virus from reproducing and generating more serious sickness.

4.2 Remdesivir (VEKLURY)

Remdesivir, an antiviral medication, received preliminary TGA approval in July 2020. Remdesivir helps speed up the healing process for COVID-19 infection sufferers .

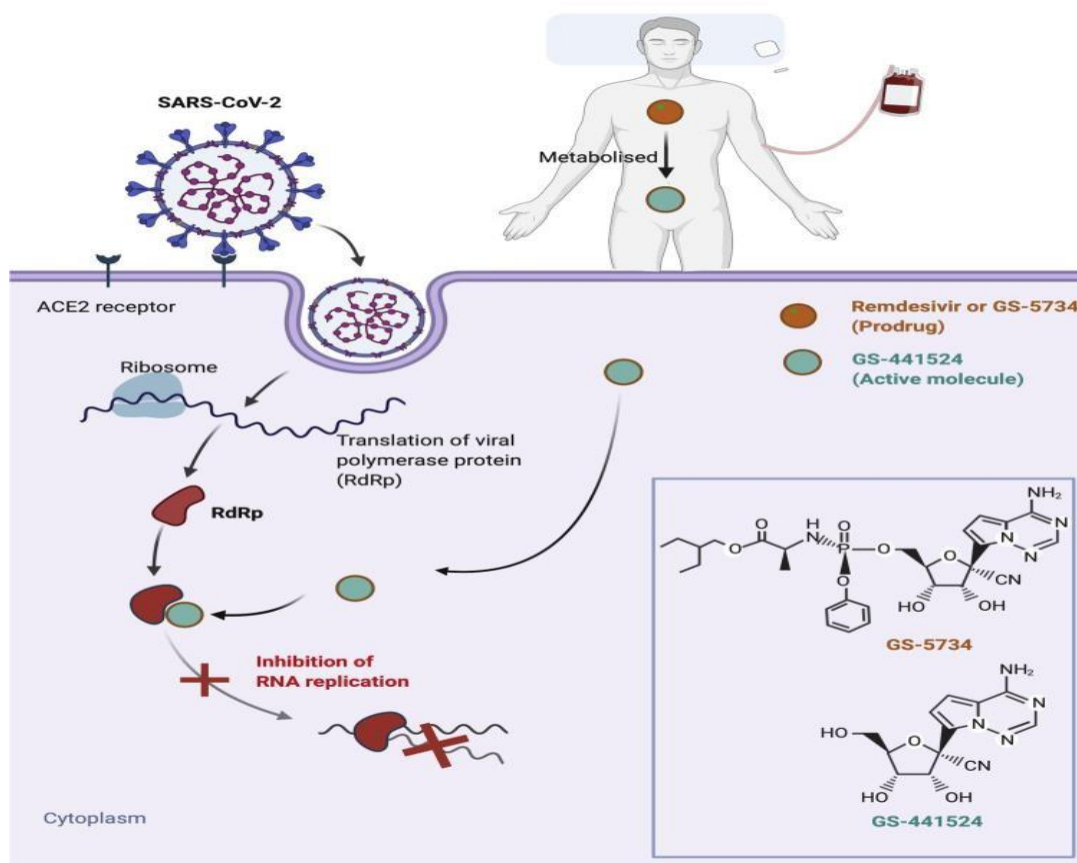


Figure 4.2 : Mechanism of Action

It has been approved for use in inpatient adults and adolescents with severe COVID-19 symptoms who are critically ill and need oxygen or high-level help to breathe.

Within five days following the start of illness and as soon as possible as feasible after diagnosis, it should be given. If you are considering a pregnancy, are pregnant, or are nursing, you should not use Paxlovid. Also, those with extremely compromised liver or renal function shouldn't take it [24].

4.3 Paxlovid (nirmatrelvir/ritonavir)

Introduction

A co-packaged oral drug called nirmatrelvir / ritonavir, created by Pfizer, is used to treat COVID-19. It comprises the antiviral drugs nirmatrelvir and ribavirin, and because of ritonavir's powerful CYP3A inhibition, there is a high risk of potentially harmful drug interactions .

Medicinal uses

It is recommended to use nirmatrelvir/ritonavir for the treating of moderate to serious COVID-19 in patients 12 years of age or older who weigh at least 40 kilograms, have positive direct SARS-CoV-2 test findings, and are at high risk of developing severe COVID-19 . Nirmatrelvir/ritonavir was investigated in a random, double-blind, non - randomized clinical trial for the treatment of symptomatic people who were not hospitalized and had a laboratory-confirmed indication of SARS-CoV-2 infection. Nirmatrelvir/ritonavir dramatically decreased the proportion of persons who experienced COVID-19-related hospitalization or mortality from any cause by 88% as compared to placebo, according to the findings .



Figure 4.3 : Nirmatrelvir/ritonavir (Paxlovid).

Dosages

Two nirmatrelvir pills and one ritonavir tablet, taken twice daily, make up the 5-day regimen of nirmatrelvir/ritonavir (Paxlovid) .

Side effects

Negative side effects of nirmatrelvir/ritonavir include dysgeusia, diarrhea, hypotension, and chronic fatigue. 2% of patients in clinical trials stopped their medication as a result of side effects. Hypersensitivity responses, liver damage, and HIV medication resistance are a few more negative effects .

Drug Interaction

Paxlovid should not be used concurrently with some medications since it may have fatal consequences. Before administering Paxlovid, the FDA has developed a checklist to assist in assessing potential medication interactions [25,26].

Using nirmatrelvir/ritonavir Paxlovid with over-the-counter painkillers and fever reducers is safe.

4.4 Molnupiravir

Introduction

An antiviral drug called molnupiravir is used to treat Patients with SARS-CoV-2 infection and COVID-19. It functions as an active drug of the artificial adenosine derivative N4-hydroxycytidine and causes copy errors during viral RNA replication to have an antiviral effect. In the UK, it was authorized for medicinal use in November 2021 and for emergency use in December 2021 .

Medicinal Uses

Another oral COVID-19 treatment, molnupiravir, has a 30% effectiveness rate against hospitalization or mortality in individuals who have not had the vaccine .

Dosages

Be sure to take this medication exactly as directed by your doctor or the label. Men must take 800 mg (4 capsules) orally once every twelve hours for 5 days, while kids should follow their doctor's recommendations for dosage .



Figure 4.4 : Molnupiravir

Side Effects :

Dizziness, headaches, nausea, vomiting, diarrhea, and other common side effects are possible with molnupiravir [27,28].

4.5 Baricitinib (Olumiant)

The study's objective was to ascertain how baricitinib (Olumiant) affected COVID-19's progress. According to a multivariate analysis, using baricitinib was linked to a lower incidence of death and the requirement for intrusive lung ventilation . Patients with a healthy Bmi were discovered to be more responsive to treatment than those who were overweight. Although the fever was higher than 38.0 C⁰ in 75% of the patients, it steadied all day and never rose again. Baricitinib can be thought of as a supplementary therapy for moderate types of pneumonia in individuals over 65 or in people with concurrent chronic conditions, according to the authors' findings[29] .

Medicinal Uses :

Baricitinib (Olumiant), the first immunomodulatory treatment for COVID-19, was recently approved by the FDA. The government approved it for the management of COVID-19 in hospital patients requiring o₂, intrusive or silent ventilators, or extracorporeal oxygen (ECMO) .

Dosage : For alopecia areata, baricitinib should be given once daily at a dose of 4 mg.



Figure 4.5 : baricitinib (Olumiant)

Side Effects : Baricitinib use can increase the chance of serious infections, a hole or rip in your digestive system, a heart condition or strokes, blood clots, or cancer, among other life-threatening medical conditions. Inform you physician if you have .

a compromised immune system or a persistent infection (such HIV, hepatitis, shingles, tuberculosis, or

shingles);

cancer of any kind, cardiac issues, a heart problem, stroke, or blood clot; high cholesterol; cellulitis, an ulcer in your gastrointestinal or likewise if you have ever smoked [30.31].

4.6 Interferons:

Interferons have antiviral activities in vivo and in vitro, and have been approved by the FDA to treat COVID-19, multiple sclerosis, hepatitis B and C, and viral infections .

Interferons are a group of cytokines that have antiviral properties in both in vitro as well as in vivo. The FDA has authorized the use of interferon beta-1a to treat multiple sclerosis relapse types after it was studied in medical tests for treatment of COVID-19. Interferon alfa has been approved by the FDA to cure hepatitis B and hepatitis C virus infections, but interferon lambda has not yet received this same approval .

Virions are being used in healthcare situations to manage viral infections like hep C, non-autoimmune Hodgkin's diseases like multiple sclerosis, and non-lymphoma. This exercise includes a detailed description of the influenza alpha, beta, and γ strains [32].

Chapter-5

Side effects of steroid

5.1 Overuse or prolonged use of steroid can cause Black fungus :

The current increase in black fungus cases has sparked fear as the country struggles to cope with the fierce second wave of Covid-19. The condition, also known as mucormycosis, has made medical professionals and researchers concerned about the overuse of steroids in COVID-19 treatment [33].

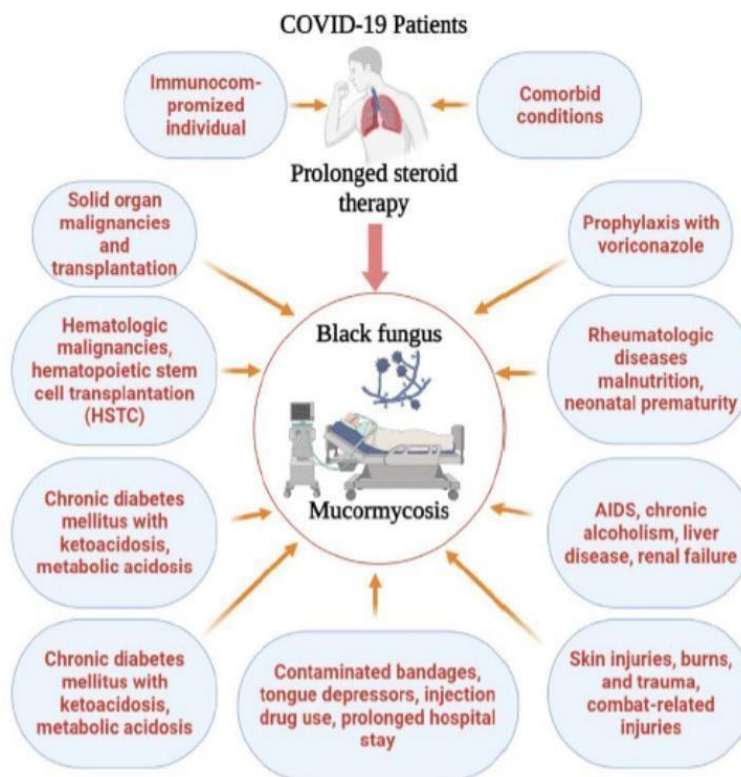


Figure 5.1 : Prolonged use of steroid

The usage of steroids (such dexamethasone), which are used to treat coronavirus, has been associated to an increase in occurrences of fungal infections in severe COVID-19. After continuous use, such hormones might damage the immune system. Due to the exposure of the airways to moisture and humidity, it has also been linked to the usage of ventilators in COVID patients in ICUs .

Systemic corticosteroid treatment has been demonstrated in numerous randomized trials to enhance medical outcomes and reduce mortality in hospitalized COVID-19 cases who require supplemental oxygen¹. This is most likely because it lowers the systemic inflammatory response brought on by COVID-19, which can result in lung injury and multi - system organ dysfunction . The use of systemic corticosteroids in COVID-19 patients who do not require supplemental oxygen has not been demonstrated to be helpful. ² The COVID-19 Methodology[34,35].

5.2 Systemic Corticosteroids in Patients With COVID-19 Non-hospitalized Patients

A rise in the incidence of fungal infections in severe COVID-19 has been linked to the use of coronavirus-treating drugs (such dexamethasone). Those hormones may weaken the immune system if used frequently. Because of the frequent exposure of the airway to moisture and humidity, it has also been linked to the usage of respirators in COVID people in ICUs .

Systemic corticosteroid therapy has been shown to enhance clinical outcomes and decrease mortality in hospital COVID-19 patients in multiple randomized trials. who require supplemental oxygen¹. This is most likely because it lowers the systemic inflammatory response brought on by COVID-19, which may cause multisystem organ failure and lung damage. The use of systemic corticosteroids in COVID-19 hospital patients who do not require supplemental oxygen has not been demonstrated [36] .

condition should continue this therapy as directed by their health care provider (AIII).

5.3 Hospitalized Patients

In the Rehabilitation research, a multicenter, open-label study carried out in the UK, 6,425 hospitalised patients were randomly assigned to receive traditional Midodrine for a maximum of ten days or just therapy. the winners Dexamethasone recipients had a reduced 28-day death rate than those who only received conventional care. 2 Dexamethasone provided this benefit to patients who required extra oxygen or were endotracheal at the at the time of enrollment; people who did not at the time did not .

In Brazil, the CoDEX trial was a multicenter, open-label study that looked at dexamethasone's effectiveness in treating COVID-19-induced acute respiratory distress syndrome (ARDS) in patients who were mechanically ventilated . Despite the trial's early termination, the findings of this investigation confirm the RECOVERY trial's conclusion the fact that systemic corticosteroids helpful for COVID-19 hospitalized patients. In the trial, 299 patients were randomized to receive standard care alone, standard care along with Dexamethasone 20 mg Dexamethasone 10 mg was administered intravenously (IV) each daily for five days after that. The dexamethasone arm outperformed the usual care alone arm in terms of mean days alive and without mechanical breathing throughout a 28-day period. There were no variations between the arms, though.

Systemic corticosteroids have demonstrated clinical benefits in select groups of hospitalized patients with certain diseases when taken with other drugs, such as immunotherapies like tocilizumab or baricitinib[37,38].

COVID-19, especially when a severe sickness is present at an early stage or when there is systemic inflammation .

5.4 Inhaled Corticosteroids in Patients With COVID-19

Inhaled corticosteroids are known to have unique anti-inflammatory effect on the lung, making them potential COVID-19 therapy options. Also, it has been shown that some inhalers decrease the transcription of the cell entry receptor and prevent the proliferation of the SARS-CoV-213 virus. Further details on how inhaled corticosteroids work in outpatients with COVID-19 are provided by two dual placebo-controlled trials and 2 different randomized controlled trials [39,40].

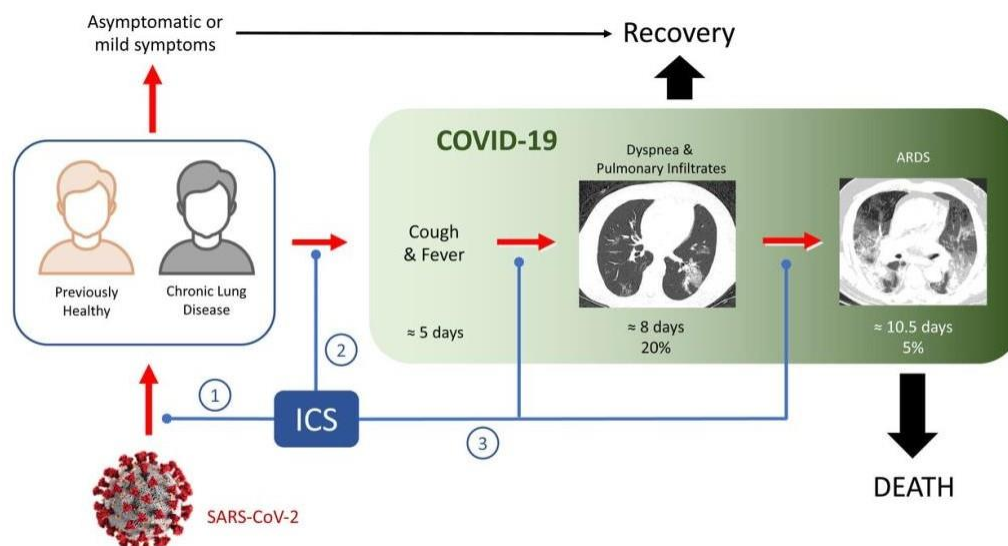


Figure 5.4 : Inhaled Corticosteroids in Patients With COVID-19

Chapter-6

Discussion

Discussion :

If a Covid patient exhibits any sinus signs, do not mistake them for sinusitis because they are immune compromised, diabetic, and have uncontrolled blood sugar levels. Given how invasive and capable of destroying all tissues the fungus is, the index of suspect should be extremely high. The signs may include double vision, blurred vision, headaches, jaw pain, tooth pain, and so on. If the tumor is in the lungs, symptoms to watch for include chest pain, shortness of breath, and breathlessness. Surgery is the recommended course of action [41].

If it's on your face, you must remove the affected tissue, which may include removing the eyeballs if it is invasive. Hence, a really deforming procedure. In addition, it must be followed by the costly, protracted administration of the antifungal medication amphotericin B .

Yet as I already mentioned, the uncontrolled use of steroids is the cause of many diseases. What are the steroid indications for COVID patients now? Therefore, in essence, steroids save lives. There is sufficient proof [of their efficacy] in critically ill COVID patients who require oxygen, BiPAP, or ventilation or who are in respiratory distress .

For COVID patients who do not have respiratory distress or a need for oxygen, steroids are not recommended.

Hence, the virus assembly phase of COVID occurs during the first week. You then experience the classic flu symptoms, such as fever, headache, body aching, cough, and cold. Steroid use is not appropriate during that time. But, despite the fact that you have an extremely high temperature, you insist on seeing your doctor and pressuring them since someone who took steroids recovered .

People demand that their doctors write prescriptions for steroids, and some patients use steroids as self-medication without telling their doctors. Your infection rate will actually go up at that point. Steroids will momentarily hide your symptoms; the temperature may sort of subside, giving you the impression that things are improving . You will, however, get a very high temperature, a cough, and respiratory involvement in three to five days. Many patients who first took steroids had severe pneumonia, as demonstrated in our experience [42,43].

Chapter-7

Conclusion

Conclusion :

It exists in the soil and the air, but only those with impaired immune systems become infected. As I previously stated, diabetics who have extremely high blood sugar levels are most susceptible to getting mucormycosis . If you are currently immune compromised, such as a diabetic with chronic kidney or liver illness, a transplant recipient, or someone who has taken steroids for an autoimmune disorder, you are at a higher risk because Covid alone lowers immunity. Whether you have diabetes or not, if you have cancer, you will receive steroids.

Steroids raise your blood sugar levels, and having high sugar levels puts you at a higher risk of getting mucormycosis [44,45].

Chapter-8

References

References :

1. Maini, A., Tomar, G., Khanna, D., *et al.* (2021). Sino-orbital mucormycosis in a COVID-19 patient: A case report. *International Journal of Surgery Case Reports* 82.Szarpak, L. (2021). Mucormycosis – a serious threat in the COVID-19 pandemic? *Journal of Infection*.Singh, A. K., Singh, R., Joshi, S. R., & Misra, A. (2021). Mucormycosis in COVID-19: A systemic review of cases reported worldwide and in India. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*.
2. Werthman-Ehrenreich, A. (2021). Mucormycosis with orbital compartment syndrome in a patient with COVID-19. *The American Journal of Emergency Medicine* 42; 245.e5-264.e8
Rhen T, Cidlowski JA: Antiinflammatory action of glucocorticoids--new mechanisms for old drugs. Rizk JG, Kalantar-Zadeh K, Mehra MR, Lavie CJ, Rizk Y, Forthal DN: Pharmac-immunomodulatory therapy in COVID-19.
3. Russell CD, Millar JE, Baillie JK: Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury.Alhazzani W, Møller MH, Arabi YM, et al.: Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). *Intensive Care Med.* 2020.
4. Shang L, Zhao J, Hu Y, Du R, Cao B: On the use of corticosteroids for 2019-nCoV pneumonia. *Lancet*.Villar J, Confalonieri M, Pastores SM, Meduri GU: Rationale for prolonged corticosteroid treatment in the acute respiratory distress syndrome caused by coronavirus disease 2019. *Crit Care Explor.* 2020.Stern A, Skalsky K, Avni T, Carrara E, Leibovici L, Paul M: Corticosteroids for pneumonia. *Cochrane Database Syst Rev.* 2017.

6. Montón C, Ewig S, Torres A, El-Ebiary M, Filella X, Rañó A, Xaubet A: Role of glucocorticoids on inflammatory response in nonimmunosuppressed patients with pneumonia: a pilot study. Wunderink RG: Corticosteroids for severe community-acquired pneumonia: not for everyone.
7. Laterre PF: Severe community acquired pneumonia update: mortality, mechanisms and medical intervention. Steinberg KP, Hudson LD, Goodman RB, et al.: Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. *N Engl J Med.* 2006, 354:1671-1684.
Confalonieri M, Urbino R, Potena A, et al.: Hydrocortisone infusion for severe community-acquired pneumonia: a preliminary randomized study. *Am J Respir Crit Care.*
Naserghandi A, Allameh SF, Saffarpour R: All about COVID-19 in brief. *New Microbes New Infect.* 2020,
8. Chen Y, Liu Q, Guo D: Emerging coronaviruses: genome structure, replication, and pathogenesis. *J Med Virol.* 2020, 92:418-423.
Qin YY, Zhou YH, Lu YQ, Sun F, Yang S, Harypursat V, Chen YK: Effectiveness of glucocorticoid therapy in patients with severe coronavirus disease 2019: protocol of a randomized controlled trial. *Chin Med J (Engl).* 2020.
Solinas C, Perra L, Aiello M, Migliori E, Petrosillo N: A critical evaluation of glucocorticoids in the management of severe COVID-19. *Cytokine Growth Factor Rev.* 2020.
Chatterjee K, Wu CP, Bhardwaj A, Siuba M: Steroids in COVID-19: an overview. *Cleve Clin J Med.* 2020.
9. Fu L, Wang B, Yuan T, Chen X, Ao Y, Fitzpatrick T, et al. Clinical characteristics of coronavirus disease 2019 (COVID-19) in China: A systematic review and meta-analysis. *J Infect.* 2020. World Health Organization. Coronavirus Disease 2019 (COVID-19): Situation Report, 51 (2020). <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports>
World Health Organization. Coronavirus Disease 2019 (COVID-19): Situation Report, 36 (2020). <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports>
a. reports (accessed January 15 2020).
10. Lee KY, Rhim JW, Kang JH. Early preemptive immunomodulators (corticosteroids) for severe pneumonia patients infected with SARS-CoV-2.
Montón C, Ewig S, Torres A, El-Ebiary M, Filella X, Rañó A, et al. Role of glucocorticoids on inflammatory response in nonimmuno suppressed patients with pneumonia: a pilot study.
Mattiuzzi C, Lippi G. Which lessons shall we learn from the 2019 novel coronavirus outbreak?
Zhong H, Wang Y, Zhang ZL, Liu YX, Le KJ, Cui M, et al. Efficacy and safety of current therapeutic options for COVID-19—lessons to be learnt from SARS and MERS epidemic: A systematic review and meta-analysis. *Pharmacol .*
11. SARS-CoV-2 Vaccine Clinical Trials Using ACTIV-Informed Harmonized Protocols.
<https://www.nih.gov/research-training/medical-research-initiatives/activ/sars-cov-2-vaccine-clinical-C>, Fan Q-H, Chen H-B, Zhao X-G, Xie Z-G, et al. Clinical Characteristics of

- a. Children with Coronavirus Disease 2019 in Hubei, China. *Current medical science*. 2020;N-using-activ-informed-harmonized-protocols.
13. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med*. Sung JJ, Wu A, Joynt GM, Yuen KY, Lee N, Chan PK, et al. Severe acute respiratory syndrome: report of treatment and outcome after a major outbreak. *Thorax*. 2004.
14. Arabi YM, Mandourah Y, Al-Hameed F, Sindi AA, Almekhlafi GA, Hussein MA, et al. Corticosteroid Therapy for Critically Ill Patients with Middle East Respiratory Syndrome. *Am J Respir Crit Care Med*. 2018.

Organization WH. World Health Organization. Coronavirus Disease 2019 (COVID-19): technical-guidance-publications. <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance-publications>.

Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury.

Therapeutic management of Patients with COVID-

<https://www.covid19treatmentguidelines.nih.gov/therapeutic-management/>.

Nasim S, Kumar S, Azim D, Ashraf Z, Azeem Q. Corticosteroid use for 2019-nCoV infection: A double-edged sword.

15. Russell B, Moss C, Rigg A, Van Hemelrijck M. COVID-19 and treatment with NSAIDs and corticosteroids: should we be limiting their use in the clinical setting.
Wang Y, Jiang W, He Q, Wang C, Wang B, Zhou P, et al. A retrospective cohort study of methylprednisolone therapy in severe patients with COVID-19 pneumonia.
Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China.
16. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range.
Luo D, Wan X, Liu J, Tong T. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range.
- Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary.
- Cao J, Tu WJ, Cheng W, Yu L, Liu YK, Hu X, et al. Clinical Features and Short-term Outcomes of 102 Patients with Corona Virus Disease 2019 in Wuhan, China.
17. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study.

18. Ding Q, Lu P, Fan Y, Xia Y, Liu M, AUID- Oho. The clinical characteristics of pneumonia patients coinfecting with 2019 novel coronavirus and influenza virus in Wuhan, China
19. Du Y, AUID- Oho, Tu L, Zhu P, Mu M, Wang R, et al. Clinical Features of 85 Fatal Cases of COVID-19 from Wuhan: A Retrospective Observational Study.
.Fang X, Mei Q, Yang T, Li L, Wang Y, Tong F, et al. Low-dose corticosteroid therapy does not delay viral clearance in patients with COVID-19. *J Infect*. 2020.
Han Y, Jiang M, Xia D, He L, Lv X, Liao X, et al. COVID-19 in a patient with long-term use of glucocorticoids: A study of a familial cluster.
.Jacobs JP, Stammers AH, St Louis J, Hayanga J, Firstenberg MS, Mongero LB, et al. Extracorporeal Membrane Oxygenation in the Treatment of Severe Pulmonary and Cardiac Compromise in COVID-19: Experience with 32 patients.
Li R, Tian J, Yang F, Lv L, Yu J, Sun G, et al. Clinical characteristics of 225 patients with COVID-19 in a tertiary Hospital near Wuhan, China.
20. Li X, Xu S, Yu M, Wang K, Tao Y, Zhou Y, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan.
21. Shen Q, Guo W, Guo T, Li J, He W, Ni S, et al. Novel coronavirus infection in children outside of Wuhan, China. *Pediatric Pulmonology*. 2020.
22. Wan S, Xiang Y, Fang W, Zheng Y, Li B, Hu Y, et al. Clinical features and treatment of COVID-19 patients in northeast Chongqing.
23. Zhang Y, Li H, Zhang C, Fan Q-H, Chen H-B, Zhao X-G, Xie Z-G, et al. Clinical Characteristics of Children with Coronavirus Disease 2019 in Hubei, China. *Current medical science*.
24. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China.
25. Hong KS, Lee KH, Chung JH, Shin KC, Choi EY, Jin HJ, et al. Clinical Features and Outcomes of 98 Patients Hospitalized with SARS-CoV-2 Infection in Daegu.
26. Emmi G, Betiol A, Mattioli I, Silvestri E, Scala GD, Urban ML, et al. SARS-CoV-2 infection among patients with systemic autoimmune diseases.
27. Petersen MW, Meyhoff TS, Helleberg M, Kjaer MN, Granholm A, Hjortso C, et al. Low-dose hydrocortisone in patients with COVID-19 and severe hypoxia (COVID STEROID) trial-Protocol and statistical analysis plan.
28. Luo P, Liu Y, Qiu L, Liu X, Liu D, Li J. Tocilizumab treatment in COVID-19: A single center experience.
29. Sun L, Shen L, Fan J, Gu F, Hu M, An Y, et al. Clinical Features of Patients with Coronavirus Disease 2019 (COVID-19) from a Designated Hospital in Beijing, China. *Journal of medical virology*.
30. Wang Y, Zhang D, Du G., Du R., Zhao J, Jin Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial.
31. Xu K, Chen Y, Yuan J, Yi P, Ding C, Wu W, et al. Factors associated with prolonged viral RNA shedding in patients with COVID-19.
32. Chen T, Dai Z, Mo P, Li X, Ma Z, Song S, et al. Clinical characteristics and outcomes of older patients with coronavirus disease 2019 (COVID-19) in Wuhan, China (2019): a single-centered, retrospective study.
33. Deng Y, Liu W, Liu K, Fang YY, Shang J, Zhou L, et al. Clinical characteristics of fatal and recovered cases of coronavirus disease 2019 (COVID-19) in Wuhan, China: a retrospective study.
34. Lian J, Jin X, Hao S, Jia H, Cai H, Zhang X, et al. Epidemiological, clinical, and virological characteristics of 465 hospitalized cases of coronavirus disease 2019 (COVID-19) from Zhejiang province in China. *Influenza Other Respir Viruses*.

35. Qiu C, Deng Z, Xiao Q, Shu Y, Deng Y, Wang H, et al. Transmission and clinical characteristics of coronavirus disease 2019 in 104 outside-Wuhan patients, China.
36. Wang L, Duan Y, Zhang W, Liang J, Xu J, Zhang Y, et al. Epidemiologic and Clinical Characteristics of 26 Cases of COVID-19 Arising from Patient-to-Patient Transmission in Liaocheng, China.
37. Yang W, Cao Q, Qin L, Wang X, Cheng Z, Pan A, et al. Clinical characteristics and imaging manifestations of the 2019 novel coronavirus disease (COVID-19): A multi-center study in Wenzhou city, Zhejiang, China.
38. Zhao XY, Xu XX, Yin HS, Hu QM, Xiong T, Tang YY, et al. Clinical characteristics of patients with 2019 coronavirus disease in a non-Wuhan area of Hubei Province, China: a retrospective study.
39. Huang Q, Deng X, Li Y, Sun X, Chen Q, Xie M, et al. Clinical characteristics and drug therapies in patients with the common-type coronavirus disease 2019 in Hunan, China. *Int J Clin Pharm.* 2020: 1–9.
40. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China.
41. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study.
42. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study.
43. Bai Peng HW, Zhang Xichun LS, Jianmin J. Analysis of clinical features of 58 patients with severe or critical 2019 novel coronavirus pneumonia. *Chinese Journal of Emergency Medicine.* 2020; 29:483–7.
44. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19.
45. WHO Rapid Evidence Appraisal for COVID-19 Therapies Working Group, Sterne JAC, Murthy S, et al. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. *JAMA.* 2020;324(13):1330-134

