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COVID19: PATHOPHYSIOLOGY, CLINICAL FEATURES, DIAGNOSIS AND MANAGEMENT

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ABSTRACT: SARS-CoV-2 viral cause infection called COVID-19 was initially reported in China has resulted in a pandemic because it has spread in over 210 countries. This review summarized pathophysiology, clinical features, diagnosis, and COVID 19. The spread of SARS-CoV-2 viral infections is a matter of concern because of a mutant variant of virus. The COVID-19 infection is having 14 days incubation period. Fever, sore throat, cough, severe headache, breathlessness, myalgia and weakness are common symptoms observed in patients with COVID-19. Steps of replication of SARS-CoV-2 virus are attachment, penetration, uncoating, replication, assembly and release. Patients' screening tests are complete blood count, C-reactive protein (CRP) and erythrocyte, sedimentation rate (ESR), D-dimer, serum ferritin, and others. The reverse transcription-polymerase chain reaction (RT-PCR) is the important diagnostic test of molecular genetic assays for detecting viral RNA. In-Patient of COVID 19 CT scan shows ground-glass opacities with or without consolidations in lung regions. In CT scan, standardized assessment scheme is CORAD classification and assessment of lung involvement can be done CT severity score index. Management: Management of COVID -19 starts with supportive and symptomatic treatment. As soon as the patient gets an infection, the patient should maintain adequate isolation to prevent transmission to other contacts, patients, and healthcare workers. Mild infection can be managed at home with counseling about danger signs. The patient should be advised to maintain hydration and nutrition, and symptomatic treatment should be given. A variety of therapeutic options currently include remdesivir, favipiravir, bamlanivimab / etesevimab, casirivimab / imdevimab dexamethasone, baricitinib, tocilizumab are available.

INTRODUCTION: Coronavirus disease 2019 (COVID-19) has become a major public health risk worldwide. The outbreak of novel coronavirus was initially reported in Wuhan, Hubei Province, China, in late December 2019. On January 12, 2020, it was named as novel coronavirus "2019-nCoV" by WHO [1] and later, the International Committee on Taxonomy of Viruses (ICTV) named it as the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [2].

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It was termed coronavirus disease 2019 (COVID-19) by WHO 3 and WHO declared it a global pandemic on March 11, 2020, because it was spreading rapidly in many countries worldwide, devastating many healthcare systems [4]. In spite of considerable progress in clinical research, the spread of this virus has become a matter of increasing concern, as the second and third waves of COVID 19 have emerged because of a mutant variant of the virus worldwide.

However, COVID-19 is highly contagious and rapidly spreading via respiratory droplets carrying the infectious virus from close contact or droplet transmission from persons harboring the virus. Individuals of all ages are at risk of contracting this infection and severe disease.

However, patients aged ≥60 years and patients with underlying medical comorbidities (obesity, cardiovascular disease, chronic kidney disease, diabetes, chronic lung disease, smoking, cancer, solid organ or hematopoietic stem cell transplant patients) have an increased risk of developing severe COVID-19 infection. The COVID-19 infection has 14 days incubation period [5, 6]. Fever, sore throat, cough, severe headache, breathlessness, myalgia, and weakness are common symptoms observed in patients with COVID-19 [7, 8]. Many COVID-19 patients are mild, but patients with comorbidities or immune-compromised patients may become severe [9-13].

Pathophysiology: SARS-CoV-2 is encapsulated single-stranded positive-sense RNA virus, with glycoprotein spikes on the membrane giving it a crown-like appearance. SARS-CoV-2 genome is around 30 K nucleotides long. The SARS-CoV-2 viral genome has Four main structural proteins-spike surface glycoprotein(S), membrane protein (M), an envelope protein (E), and nucleocapsid protein (N) and non-structural proteins like RNA polymerase, RdRp; papain-like protease, PLpro; main coronavirus protease, 3CLpro [14]. Genotypically classification of Coronavirus is: Alpha coronaviruses (a), Beta coronaviruses (b), Gamma coronaviruses (g) and Delta coronaviruses (d) [15]. Steps of replication of SARS-CoV-2 virus are attachment, penetration, uncoating, replication, assembly, and release **Fig. 1** [16]. SARS-CoV-2 virus' Spike glycoprotein bind to angiotensin-converting enzyme 2 (ACE2) receptor and this invasion is facilitated by Serine protease TMPRSS211 of host cell; it is receptor-mediated endocytosis. After that, it releases single-stranded positive RNA, and the host ribosome translates it into viral polyproteins.

The effector proteins are formed from polyproteins by enzyme-mediated cleavage. A negative-strand RNA template is formed by RNA-dependent RNA polymerase. Viral RNA is formed from Negative strand RNA template genomic replication forms viral genome. After subgenomic transcription and translation form essential structural viral proteins. Three structural proteins (S, M, and E) are incorporated with the membrane of the endoplasmic reticulum (ER), and the endoplasmic reticulum-Golgi intermediate compartment (ERGIC) is formed. Nucleocapsid protein binds to genomic RNA and is encapsulated into ERGIC, forming mature virion. Mature virion is transported to the host cell membrane, and exocytosis of the virus occurs.

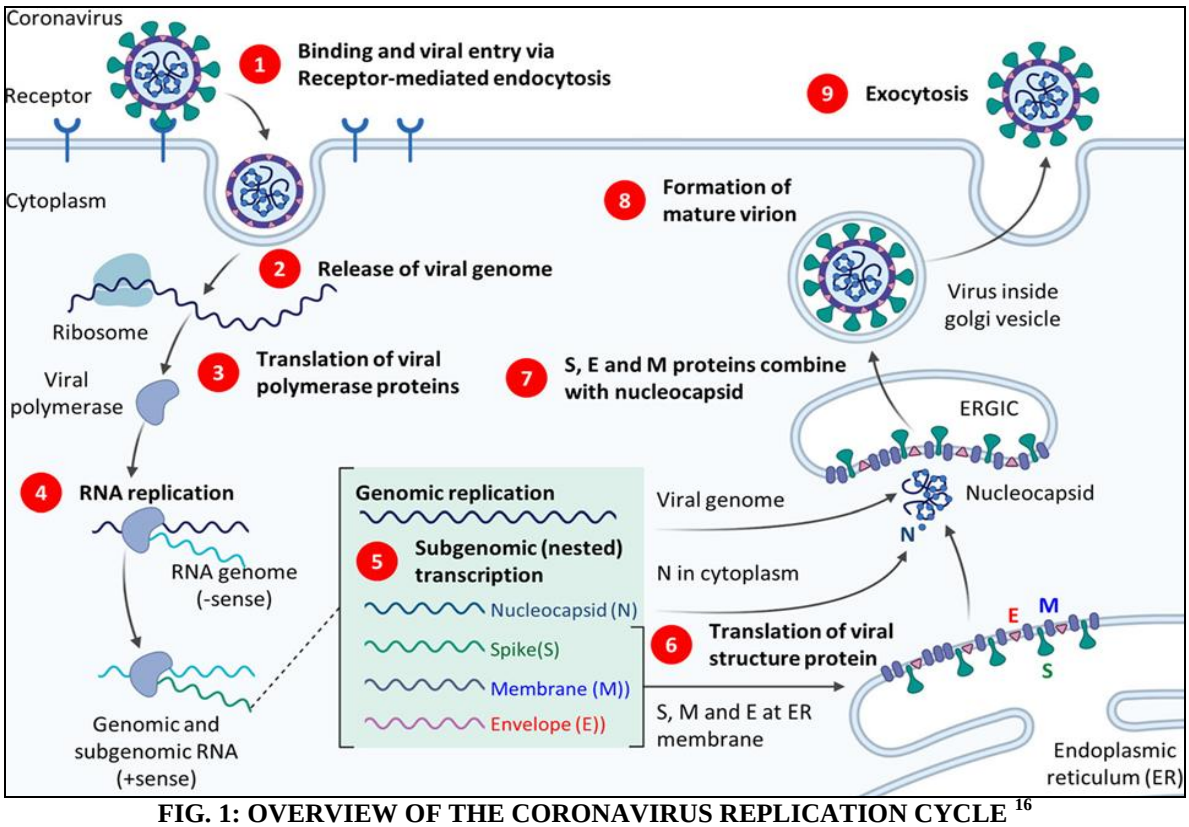


FIG. 1: OVERVIEW OF THE CORONAVIRUS REPLICATION CYCLE [16]

Clinical Manifestations of COVID-19: After exposure to the COVID-19 virus, symptoms may appear within 1- 14 days, on average patients develop symptoms after 5 days [17]. Common symptoms are fever, cough, sore throat, malaise, headache, muscle pain, anorexia, nausea, vomiting, diarrhea, anosmia (loss of smell), or dysgeusia (loss of taste) [18, 19]. Other than this confusion, hemoptysis, shortness of breath, chest tightness, conjunctivitis, rash on skin, discoloration of fingers and toes have been also observed [20, 21]. Children infected with COVID 19 have shown similar but mild signs and symptoms compared to adults [22, 23]. There are chances of venous thrombosis due to hyper-coagulation, muscle damage, neurological symptoms like fatigue, dizziness and disturbed awareness, ischemic and hemorrhagic strokes [24, 25].

TABLE 1: CLASSIFICATION OF COVID-19 AS PER THE NATIONAL INSTITUTES OF HEALTH (NIH) GUIDELINES [26]

Asymptomatic or Presymptomatic Infection	Mild illness	Moderate illness:	Severe illness	Critical illness
Individuals with positive SARS-CoV-2 test without any clinical symptoms consistent with COVID-19	Individuals who have any symptoms of COVID-19 such as fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, anosmia, or dysgeusia but without shortness of breath or abnormal chest imaging	Individuals who have clinical symptoms or radiologic evidence of lower respiratory tract disease and who have oxygen saturation (SpO2) ≥ 94% on room air	Individuals who have (SpO2) ≤ 94% on room air; a ratio of partial pressure of arterial oxygen to fraction of inspired oxygen, (PaO2/FiO2) <300 with marked tachypnea with respiratory frequency >30 breaths/min or lung infiltrates >50%	Individuals who have acute respiratory failure, septic shock, and/or multiple organ dysfunction. Patients with severe COVID-19 illness may become critically ill with the development of acute respiratory distress syndrome (ARDS) that tends to occur approximately one week after the onset of symptoms

Diagnosis of Covid-19:

A. Clinical Presentation: Median for the incubation period of COVID-19 symptoms onset is 5.1 days, and in infected people, symptoms may appear for 11.5 days which depends on patient's immune response and age [27]. Research shows Median age of COVID-19 patients is 59 years ranged from 15-89 years with a male predominance [19]. Patients presented with different symptoms like fever, headache, cough, fatigue, pneumonia, dyspnea, hemoptysis, and diarrhea [28]. The largest study of data analysis in china showed that Mortality is higher in more than 60years, and the highest case fatality rate is 14.8% in more than 80 years age group patients. COVID-19 patients with comorbid conditions hypertension, diabetes, cardiovascular disease, chronic respiratory disease, and cancer had a higher case fatality rate than without comorbid conditions [29].

B. Screening Tests for Covid-19 in Exposed Patients: Different nonspecific tests recommended in COVID 19 patients are complete blood count, C-reactive protein (CRP) and erythrocyte, sedimentation rate (ESR), D-dimer, ferritin, Creatine kinase plus myoglobin, aspartate aminotransferase, lactate dehydrogenase, and creatine phosphokinase. These tests can help to find the cause of infection. Results seen in COVID 19 patients are a low count of WBC, lymphopenia, raised erythrocyte sedimentation rate, and CRP. CRP, ESR should be repeated on the third, fifth, and seventh day of admission [30, 31]. In severe disease, there is an increased D-dimer level, elevated ferritin levels, Creatine kinase plus myoglobin, lactate dehydrogenase, creatine phosphokinase, and aspartate aminotransferase [32, 33].

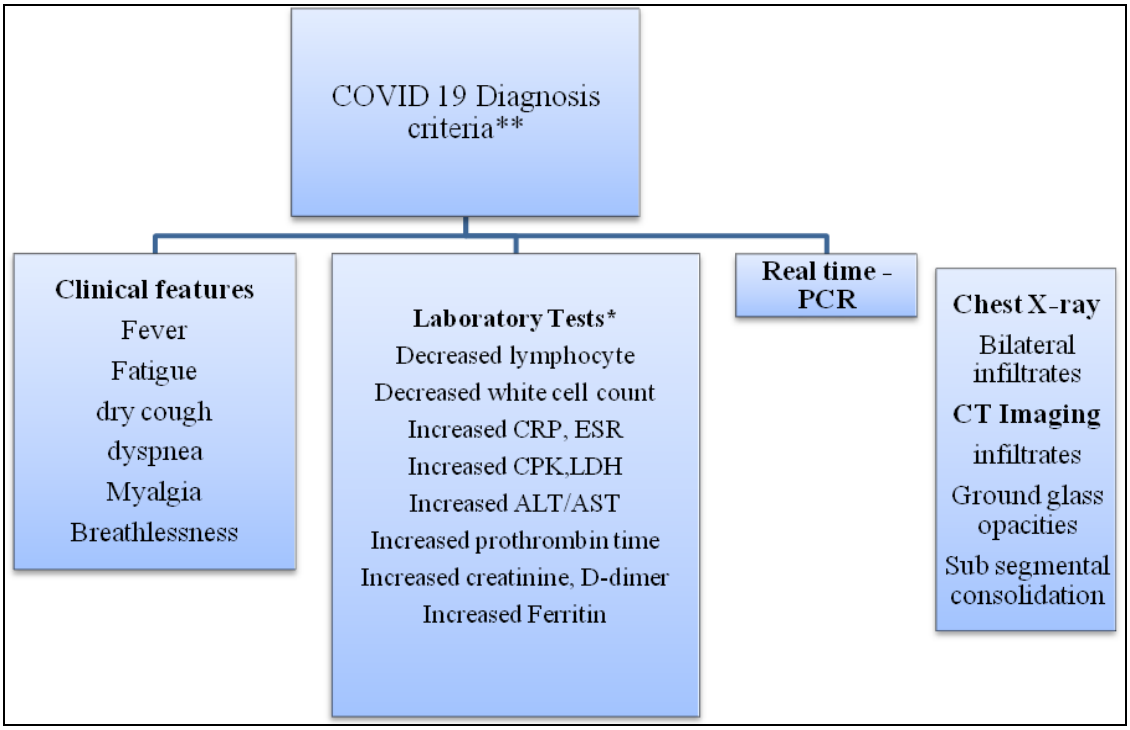
The elevated CRP can be due to the overproduction of inflammatory cytokines in severe patients with COVID-19. Cytokines are produced to fight the virus, but if the immune system is hyperactive, that can damage the lungs. A positive D-dimer result shows a high level of fibrin degradation products because of significant blood clot formation and breakdown. Elevated serum ferritin level indicates the presence of viral or bacterial infection in the body. To check virus effect in acute phase, tumor necrosis factor (TNF)-α and interleukin (IL), plasma cytokines/chemokines are measured, because inflammatory reactions can lead to

systemic inflammatory phase to prevent transmission fecal and urine test should be performed [34, 35].

C. PCR-Based Test: Currently, the reverse transcription-polymerase chain reaction (RT-PCR) is the important diagnostic test of molecular genetic assays for the detection of viral RNA from a swab sample of the patient. The sample is taken by swabbing of nose and throat. The results of the test are highly accurate. Steps of procedure in RT-PCR test are isolation of viral RNA from swab sample, and by RNA-dependent DNA polymerase reaction, complementary DNA (cDNA) is generated. In the RTPCR test, detection of template DNA requires around 25–50 cycles and more time to get the results. The cycle threshold (Ct) value of an RT-PCR reaction is the number of cycles at which fluorescence of the PCR product is detectable over and above the background signal. Ct value is inversely proportional to the presence of genetic material RNA in the sample. If Ct values are on the lower side, it shows high viral load and on the higher side shows less viral load in COVID19 Patients. There are no reliable studies to prove the association of CT value and disease severity/infectiousness. In-Patient management, CT Value, and viral load do not have much role. Patients with CT values equal to or less than 35 may be considered positive, and more than 35 are negative [36]. ICMR states that the cut-off CT value is from 35-40 for COVID 19 according to instructions by manufacturers is universally accepted.

Other tests to detect SARS-CoV-2, one-step single-tube nested quantitative real-time PCR (OSN-qRT-PCR) method designed by Wang *et al.* for the rapid results [37], reverse transcription loop-mediated isothermal amplification (RT-LAMP) test by Park *et al.* [38], reported a field-effect transistor (FET)-based biosensor for quick detection and biosensor could detect SARS-CoV-2 spike protein at a very low concentration by Seo et al. [39]. OSN-qRT-PCR can detect low viral load, so more sensitive than the other qRT-PCR methods.

D. Rapid Diagnostic tests (RDT): In RDT, Viral proteins (antigens) on COVID 19 virus present in the sample will bind with antibody fixed to paper strip in plastic casing and signal can be seen in 30 minutes. The rapid test gives results within minutes, early access, more portable, less specific, and less sensitive [40].



*CRP C-reactive Protein, ESR-Erythrocyte sedimentation rate, CPK-Creatine-phosphokinase, LDH-Lactate dehydrogenase, ALT-alanine transaminase,

AST-aspartate aminotransferase **recently some immunological and Novel techniques have been developed to diagnose COVID-19.

CT scan: Currently, CT scan is done in COVID patients to know the severity of lung involvement. In-Patient of COVID 19 CT scan shows ground-glass opacities with or without consolidations in lung regions close to visceral plural surfaces, including fissures and multifocal bilateral distribution.

In The later stage of the disease, irregular-shaped paving patterns were seen in CT scan [41, 42]. Some radiologists use Coronavirus disease 2019 (COVID-19) Reporting and Data System (CO-RADS) for pulmonary involvement of COVID-19 [43].

TABLE 2: STANDARDIZED ASSESSMENT SCHEME CORONAVIRUS DISEASE 2019 (COVID-19) REPORTING AND DATA SYSTEM (CO-RADS) [43]

CO-RAD	Level of suspicion	CT findings
CO-RAD1	No	Normal or non-infectious abnormalities
CO-RAD2	Low	Abnormalities consistent with infections other than COVID 19
CO-RAD3	Indeterminate	Unclear whether COVID 19 is present
CO-RAD4	High	Abnormalities suspicious for COVID 19
CO-RAD5	Very high	Typical COVID 19
CO-RAD6	PCR +	Definite COVID 19

TABLE 3: PROGNOSIS OF THE DISEASE CAN BE KNOWN BY CHEST CT FINDING FOR DISEASE SEVERITY AND THE PERCENTAGE OF LUNG INVOLVEMENT

CT severity score index for assessment of lung involvement in COVID 19	
Percentage of lung involvement	**Score**
<5% lobar involvement	1
5–25% lobar involvement	2
26–50% lobar involvement	3
51–75% lobar involvement	4
> 75% lobar involvement	5

In this scoring system, each lobe in five lobes of the lung is scored visually from 1-5. The total score is the addition of all lobes score that is out of 25. Severity is mild if Total score<= 7, Moderate if the total score is 8-17, severe if the total score is >=18.

Management of Covid-19 Patients: COVID-19 starts with supportive and symptomatic treatment. As soon as the patient gets an infection, patient should maintain adequate isolation to prevent transmission to other contacts, patients, and healthcare workers. Mild infection can be managed at home with counseling about danger signs. The patient should be advised to maintain hydration and nutrition, and symptomatic treatment should be given. (Fever, cold, cough, weakness, *etc*.

Pharmacological Aspects: Currently, a variety of therapeutic options that include antiviral drugs (*e.g.,* remdesivir), anti-SARS-CoV-2 monoclonal antibodies (*e.g.,* bamlanivimab/etesevimab, casirivimab/imdevimab), anti-inflammatory drugs (*e.g.,* dexamethasone), immunomodulators agents (*e.g.,* baricitinib, tocilizumab) under FDA issued Emergency Use Authorization(EUA) or being evaluated in the management of COVID-19 [45]. Treatment of COVID-19 infection is based on the severity of illness or certain risk factors. There are two phases of COVID-19 infection. 1st phase is replication, in which antiviral medications and antibody-based treatments are more effective. 2nd phase is a hyperinflammatory state (release of cytokines and the coagulation system's activation that causes a prothrombotic state) in which anti-inflammatory drugs such as corticosteroids, anticoagulants, immunomodulating therapies, or a combination of these therapies may help [40]. A summary of the latest potential therapeutic options available for the management of COVID-19 is given below:

1. Antiviral Therapies:

Remdesivir: Remdesivir is a broad-spectrum antiviral agent that demonstrated antiviral activity against various single-stranded RNA viruses [45, 46]. The SARS-CoV active metabolite of remdesivir interferes with the nsp12 polymerase, a multisubunit RNA synthesis complex of viral non-structural proteins (nsp's) produced as cleavage products of viral polyproteins. So, it inhibits the replication of the viral RNA genome, a highly conserved element of the viral life cycle.

It also causes premature termination of RNA synthesis, which will inhibit further transcription and translation processes needed to generate new virions [47]. On 22 Oct 2020 the U.S. Food and Drug Administration (FDA) approved the use of remdesivir for clinical use in adults and pediatric patients (more than 12 years and weight 40 kilograms or more) to treat admitted patients with COVID-19. It was observed during the clinical trial that recovery period of hospitalized adult patients with mild-to-severe COVID-19 was shortened with remdesivir as compared to placebo[48, 49, 50]. Remdesivir injection should be diluted in 100 ml normal saline. The recommended dose for Ramdesivir is on Day 1 loading dose: 200 mg IV infused over 30-120 min, on day followed by 100 mg IV once a day for next 4 days [51]. Patients on remdesivir should be watched for adverse drug reactions like increase in hepatic enzymes, Renal Injury (Blood creatinine increased, Glomerular filtration rate decreased, Renal failure), Respiratory failure, Tachy or Bradyarrythmia, Hypotension, Rash, Sepsis and Septic Shock, Cardiac and Cardiorespiratory Arrest, Nausea/Vomiting, Abnormal Hemogram, Multiorgan Disorder / Organ Failure, Pyrexia, Hypoxia, Diarrhea, Acidosis [52].

Favipiravir: Favipiravir is an antiviral drug that belongs to the pyrazine class, which was mainly used to treat influenza [53, 54]. It inhibits RNA-dependent RNA polymerase (RdRp), so transcription and replication of viral genomes are inhibited[55]. The recommended dosage of favipiravir for adults is 1800 mg orally twice daily (4.5 tablets of 400 mg should be taken twice a day in the morning and evening) on 1st day, followed by 800 mg orally twice daily (2 tablets of 400 mg should be taken twice a day in morning and evening), up to a maximum of 14 days. Very few adverse drug reactions have been observed, like hyperuricemia and reduced neutrophil count and transaminitis, teratogenicity [56].

Lopinavir / Ritonavir: Lopinavir / ritonavir is an FDA-approved drug for AIDS treatment. It acts on Viral proteases, so the activity of viral proteases is inhibited, and initially, it was anticipated as antiviral therapy against COVID-19 [57]. At present Lopinavir / Ritonavir is not indicated for the treatment of COVID-19.

Hydroxychloroquine and Chloroquine: were suggested as antiviral treatments in the beginning of the pandemic. But there was no improvement in hospitalized patients' status [58, 59] and did not prevent SARS-CoV-2 infection or symptomatic COVID-19 illness [60].

Ivermectin is an FDA-approved anti-parasitic drug used globally. During the early onset of the pandemic, it was used to treat COVID-19 as it inhibits SARS-CoV-2 replication. But compared to placebo, it did not achieve significant improvement [61]. So, Ivermectin is currently not indicated for the treatment of COVID-19 patients.

Zinc: Generates both innate and acquired (humoral) immunity, enhancement of the normal functioning of the innate immune system, stabilization of cell membrane inhibiting the entry of the virus (Amit Kumar). Zinc deficiency leads to an increase in pro-inflammatory cytokine (IL-1, IL-6 = and TNF alpha) concentrations and decreases the production of antibodies. When there is an increase in intracellular concentrations of zinc, it will inhibit RNA polymerase activity and viral replication [62].

Ascorbic Acid: Acts as an antioxidant by savaging Reactive oxygen species, enhances immune response. It produces type I interferons, so it shows antiviral immune response [63]. Also, vitamin C is present in the respiratory tract's epithelial lining, where it acts as a local mucosal protecting agent, reliving upper respiratory tract infection symptoms [64].

2. Immuno-Modulatory Agents:

Corticosteroids have been recommended for COVID-19 patients to prevent 'cytokine storm" and its consequences like disseminated intravascular coagulation, hypotension, ARDS, shock, and death. It happens in the early phase, around first 5 - 7 days, so steroids should be started in this time, particularly before or at the onset of dyspnea to prevent the advancement of the "cytokine storm" [65, 66]. Inflammatory lung injury can be caused due to rise in inflammatory markers in severe COVID-19 patients. A trial named "The Randomized Evaluation of Covid-19 Therapy (Recovery) trial, was done on hospitalized patients. It indicated that the use of dexamet has decreased

Mortality in patients who were on invasive mechanical ventilation or oxygen support but not in patients who were not receiving any respiratory support [67]. So, based on the severity of illness in hospitalized patients who require supplemental oxygen or non-invasive or invasive mechanical ventilation dexamet has one is currently used as the standard of care either alone or in combination with remdesivir. Recommended for the total daily dose for dexamethasone 6 mg (oral or intravenous [IV]), Prednisone 40 mg, Methyl-prednisolone 32 mg, Hydrocortisone 160mg [68].

Anti-IL-6 Receptor Monoclonal Antibodies: In COVID-19 hyper-inflammatory state is due to proin-flammatory cytokine Interleukin-6 (IL-6). So inflammation could be decreased by targeting this cytokine with an IL-6 receptor inhibitor, and it showed favorable outcomes in patients with severe COVID-19 [69, 70]. Tocilizumab, Sarilumab, Siltuximab were approved by the FDA for various rheumatological conditions.

Tocilizumab is an anti-interleukin-6 receptor alpha receptor monoclonal antibody; the data regarding the use of this agent is mixed. It was observed that to cilizumab did not show significant improvement in clinical status or lower the 28-day Mortality compared to placebo [71] another study showed that the use of tocilizumab was not effective in preventing intubation or death rate [72]. It recommended dose 4 to 6 mg/kg (400 mg in 60 kg adult) in 100 ml NS over 1 hour.

Sarilumab and Siltuximab are IL-6 receptor antagonists that may have a similar effect on the hyperinflammatory state associated with COVID-19 as to cilizumab. A trial was done, but patients did not significantly improve clinical status or mortality rate [73].

3. Anticoagulants: In COVID-19 patients, there is an increased risk of thrombosis. Heparin prevents clot formation and resolves the clots present inside the blood. To prevent venous thromboembolism, patients admitted in ICU with a lower risk of bleeding should be administered low-intensity pharmacological prophylaxis comprising of low-molecular-weight heparin (dalteparin 5000 IU/day OR nadroparin 65 IU/kg/ day, OR enoxaparin 40 mg/day) along with low-dose unfractionated heparin (5000 units two times a day) [74].

4. Convalescent Plasma therapy was evaluated, but its actual efficacy was not proven. For serious COVID-19 patients, convalescent plasma therapy was approved under EUA by the FDA[75]. However, no significant difference was observed in clinical improvement or overall Mortality by use of convalescent plasma compared to standard therapy in serious COVID-19 [76, 77]. ICMR did a trial named PLACID trial, and it was observed there was no significant improvement by the use of plasma, so ICMR has dropped the use of plasma from the recommended treatment guidelines of COVID-19 [51].

5. Anti-SARS-CoV-2 Neutralizing Antibody Products: Neutralizing antibodies developed against SARS-CoV-2 in patients recovering from COVID-19, but the duration of how long this immunity persists is not clear.

REGN-COV2 (Casirivimab and Imdevimab): REGN-COV2 is a cocktail antibody with two IgG1 antibodies (casirivimab and imdevimab) that act on the SARS-CoV-2 spike protein that lower the viral load and prevents virus-induced pathological sequelae [78]. A clinical trial demonstrated the REGN-COV2 antibody reduced viral load compared to placebo [79]. There was 70% fall in hospitalization or death in nonhospitalized patients with COVID-19. REGN-COV2 also affects the two new SARS-CoV-2 variants of concern (B.1.1.7; B.1.351 variants).

Bamlanivimab and Etesevimab Baml-anivimabis derived from convalescent plasma of COVID-19 patients. Like REGN-COV2, it also acts on the spike protein of SARS-CoV-2 decreases viral replication (59, 60) *While* tesevimab binds to a different epitope than bamlanivimab and neutralizes resistant variants with mutations in the epitope bound by bamlanivimab [80]. Bamlanivimab / etesevimab is effective on the new SARS-CoV-2 variants of concern (B.1.1.7; B.1.351) [81]. The FDA has approved REGN-COV2 (casirivimab and imdevimab) and bamlanivimab / etesevimab under two separate EUAs issued in Nov 2020 and Feb 2021. They can be used only in mild to moderate, nonhospitalized COVID -19 patients (aged more than 12 years and weighing ≥40 kg) and at high risk of progressing to severe disease and/or hospitalization.

Oxygenation and Ventilation Management in COVID-19:

Conventional Oxygen Therapy: With continuous pulse oximetry, COVID-19 patients should be watched closely. Supplemental oxygen supplementation via nasal cannula or venturi mask must be administered to maintain oxygen saturation (SpO2) between 92 to 96% (< 88-90% if COPD). It should be checked periodically; if there is improvement in clinical and oxygen saturation, supplemental oxygen should be continued. High-Flow Nasal Cannula (HFNC) or Noninvasive Positive Pressure Ventilation (NIPPV) should be used if there is no clinical improvement or worsening of symptoms and/or oxygen saturation.

Management of Acute Hypoxemic Respiratory Failure in COVID-19: Most common complication in adult patients with COVID-19 in acute hypoxemic respiratory failure and conventional oxygen therapy is not helpful, so these patients should be managed with endotracheal intubation, a high-flow nasal cannula (HFNC), noninvasive positive pressure ventilation (NIPPV) and invasive mechanical ventilation (IMV) or extracorporeal membrane oxygenation (ECMO**).**

High-Flow Nasal Cannula (HFNC) and Noninvasive Positive Pressure Ventilation (NIPPV): In selective patients with COVID-19-associated acute hypoxemic respiratory failure, HFNC and NIPPV (bilevel positive airway pressure [BiPAP] / continuous positive airway pressure [CPAP]) are noninvasive enhanced respiratory support modalities available to avoid invasive mechanical ventilation. It was observed when HFNC was used before mechanical ventilation it could improve the prognosis of patients compared to conventional oxygen therapy and NIPPV [82].

Endotracheal Intubation and Lung Protective Invasive Mechanical Ventilation: In case of Impending respiratory failure, it should be identified immediately, and endotracheal intubation should be performed [83].

- Preoxygenation (100% O_2 for 5 min) should be performed via HFNC.
- Use of neuromuscular blocking agents (NMBA) should be used as needed to facilitate lung-protective ventilation.
- The National Institutes of Health (NIH) Covid-19 Treatment Guidelines Panel recommends against inhaled pulmonary vasodilators such as nitric oxide.

ICMR Guideline for Management of Adult Covid-19 Patients:

Mild disease:

Sign & Symptoms: Upper respiratory tract symptoms (&/or fever) WITHOUT shortness of breath or hypoxia

Management: Home Isolation & Care Physical distancing, indoor mask use, strict hand hygiene.

Symptomatic management (hydration, antipyretics, antitussive, multivitamins). Stay in contact with the treating physician. Monitor temperature and oxygen saturation.

Seek immediate medical attention if Difficulty in breathing, High-grade fever/severe cough. A low threshold is to be kept for those with any of the high-risk features.

Therapies based on low certainty of the evidence

- Tab Ivermectin (200 mcg/kg once a day for 3 days). Avoid in pregnant and lactating women. OR
- Tab HCQ (400 mg BD for 1 day f/b 400 mg OD for 4 days) unless contraindicated.
- Inhalational Budesonide (given via Metered dose inhaler/ Dry powder inhaler) at a dose of 800 mcg BD for 5 days) to be given if symptoms (fever and/or cough) are persistent beyond 5 days of disease onset.
- High-risk for severe disease or Mortality: Age > 60 years, Cardiovascular disease, hypertension, and Coronary artery disease, DM (Diabetes mellitus) and other immuno-compromised states, chronic lung/kidney/liver disease, Cerebrovascular disease, obesity.

Moderate disease

Sign & Symptoms: Any one of Respiratory rate > 24/min, breathlessness,

SpO2: 90% to < 93% on room air

Management: Admit in Ward

Oxygen Support:

a. Target SpO2: 92-96% (88-92% in patients with COPD).

b. Preferred devices for oxygenation: non-rebreathing face mask.

c. Prone position is encouraged in all patients requiring supplemental oxygen therapy (sequential position changes every 2 hours).

d. Anti-inflammatory or immunomodulatory therapy: Inj. Methylprednisolone 0.5 to 1 mg/kg in 2 divided doses (or an equivalent dose of dexamethasone), usually for a duration of 5 to 10 days. Patients may be initiated or switched to the oral route if stable and/or improving.

e. Anticoagulation: Conventional dose prophylactic unfractionated heparin or Low Molecular Weight Heparin (weight-based, *e.g.,* enoxaparin 0.5mg/kg per day SC).

f. There should be no contraindication or high risk of bleeding.

Monitoring:

- Clinical Monitoring: Work of breathing, Hemodynamic instability, Change in oxygen requirement.
- Serial CXR; HRCT chest to be done ONLY If there is worsening.
- Lab monitoring: CRP and D-dimer 48 to 72 hrly; Complete blood count, Kidney function test, Liver function test 24 to 48 hrly; IL-6 levels to be done if deteriorating (subject to availability).
- After clinical improvement, discharge.

Severe disease:

Sign & Symptoms: Any one of Respiratory rate >30/min, breathlessness, SpO2 < 90% on room air

Management: Admit in ICU

Respiratory Support:

a. Consider using Non invasive ventilation (Helmet or face mask interface depending on availability) in patients with increasing oxygen requirement if work of breathing is LOW.

b. Consider the use of HFNC in patients with increasing oxygen requirements.

c. Intubation should be prioritized in patients with high work of breathing /if Non invasive ventilation is not tolerated.

d. Use conventional ARDS net protocol for ventilator management.

e. Anti-inflammatory or immunomodulatory therapy: Inj Methylprednisolone 1 to 2mg/kg IV in 2 divided doses (or an equivalent dose of dexamethasone), usually for duration 5 to 10 days.

f. Anticoagulation: Weight-based intermediate dose prophylactic unfractionated heparin or Low Molecular Weight Heparin (e.g., Enoxaparin 0.5mg/kg per dose SC BD). There should be no contraindication or high risk of bleeding.

g. Supportive measures: Maintain euvolemia (if available, use dynamic measures for assessing fluid responsiveness).

h. If sepsis/septic shock: manage as per existing protocol and local antibiogram.

Monitoring:

- ✓ Serial CXR; HRCT chest to be done only if there is worsening.
- ✓ Lab monitoring: CRP and D-dimer 24-48 hourly; CBC, RFT, LFT daily; IL-6 to be done if deteriorating (subject to availability).
- ✓ After clinical improvement, discharge.

Emergency Use Authorization (EUA) / Off label use (based on limited available evidence and only in specific circumstances):

1. Remdesivir (EUA) may be considered ONLY in patients with

- Moderate to severe disease (requiring supplemental oxygen)

- No renal or hepatic dysfunction (eGFR<30 ml/min/m2; AST/ALT >5 times ULN (Not an
- absolute contradiction), and
- Who are within 10 days of onset of symptom/s.

2. Recommended dose: 200 mg IV on day 1 f/b 100 mg IV OD for next 4 days.

Not to be used in patients who are NOT on oxygen support or in-home settings.

3. Tocilizumab (Off-label) may be considered when all of the below criteria are met

- Presence of severe disease (preferably within 24 to 48 h of onset of severe disease / ICU admission).
- Significantly raised inflammatory markers (CRP &/or IL-6).
- Not improving despite the use of steroids.
- No active bacterial / fungal / tubercular infection. Recommended single dose: 4 to 6 mg/kg (400 mg in 60kg adult) in 100 ml NS over 1 h.

CONCLUSION: COVID-19 is a highly contagious disease that spreads very fast in the community & leads to High morbidity and mortality in affected individual. So, it is very important to diagnose & start management of COVID 19 as early as possible. This leads to decrease mortality and morbidity due to COVID-19. We should wear mask, regular hand washing by hand sanitizer, maintain social distance as a prevention of spread of infection.

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