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Review Article

A Comprehensive Review on Covid-19: Pathophysiology and Pharmacotherapy

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Abstract

Introduction: The year 2019 heralds one of the darkest times human beings have ever encountered. A novel corona virus outbreak (COVID-19) was declared a global pandemic by the World Health Organization on March 11, 2020. The terminal virus has quickly swept at such an alarming rate around the globe with a severity that has confounded people, including scientists and medical fraternities all over the world. The pandemic has exploded and become a global health emergency.

Objective: This comprehensive review explores the pathophysiology of COVID virus, the transmission of its variants, symptoms, long-term COVID complications, diagnosis, and current pharmacotherapy, including vaccines.

Methods: The published literature was assessed for appraisal of all information available on COVID virus, its diagnosis, and pharmacotherapy; as per the guidelines for the use of electronic and internet media, high-quality and reliable medical information from the internet was retrieved only from reliable sources.

Results: The number of cases and deaths due to COVID is much higher than the ones reported. Currently, the sub-variant of omicron, BA.5, is the one actively prevailing countrywide. There is no end in sight for the pandemic, as active cases and related mortality are still reported.

Conclusion: The trend for SARS-CoV-2 infection, hospitalizations, and deaths remains unpredictable at best. Extra precautions are still advised.

Key words: covid-19; covid transmission; pathophysiology; long covid complications; diagnosis; pharmacotherapy; anti-covid vaccines

1.Introduction

The first instance of COVID-19, also known as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), was reported in Wuhan, China, in December 2019 [1]. It was thought that the infectious virus first appeared in bats, pangolins, and rodents before quickly spreading to people all over the world. The COVID-19 did not appear overnight. It is a sizable family of viruses that has always existed and is responsible for a wide range of ailments in both humans and animals, from minor colds to serious respiratory conditions. In February 2020, as human cases began to rise, it was given the formal designation Infectious Corona Virus Disease 2019 (COVID-19) [2]. By March 2020, as the virus had already wreaked havoc on the globe, killing millions of people, destroying economies, overwhelming medical professionals, and seriously challenging the scientific community worldwide, WHO had finally declared the situation a global pandemic [3]. "The first case of COVID-19 in India occurred on January 30, 2020, and since then, it has spread to millions of humans, resulting in more than 5–6 million fatalities in the nation. People of all ages were discovered to be at risk of contracting this COVID and its severity, but elderly patients (aged more than 60 years) and those with underlying pre-existing medical conditions or co-morbidities like obesity, cardiovascular disease, chronic kidney disease, diabetes, chronic lung disease, smoking, or cancer, as well as associated immunocompromised patients, were discovered to have an increased risk of developing severe COVID infection [4]. As of March 2022, there were more than 472 million cases of COVID documented worldwide, along

with more than 6 million fatalities. COVID spread to about 223 nations [5]. The death rate in real life was much greater compared to what had been reported. Following heart disease and cancer as the second and third main causes of death in 2020, respectively, the United States had the largest number of COVID infections and fatalities [6]. An investigation of all information on the COVID virus and treatment was conducted based on the published literature. According to the rules regarding the use of electronic and internet media, high-quality and trustworthy medical information was only gathered from the internet from sources like WHO, CDC.gov, Wikipedia, and other Health On Net (HON) reviews conducted by certified and accredited websites like PubMed, the Allied and Complementary Medicine Database, the Natural Medicine Comprehensive Database, Embase, and the Cochrane Library.

2. Variants and Transmission

The virus is constantly evolving its strains. They change in order to survive and adapt. RNA (ribonucleic acid) is the genetic substance that makes up all coronaviruses. When a cell gets infected by a virus, the virus adheres to it and enters it to create copies of the host cell's RNA, which helps in the spread of the virus. The viral RNA changes if copies contain mistakes. These modifications are the reason for the virus's mutations, which cause it to behave differently than in its earlier versions. As a typical byproduct of virus reproduction and propagation, these ongoing mutations in variations occur accidentally at random. When infected, this can have a variety of negative effects on a person's health. Since virus strains are constantly evolving, new medications or vaccines are frequently needed to combat them. Random virus mutations that make it simpler to infect humans increase the prevalence of that variation because they are propagated more quickly and easily. COVID has been shown to exist in a number of different forms worldwide. The Alpha, Beta, Gamma, Delta, and Omicron variations have been identified as variants of concern among these [7, 8]. Although there were fewer infections in the early stages of the pandemic than in the later ones, as time passed, the COVID-19 virus evolved into different genetic forms that were more contagious. This was due to random mutations that occurred during this process. In particular, both the alpha and delta versions were shown to be more contagious and virulent than previously known viral strains [8]. "The annoying delta variation, or B.1.617.2, was first discovered in India in December 2020, and this discovery sparked a huge pandemic that caused the most hospitalizations and fatalities in the nation. Then, within a few months, it spread quickly to a number of other countries, eventually emerging as the dominant variant. The U.K. was the place where it was initially discovered, and it was also roughly 50% more contagious than the previous one" [10, 11]. The spike protein has changes in the delta strain of COVID, which make it simpler for it to infect human cells and thus more contagious. Once infected, the patient was more likely to distribute it to others. Furthermore, the strain was more dangerous. According to a study, virus loads were 1,000 times higher in infections induced by delta than by other variations [12]. The delta Plus variant was regarded as a sub-variant of the delta version and was also known by the names B.1.617.2.1 and AY.1. The virus had a mutation that made it possible for it to effectively target lung cells and maybe avoid being protected by immunizations. There were many more strains of COVID reported in the months that followed, with sub-variants of Omicron having the highest R value (reproduction rate of COVID-19), indicating the most people infected by any other variant even though it was found to be less lethal than the delta variant that produced the highest mortality [11, 12].

3. Pathophysiology of covid 19: mechanism of action: (fig. 1. Appendix)

"The COVID virus infects the host mechanism in the human body and takes over. The spike (S), membrane (M), envelop (E), and nucleocapsid (N) proteins are the four structural proteins that make up the virus. The S protein, which protrudes from the viral surface, is crucial for host attachment and penetration. Two functional subunits, designated S1 and S2, make up this spike protein [13, 14]. "The virus transmits from person to person by infecting respiratory droplets. When the virus enters the body, its S1 unit binds to the angiotensin-converting enzyme 2 (ACE-2) host receptor, which is highly expressed in the pulmonary epithelial cells of the lungs. Thus, the virus enters the body's host cell and combines with the membrane via its S2 unit. Viral spike proteins undergo significant changes in structure as a result, enabling the virus to become stable inside the host cell. The COVID virus releases its viral components after it gets inside the pulmonary alveolar epithelial cells of the lungs. Once within the host cell, the virus replicates by using RNA polymerase activity (also known as transcription) to create a negative strand of RNA from single-strand positive RNA that already exists. Translation—the process by which new proteins are made in the cytoplasm of the cell—is caused by this newly developed negative strand RNA [15]. " This stage lasts a few days, and the immunological response that develops during this phase is comparatively weak. Despite the patients' low viral load at this time, they are very contagious, even if they are asymptomatic. Nasal swab testing can currently be used to identify the virus. As soon as infected respiratory droplets touch the host's mucosal surfaces, such as the eyes, nose, and mouth, the freshly created virus particles are prepared to infiltrate the nearby bodily cells and disseminate the illness to further people who come into contact with the "As soon as infected respiratory droplets touch the host's mucosal surfaces, such as the eyes, nose, and mouth, the freshly created virus particles are prepared to infiltrate the nearby bodily cells and disseminate the illness to further people who come into contact with the air" [16]. At this stage, the virus travels from the nasal epithelium to the upper respiratory tract using the conducting airways. A dry cough, lethargy, and fever are possible symptoms for the patient. The release of cytokines and other inflammatory indicators by the virus-infected cells in the host body triggers a stronger immune response during this phase. When a virus reaches the lower respiratory tract from the upper respiratory tract, it enters the type 2 alveolar epithelial cells deeper in the lung via the host receptor ACE-2 and begins to replicate to make additional viral nucleocapsids. As a result, a significant immune response is triggered. This 'cytokine storm' of cytokines and inflammatory markers, including interleukins (IL-1, IL-6, IL-8, IL-120, and IL-12), tumour necrosis factor (TNF), IFN, and IFN, CXCL-10, monocyte chemoattractant protein-1 (MCP-1), and macrophage inflammatory protein-1 (MIP-1), draws neutrophils, Further inflammation and lung damage are brought on by this process. Acute respiratory distress syndrome results from this cycle's ongoing chronic inflammation and damage to the tiny lung cells (alveoli) [5, 17]. The disease progresses to this stage in around one-fifth of all infected patients, who then experience severe symptoms.

4. Symptoms

The symptoms usually begin between 6 and 11.5 days after exposure [18], and moderate cases typically resolve within 2 weeks; however, more severe cases may require up to 6 weeks. After a period of initial recovery, the symptoms of extended COVID may reappear or last for weeks or months [19]. The spectrum of symptoms of COVID infection ranges from asymptomatic to symptomatic and includes the grave signs and symptoms of the illness marked by abrupt respiratory failure necessitating mechanical ventilation, septic shock, and multiple organ failure. The majority of symptomatic COVID patients commonly presented with hallmark symptoms such as fever, cough, headache, and shortness of breath (with $SpO2 \leq 94\%$) that were sometimes accompanied with a sore throat, loss of taste (ageusia) or dysgeusia (altered or metallic taste), loss of smell (anosmia), anorexia, nausea, malaise, myalgias, and diarrhoea" (Cascella et al., 2020) (Cascella et al., 2020). According to the many COVID variants, the symptoms were also distinct. Common testing results in COVID patients include elevated C-reactive protein (CRP) levels, decreased immunity as confirmed by reduced WBC lymphocytes

(leukopenia/lymphopenia), reduced heart function as indicated by increased cardiac enzymes, abnormal liver function tests, elevated D-dimer (responsible for increased blood coagulation), elevated erythrocyte sedimentation rate (ESR), and occasionally increased WBC (leukocytosis), and elevated procalcitonin [21]. Patients with co-morbidities such as cancer, diabetes, heart disease, liver or renal illness, and immune system impairment are at a significant risk of severe COVID and its associated complications. Due to issues with the heart, lungs, or cytokine storm, the mortality rate was also increased in these patients.

5. Effect on Various Organs: Complications of Long Covid

Several important organ systems are damaged by COVID. The lungs are one of the major organ systems that the virus can damage because it enters host cells through the receptor for the angiotensin-converting enzyme 2 (ACE2) enzyme, which is mostly found on the surface of type II alveolar cells in the lungs. The most frequent side effect of severe COVI is rapid or gradual clinical deterioration, which can result in acute respiratory failure, acute respiratory distress syndrome (ARDS), and/or multiorgan failure, which can result in death. In these patients, who were identified by chest imaging such as a chest radiograph, CT scan, or lung ultrasound, the development of ARDS often takes place around a week following the onset of symptoms. With the severity of ARDS, the probability of a 28-day death increased [22]. The COVID virus has a wide range of impacts on heart function. Chest pain and related consequences are caused by ischemic stroke, which is caused by increased blood viscosity and increased blood coagulation (thrombosis). As a serious symptom of a cytokine storm, an irregular heartbeat, abrupt cardiac arrest, or cardiogenic shock can ensue [23]. Cardiac arrest may occur as a result of an acute loss of oxygen saturation brought on by lung disease or a blood clot obstructing the flow of blood to the frail heart. The severity of COVID has been shown to be related to an increase in deep vein thrombosis (DVT) [24]. DVT is a blood clot that forms as a thrombus or an embolus and travels to other organs, such as the heart or lungs, where it can impede blood flow and cause death. A minimum of one gastrointestinal (GIT) symptom, such as nausea, vomiting, abdominal pain, diarrhoea, or acute constipation, was also present in COVID patients [25, 26]. These consequences included bowel ischemia, gastrointestinal haemorrhage, and pancreatitis. One of the most severe extra-pulmonary signs, acute renal failure, was also observed as a kidney disorder and was linked to a higher risk of patient death [27]. Along with chronic lung problems, patients seeking long-term COVID rehabilitation often experienced recurrent symptoms of exhaustion, muscle weakness, difficulty sleeping, anxiety, or depression. This was especially true in cases of severe infections. COVID patients' mental health is significantly impacted, as seen by a high level of dread, worry, or concern, forgetfulness, or brain fog, and some consequences include symptoms associated with neurological and psychotic illnesses [27]. Particularly as a consequence of overuse of corticosteroids, co-morbid conditions like uncontrolled diabetes or immunocompromised conditions, or secondary invasive black fungal infections like mucormycosis, cases of morbid complications like these have been more frequently reported in patients recovering from COVID [28]. There have also been reports of cryptococcal infections and other COVID-associated illnesses like candidiasis (Candida auris), pulmonary aspergillosis, and pneumocystis pneumonia [29]. Mucormycosis is a rare but dangerous, potentially fatal illness that affects many different organ systems in the body, including the sinuses, lungs, skin, and brain. If it is not treated in a timely manner, mucormycosis can be fatal. Mucormycosis symptoms include fever, coughing, headache, shortness of breath, swelling, and sores on the skin or mouth, as well as stomachaches, vomiting, diarrhoea, and chest pain. The serious side effects included nerve damage, blood clots, and blindness. Regular blood tests, tissue biopsies, and radiological imaging tests like CT or MRI are used to make diagnoses. Primary risk factor reversal, surgery, intravenous antifungal drugs like Amphotericin B, empirical antibiotics, common antivirals like Toclizumab, and steroids like methylprednisolone are all part of the conventional protocol for therapy [29].

6. Detection of Covid

Using a nasopharyngeal swab (NPS) to collect a sample from patients is the traditional screening method. A real-time PCR assay is used to identify viral proteins as well as the genetic material (ribonucleic acid, or RNA) that makes up the virus or its pieces when it breaks down. This technique is a reverse transcription-polymerase chain reaction (RT-PCR) based on real-time fluorescence. The technician positions the patient to sit up straight with their head straight, then inserts a tiny swab tip with a flexible wire or plastic shaft via the nostril.

The nasal and septum floor is the target, and the swab is pointed parallel to that surface (not upward). The swab moves along this route with no obstructions inside the nasal cavity until it reaches the nasopharynx, when the technician taking the sample feels the patient's discomfort. The discharges from this area are then allowed to be absorbed by the swab by gently rolling, rubbing, and leaving it in place for a short period of time. As soon as the swab is taken out of the nose, it is put into a vial filled with culture media and sealed [30, 31]. The test tube contains substances. For the results to be accurate, the sample collection process must be done correctly. Genetic material is then removed from the sample and sent for analysis using RT-PCR in the lab. Small amounts of RNA from samples are expanded by professionals using PCR technology into deoxyribonucleic acid (DNA), which is duplicated until the presence of the COVID virus can be detected. Thermal cyclers, which are PCR machines, use specialised chemicals and enzymes. The amount of genetic material that is being particularly targeted in the test tube grows with each heating and cooling cycle. A small fraction of the viral genetic material is replicated millions of times after many cycles. If one of the tube's compounds is activated, a fluorescent light will result. When sufficiently enhanced, the PCR machine can pick up this signal. The software signal is perceived as a successful test outcome. A positive test result means that the subject was probably infected with COVID when the sample was taken. The time it takes for the sample to get to the lab or be processed can sometimes cause test results to take several days, although they can sometimes be available as soon as 24 hours after the sample is collected. Making an accurate diagnosis requires a thorough clinical history of the patient, including information on the start and duration of symptoms, travel history, contact with individuals who have the COVID infection, underlying medical disorders, and drug history. Sometimes a patient is requested to repeatedly spit into a tube to obtain a sample of saliva, or an oropharyngeal swab is used to collect the sample from the mouth by inserting a lengthy swab into the back of the patient's throat. But it was discovered that the nasal swab approach had greater accuracy than the oral swab [32].

The COVID virus was found using rapid antigen assays, sometimes referred to as Lateral Flow assays (LFT). It recognises the antigens, which are proteins found on the viral surface. When a high viral load is present in the body, antigen testing is frequently quick and effective if carried out within a few days after the onset of symptoms. Although the antigen test is often quicker than the PCR test, it is less accurate. A PCR test is recommended to validate the test result if the antigen test is negative.

For determining the existence of antibodies against COVID, commercially available serology testing using antibody testing kits is also available. The kit can assess whether antibodies that develop as a result of infection are present.

In order to monitor the course of the disease, hospitalised patients also undergo clinical lab tests like complete blood counts (CBC), renal and liver function checks, and testing for inflammatory markers like ferritin, lactate dehydrogenase, D-dimer, and procalcitonin.

Based on the clinical assessment of the patient, imaging modalities such as chest x-rays, lung ultrasounds, high-resolution chest computed tomography (HR-CT), or lung ultrasound are also taken into consideration. In the early stages of a viral infection, the lungs may appear clear, but as the infection progresses, a chest X-ray examination frequently reveals bilateral multifocal alveolar opacities, pleural effusion, or haemorrhage, as shown in a patient with COVID pneumonia.

7. Pharmacotherapy

Due to the lack of knowledge about the virus and its actions at the time of the pandemic's onset, management choices for the COVID virus were initially experimental and constrained. Since then, the COVID epidemic has been combated with the help of extensive research conducted by scientists around the globe, which has sped up the discovery of novel agents, including vaccinations. Right now, a range of therapeutic options are available, including antiviral drugs like molnupiravir, paxlovid, and remdesivir; anti-covid monoclonal antibodies like bamlanivimab or etesevimab; casirivimab or imdevimab; anti-inflammatory drugs like dexamethasone; and immunomodulator agents (e.g., baricitinib, tocilizumab) [5, 33, 34]. Early in the viral replication cycle is probably when antiviral drugs and antibody-based therapies will work best. Azithromycin and other macrolide antibiotics were initially used to prevent lung infections in people who had viral pneumonia and were suspected of having colitis. The medicine was initially recommended because of its potential to have an antiviral and anti-inflammatory effect on the airways, but it is no longer regularly used to treat COVID [35].

The first oral antiviral drug for the treatment of COVID in India was introduced by Glenmark Pharmaceuticals in June 2020 for patients with mild-to-moderate COVID. On day 1, a dose of 1800 mg twice daily was advised, and on days 2 through 14, a dose of 800 mg twice daily was advised. By converting the ribofuranosyl triphosphate derivative by host enzymes and then selectively blocking the viral RNA-dependent RNA polymerase, favipiravir operates on RNA viruses to provide a quick decline in viral load and an early improvement in symptoms. Fabiflu was first used for COVID therapy after being developed in Japan as a treatment for Ebola and resistant instances of influenza [36]. The broad-spectrum antiviral Remdesivir works by inhibiting the viral RNA-dependent RNA polymerase in order to lower the viral load. When the pandemic first began, the medicine was widely used since the Food and Drug Administration (FDA) had licenced it for clinical use in adult and paediatric patients (over the age of 12 and weighing at least 40 kilogrammes or more) to treat hospitalised patients with mild-to-severe COVID in the U.S. [37, 38, 39]. It was chosen for individuals with mild symptoms of COVID and administered as a loading dose of 200 mg intravenously over 1-2 hours on day 1, then 100 mg intravenously every day for 5–10 days. Remdesivir should not be used in patients who have acute hepatic or renal impairment, children, pregnant women, or nursing mothers [40]. Remdesivir was later found to have little to no impact on overall mortality, the start of mechanical ventilation, or hospital stay [41]. There is no additional information about the drug's effectiveness against the new COVID forms.

Initially, during the pandemic, hydroxychloroquine (HCQ) and chloroquine were also suggested as antiviral therapies for COVID-19. Chloroquine (500 mg per hour) prevents SARS-CoV receptor glycosylation and increases the endosomal pH necessary for virus/cell fusion to inhibit virus infection. An alternative to chloroquine with a higher safety profile is HCQ (200 mg every 12 hours) [42]. However, it was discovered that neither the medications containing azithromycin nor those without were successful in reducing the clinical condition or overall mortality in hospitalised patients [41, 43].

Ivermectin was initially offered as an FDA-approved antiparasitic medicine used extensively around the world to treat COVID but was later determined to be useless. The medicine is currently not approved to treat COVID in patients who are hospitalised or outpatients.

An FDA-approved HIV combination drug called lopinavir+ritonavir/Kaletra (400 mg orally every 12 hours) was proposed as an antiviral treatment for COVID in the pandemic's early stages. For patients receiving COVID therapy who are currently hospitalised or outpatients, it is not recommended.

Molnupiravir, a directly acting broad-spectrum oral antiviral drug, is one of the antiviral medications now recommended for the treatment of COVID. It lowers the risk of hospitalisation or mortality in unvaccinated individuals with mild-to-moderate, lab-confirmed COVID-19 [46, 47] and Paxlovid (ritonavir + nirmatrelvir), an oral combination drug comprising two antiviral medicines approved by the FDA for patients with mild-to-moderate COVID, to lower the risk of COVID-related hospital admission or mortality.

Convalescent plasma, an effective antibody cocktail obtained from COVID patients who are recuperating, is actively suggested as a treatment for active instances of COVID. By 2020, it will be licenced by the FDA under an EUA for patients with severe, life-threatening COVID [45]. Covid-19 has thus far produced conflicting findings, indicating little difference in clinical improvement or overall mortality in individuals treated with convalescence plasma versus standard therapy despite the fact that it appeared to have promising and highly pursued data [46, 47].

REGN-COV2 (Casirivimab + Imdevimab): This antibody cocktail, which includes the drugs Sotrovimab (VIR-7831), Bamlanivimab (LY-CoV555 or LY3819253 and LY-CoV016 or LY3832479), and Etesevimab (LY-CoV555 or LY3819253), showed promise in lowering viral load by focusing on the spike [48,49] and was approved for use in mild-to-moderate COVID patients that are at high risk of developing severe disease and/or hospitalisation, as well as non-hospitalised patients with lab-confirmed COVID infection (aged 12 years and weighting 40 kg).

The later stage of the disease known as the hyper-inflammatory state, which is brought on by the release of cytokines and the activation of the coagulation system and results in a prothrombotic state that causes blood to thicken and is indicated by an elevated level of D-Dimer in the blood, may be treated with anti-inflammatory medications like corticosteroids, immunomodulatory therapies, or any combination of these therapies. In patients with severe COVID symptoms, steroids were administered for just 3–5 days. The initial and only steroid recommended at first was methylprednisolone, at doses of 0.5–1 mg/kg/day for mild patients and 1-2 mg/kg/day for severe instances. Due to steroid-mediated immune suppression and associated adverse effects, such as extended steroid use increasing blood glucose, lowering immunity, and weakening bones, in addition to a variety of other issues, higher doses were not advised. " Dexamethasone later emerged as the preferred medication for reducing mortality in seriously ill patients. Depending on the severity of the sickness in hospitalised patients who need supplementary oxygen or noninvasive or invasive mechanical ventilation, dexamethasone became the standard of therapy either alone or combined with remdesivir based on the findings of one landmark clinical trial [50].

"Interferons are cytokines that are necessary in building an immune response to a viral infection, and IL-1 (interleukin) is an antagonist. The usage of antagonists was recommended for COVID, such as Anakinra, an interleukin-1 receptor antagonist that was essentially FDA-authorised to treat rheumatoid arthritis. But this approach was not advised to treat a COVID infection due to the scant and inadequate data available on its application and the relative possibility of harm [51].

IL-6 resistance Tocilizumab, Siltuximab, and Sarilumab—monoclonal antibodies used to treat COVID—block the interleukin-6 alpha receptor in order to prevent the cytokine storm or hyper-inflammation that occurs in patients with severe COVID. [52,53]. The dosage is 8 mg/kg

(maximum 800 mg at once), given slowly over the course of an hour in 100 mL of normal saline (N.S.). If necessary, the dosage may be repeated once after 12–24 hours. The evidence for this agent's effectiveness is conflicting.

Baricitinib and Ruxolitinib are examples of Janus kinase (JAK) inhibitors, which are oral selective inhibitors of the Janus kinase (JAK 1 and JAK 2) pathway that reduce immune system overstimulation. These medications were thought to be a promising therapy for critical or severe cases of COVID to reduce the cytokine storm and hype-inflammatory stage during the initial as well as the latter stages of the illness. They are mostly intended for people with moderate-to-highly active rheumatoid arthritis. When combined with corticosteroids or antiviral medications like lopinavir/ritonavir, hydroxychloroquine, or remdesivir in adult hospitalised patients with severe COVI, especially those receiving high-flow oxygen supplementation or noninvasive ventilation, the medication showed good overall clinical improvement and recovery [54]. Data on the combination of baricitinib and dexamethasone is scarce. Another oral selective JAK 1 and JAK3 inhibitor, tofacitinib, has been shown to reduce the risk of respiratory failure or mortality by reducing viral inflammation-mediated lung injury and inhibiting the inflammatory cascade in patients with severe COVID.

To lessen the hyper-inflammatory immune response found in severe COVID, other medications such as acalabrutinib, ibrutinib, and rilzabrutinib are inhibitors of tyrosine kinase that were FDA-approved for various hematologic malignancies [54]. Clinical trials are being conducted to confirm the true efficacy of these medications.

8. Oxygenation and Ventilation Management in Covid

"Conventional Oxygen Therapy was recommended for patients with COVID with associated respiratory issues, and they should be closely monitored with continuous pulse oximeters," the report reads. To keep the saturation level of oxygen (SpO2) between 92 and 96% (or 88 and 90% if the patient had COPD), more oxygen was given by a nasal cannula or Venturi mask. Supplemental oxygen continues with routine check-ups if clinical and oxygen saturation metrics improve. Conventional oxygen therapy is ineffective to address the oxygen demand if there is no clinical improvement or worsening of symptoms and/or oxygen saturation, as in the case of acute hypoxemic respiratory failure, the most frequent consequence in adult COVID patients. To improve respiratory support in an emergency, noninvasive procedures like High-Flow Nasal Cannula (HFNC) or Noninvasive Positive Pressure Ventilation (NIPPV), endotracheal intubation, invasive mechanical ventilation (IMV), or extracorporeal membrane oxygenation (ECMO) are advised for these patients [55, 56].

In carefully chosen patients, noninvasive positive pressure ventilation (NIPPV), also known as bi-level positive airway pressure (BiPAP) or continuous positive airway pressure (CPAP), is the mainstay in the management of acute hypoxemic respiratory failure associated with COVID. Only hospitalised COVID patients with underlying obstructive sleep apnea (OSA) or COPD who develop respiratory insufficiency due to other conditions such as COPD, cardiogenic pulmonary edoema, or other factors are eligible for NIPPV [57]. An expiratory valve with an antibacterial filter is built into the masks to help prevent infection. An experienced operator performs intubation of the endotracheal tube and lung-protective invasive ventilation during a medical emergency to avoid respiratory failure (Cook et al., 2020). When performing endotracheal intubation and manual ventilation prior to intubation, healthcare professionals such as doctors and nurses must wear the required PPE, which includes gowns, gloves, N95 masks, and eye protection. HFNC is used to do pre-oxygenation (100% O2 for 5 minutes). Carefully chosen patients who don't react to ventilation in the prone position are given ECMO consideration.

9. Stages of Pharmacotherapy Management in Covid

Patients who were mildly COVID-positive or asymptomatic and had an early infection (SpO2 levels of 94%–97% in room air) were recommended to isolate themselves and monitor their clinical symptoms. Patients with minor symptoms are handled at home with seclusion and supportive treatment. The use of OTC medications like paracetamol is advised. There is no need for routine lab tests. Only older individuals who already have conditions must be constantly watched until they get better.

For outpatients that are at risk of illness progression and need to be hospitalised for closer monitoring, virus-neutralising antibodies like REGN-COV2, casirivimab, and imdevimab, or bamlanivimab/etesevimab, or sotrovimab, can be considered.

It was advised to admit patients with moderate infections (SpO2 levels of 90%–94% in room air) for close observation. All hospitalised patients received supportive care along with any necessary isotonic fluid resuscitation, and supplemental oxygen therapy was started if the SpO2 level was below 96% [58]. For individuals who are hospitalised and need supplemental oxygen, remdesivir and dexamethasone are options. Remdesivir alone, dexamethasone alone, or remdesivir and dexamethasone combination therapy are all recommended by the National Institutes of Health (NIH) COVID-19 treatment guidelines for hospitalised patients who need supplementary oxygen but are not undergoing HFNC, NIPPV, IMV, or ECMO. Additionally, if a patient has a high D-Dimer result and is at risk for developing venous and thromboembolic events, proper anticoagulant medication is initiated.

Hospitalisation was necessary for patients with severe COVID (SpO2 values of 90% in room air) or patients with ARDS. Nebulization, upper airway suctioning, removing the patient off the ventilator, and noninvasive positive pressure ventilation to raise oxygen levels were all used to correctly ventilate the patients as needed. For individuals who do not require intubation, HFNC or NIPPV were taken into consideration. In the event that respiratory collapse was imminent, endotracheal intubation with IMV or ECMO was initiated. Additionally, all patients were kept on prophylactic anticoagulation, which is crucial when there are high D-Dimer results that are indicative of a prothrombotic state. Given the significant risk of thromboembolism (blood clots), low molecular weight heparin (LMWH) was also thought to be used for anticoagulation in mild (once daily) to severe (twice daily) individuals. Diabetes, related hypertension, hypothyroidism, and other co-morbidities should be controlled appropriately. When appropriate, renal replacement therapy was taken into account in renal failure. Dexamethasone should be used in hospitalised patients who require oxygen via noninvasive or invasive ventilation, according to the NIH guidelines for COVID-19 therapy. In hospitalised patients on HFNC or NIPPV with evidence of illness progression, combination therapy with dexamethasone plus remdesivir, baricitinib, or tocilizumab in conjunction with dexamethasone alone was also advised. Baricitinib combined with remdesivir may be used in patients who are not intubated if corticosteroids are not an option. A single intravenous dosage of the medication tocilizumab was also recommended for recently hospitalised COVID patients who experienced acute respiratory distress. You can begin taking medications like norepinephrine to keep your mean arterial pressure (MAP) between 60 and 65 mmHg. If a secondary bacterial infection is suspected during routine examinations, empirical antibacterial treatment with the appropriate medicines can be used.

10. Prevention: Anti-Covid Vaccines

As the virus grew ubiquitous and menacing, the creation of potent vaccinations to stop the COVID pandemic remained the top goal for scientific research communities around the globe. Its structure and mechanisms were meticulously investigated, and with the assistance of the public and private sectors around the world, vaccine development took

place in record time and at an unequalled rate. Vaccines were created and fast-tracked for public use within six months of the global research efforts to prevent COVID infection in communities all over the world. Typically, it takes almost 10–12 years to develop a new medication molecule. There are currently numerous technologies being researched and developed to produce a COVID vaccination that works [59]. The Pfizer-BioNTech and Moderna vaccines were among the first RNA vaccines to receive approval. These vaccines use messenger RNA (mRNA) or self-replicating RNA to elicit an immunological response in human tissue. These RNAs cause cells to express the SARS-CoV-2 spike protein, which stimulates the immune system to destroy the virus. Inactivated, attenuated, or weakened versions of the virus are used in vaccines like covaxin and CoronaVac to stimulate the immune system and produce neutralising antibodies that protect the body from the COVID virus. The FDA approved and released BioNTech/Pfizer's BNT162b2 vaccine for emergency use on December 11, 2020, for anyone 16 years of age and older receiving two-dose regimens to be given 21 days apart, providing 95% protection against COVID-19. [60] Inactivated, attenuated, or weakened versions of the virus are used in vaccines like covaxin and CoronaVac to stimulate the immune system and produce neutralising antibodies that protect the body from the COVID virus. The FDA approved and released BioNTech/Pfizer's BNT162b2 vaccine for emergency use on December 11, 2020, for anyone 16 years of age and older receiving two-dose regimens to be given 21 days apart, providing 95% protection against COVID-19 [61]. On February 27, 2021, Janssen/Johnson & Johnson (Ad26.COV2.S) issued an additional adenovirus-based vaccination with FDA approval [62].

Covishield (ChAdOx1, nCoV-19), a non-replicating adenovirus vector-based vaccination created by Oxford University and Astrazeneca, was made by the Serum Institute in Pune, India, and made available by January 2021 [63]. It demonstrated between 70 and 80 percent virus prevention. The expert group then increased the original 28-day interval between the two dosages to 84–112 days. Many nations throughout the world approved the vaccine for use in an emergency setting before the FDA approved it for use in the United States considerably later [64]. These adenovirus vector-based vaccines are non-replicating, which means that they only produce the antigen that triggers a systemic immune response to COVID rather than new virus particles. A fifth vaccine, called Novavax/Nuvaxovid/Covovax (NVX-CoV2373), was released on the market in Europe in February 2021 and has shown over 90% efficacy in active immunisation against the COVID virus. It is a recombinant SARS-CoV-2 nanoparticle, genetically designed, protein-based vaccine [65, 66]. Later, a large number of additional vaccines, including protein-based and inactivated ones created locally in China (CoronaVac), Russia (Sputnik V), and India (Covaxin), were authorised for emergency use or received approval to prevent COVID in numerous nations. Covaxin (BBV152), developed by Bharat Biotech in collaboration with the Indian Council of Medical Research and the National Institute of Virology (NIV), was given an interim emergency use authorization in January 2021. It showed 60 (to asymptomatic COVID) to 90% (severe COVID) protection against the virus in a 2-dose vaccination regimen given 28 days apart. [67,68] Sputnik V, an adenovirus vector vaccine developed by Russia and marketed by Dr. Reddy's lab, was authorised for use in India in April 2021. It was administered over a period of two days, 21 days apart, and provided 91–92% protection from the virus. Sputnik Light, a single-dose vaccination made up simply of the first dosage of Sputnik V, was introduced after this. It is registered as a vaccine for acute outbreaks and is designed to be used as a booster dose for people who have already received Sputnik V at least six months earlier. Children's immunisations were quickly created and made available for use in an emergency. By October 2021, India had approved Covaxin (for children aged 6 to 12), Corbevax (for children aged 5 to 12), and ZyCoV-D (for children aged 12 and above). A Texas-based biopharmaceutical company, Biological E. Limited (BioE), was granted a licence to develop and manufacture Corbevax, a vaccine based on protein subunits [69]. Zydus Cadila created ZyCoV-D, the first DNA-based COVID-19 vaccine in the world, for adults and children 12 years of age and older. A needle-free applicator was used to administer the three doses of the vaccine. Regardless of the many forms of technology, the majority of Corona virus vaccinations are administered through intramuscular injection. But numerous additional vaccine delivery techniques, including skin patches, oral, intranasal, and jet injectors for intradermal delivery for a shot-free manner of administration, are now being researched [70]. The vaccination schedules of many nations now include a third dose as a booster shot to help people retain immunity for an extended amount of time and provide protection against numerous virus strains. To increase protection, booster doses of the Pfizer-BionTech or Moderna vaccination are administered at least five months after the first two doses of the Johnson & Johnson (J&J)/Janssen Covid vaccine, at least two months after the first dose, and at least four to six months after the first dose for Covaxin and Covishield. For highly immunocompromised patients with cancer, HIV, and associated diseases, an additional booster dose is advised. The Centres for Disease Control and Prevention (CDC) have recommendations for who is eligible for a booster dose [71].

11. Safety of Anti Covid Vaccines

Based on the benefit-to-risk ratio, anti-covid vaccinations have been shown to be comparatively safe up to this point. The over-the-counter (OTC) medication paracetamol has been recommended for joint discomfort, which is one of the most frequent side effects of COVID vaccinations. Other side effects include fever, agitation, headaches, and soreness or swelling at the injection site [72]. Early in 2021, certain negative side effects following vaccination were noted in individuals, including blood clots (thromobosis) paired with thrombocytopenia linked to viral vaccinations [73]. A small number of allergic events, such as anaphylaxis cases where the vaccine's lipid nanoparticles were to blame, were also documented. Some cases of heart inflammation (myocarditis and pericarditis) were also observed with mRNA vaccinations [74, 75]. People who have not received the whole course of vaccination against COVID were said to be more at risk, whereas those who have had the full course of vaccination and patients who have already contracted COVID were shown to have a lower chance of contracting the disease again for at least six months [76]. The assertion is not entirely supported, however, because the vaccine's level of protection can change based on a number of circumstances, including the virus's distinct strains. Additionally, the levels of protection following both vaccination and COVID infection may be decreased in certain populations, including the elderly and immunocompromised people. When it was initially made available during the COVID epidemic, some people were a little hesitant about receiving the vaccination. But in order to immunize the populace against the virus, the Indian government has launched a widespread vaccination programme. On January 16, 2021, the first round of vaccine distribution began with volunteers for crisis management and frontline personnel such as police, paramilitary forces, sanitation workers, and health professionals. All inhabitants above the age of 60, people between the ages of 45 and 60 with one or more qualified co-morbidities, and any healthcare or frontline workers who did not receive a dose during the first phase were all covered by the second phase of the vaccine rollout. On March 1, online registration opened up through the Co-WIN website and Aarogya Setu app. Soon after, vaccination coverage was extended to the remaining adults [77].

12. Current Scenario

As of June 22, 2022, there were still 43,331,645 confirmed cases of COVID-19 in India, with 524,903 deaths reported, and there were 538,321,874 confirmed cases of COVID worldwide, with 6,320,599 deaths reported [78]. There are much more instances and deaths from COVID than are being reported. The sub-variant of omicron known as

BA.5 is currently dominating the nation. India will have provided about 1.9 billion doses of the currently licensed vaccinations by the middle of June 2022, including the first, second, and booster doses [79, 80]. By June 20, 2022, the WHO estimates that close to 12 billion vaccine doses will have been given, with over 77% of the world's population receiving at least one shot [81]. The third booster dose would be provided free of charge to all Indian citizens above the age of 18 by mid-July 2022 in order to protect the population from the COVID virus [82, 83]. The Drugs Controller General of India (DCGI) had already authorized the distribution of the intranasal needle-free vaccine developed by Bharat Biotech for use in adults and children to prevent COVID by September 2022 [84].

13. Facts and Future Projections

The trend for SARS-CoV-2 infection, hospitalizations, and deaths remains unpredictable at best. The second lethal wave of the delta variant has produced mass destruction all over the world. After that, many variants of COVID-19 kept coming, starting fresh waves of panic among the population all over again. COVID cases took a plunge intermittently during 2021–22, prompting a surge of new hope that the pandemic was likely to end by the end of that year. But then, all of a sudden, a fresh wave was predicted as the active cases started mounting again, necessitating fresh lockdowns in various countries.

There is no end in sight for the pandemic, as active cases and related mortality are still reported. Since it started in 2019, the virus has changed its form quite a few times, changing the course of the pandemic. The latest omicron, the 7th variant of COVID, has spread at a rapid pace in just 3 months from the time it was detected in early November 2021, although it was less fatal than delta but certainly more infectious.

We just learned to live with COVID and other viral threats looming large over the horizon like encephalitis and monkeypox, the cases of which boomeranged in various countries across the world, forcing WHO to declare it a pandemic or health emergency of international concern. The vaccines need to be modified from time to time to be taken as a booster dose to protect against various viral mutations, as the previous vaccine's effectiveness also waned over time. The use of the latest oral treatments released on the market for public use, like paxlovid and molnupiravir, may further increase [85]. There are certain herbal counterparts, including Solanum nigrum (black nightshade), also in various research stages or already on the market, claiming to prevent COVID and related complications.

14. Conclusion

The common viral infections like the flu or cold may pose a danger of taking a stronger hold or becoming lethal over time. Masking, sanitizing, and social distancing may become normal parts of life.

Human efforts towards inventing new strategies, from vaccines to drugs, are required to be sustained with briskness as the viruses keep getting smarter over time. The best way to tackle the bug is to keep the body's natural immunity stronger. Environmental factors like pollution and global warming certainly affect the equation to a great degree. We need to be extra careful in these unexpected times because change is the only constant. It seems equally important to be able to think on our feet in a critical situation, learn and master new things to deal with the challenges, and adapt to new changes to keep up with the unpredictable times ahead.

Competing Interests

The author has declared no competing interests.

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