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Review Article

COVID-19 Infection: An Overview of Pathophysiology, Management, and Complications

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Abstract

COVID-19 has been the most common infection worldwide for the last two years, with many clinical manifestations, complications, comorbidities, and high mortality. Cardiac and pulmonary complications contribute the most towards morbidity mortality and pose great difficulty in the management. In addition, the disease has badly damaged the global economy and lifestyle. Recently, there have been many updates in the preventative and pharmacological options available for COVID-19 disease, including vaccines and biological drugs.

This review article focuses on the pros and cons of the main aspects of the disease, its complications, and management, options currently used to manage. This article is a general review, and the management guidelines are different in different parts of the World. Hence, the reader should consult local health guidelines to manage their patients.

Keywords: COVID-19, Coronavirus, COVID-Vaccines, COVID-complications, COVID-management.

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Introduction

Coronoa Virus (Covid-19)

Why Called Corona?

Corona is derived from the crown, the club-shaped glycoprotein projections on its envelope.

Source

Corina viruses are a disease of humans and other mammalian species & are antigenically related. There is no evidence to support that animals can transmit the human variety of coronavirus.[1]

Virus Structure

It's a spherical-shaped RNA virus with a single positive-sense RNA associated with nucleoprotein. The core of the matrix protein surrounds it, and an outer lipid bilayer envelop it. The envelope is studded with glycoproteins responsible for the attachment of the virus to the host cells.[1,2]

1. **Spike protein (S):** it projects through the envelope & forms characteristic spikes in the crown of the virus. It's a major antigen of the virus. It mediated binding with the receptor on the host cell membrane.
2. **Membrane protein (M):** C terminal is inside the envelope, and N terminal projects out of the envelope. M protein spans the envelope three times and helps the viral assembly.
3. Envelop (E) protein has many similarities in its role and location with M protein. It also has a C terminal inside the envelope, and N is projecting out and spans the envelope. It also helps viral assembly.
4. Nucleocapsid protein (N) is associated with RNA. It regulates RNA replication & also interacts with M protein for viral division.
5. Haemagglutinin-Esterase Glycoproteins (HE) is present only in the beta coronavirus. It has homology with the influenza HE Glycoproteins & helps in recombination between the two viruses. It helps with viral adsorption with the host cell membrane.[2]

Serotypes of Coronavirus

- **Alpha coronavirus:** there are two human varieties

(229E & Nl63). 229E uses aminopeptidase N as its receptor, whereas NL63 uses ACE 2. Alpha coronavirus is also present in animals, including bats, pigs & felines.

- **Beta coronavirus:** Two non-SARS human species are OC43 & HKU1. The beta virus also has bat viruses, MERS-CoV, SARS-CoV & SARS-CoV2. Both have HE protein and use Sialic acid as its receptor.
- **Gamma Corona Virus:** it's primarily a virus in the birds & causes bronchitis, lower respiratory, and genital infection.

Variants of concern (VOC)

VOC are the variants that can interfere with diagnostic testing, have low vaccine response, or be highly transmissible. They can also have reduced neutralization by antibodies produced by infection or vaccine—also, reduced response to monoclonal antibodies used for treatment. Previously the VOCs in 2020 were alpha, beta, and gamma variants. According to the CDC statement, there are two current VOCs [Tab.1].

- Omicron (B.1.1.529) is a recent variant discovered in SA with a high transmission rate. It also has lower neutralization with monoclonal antibodies. Also, the post-vaccine serum has a lower neutralizing ability against this variant. Production of neutralizing antibodies is considerably less, but Immunity is provided by the T cells and helps against severe disease.[3]
- Delta (B.1.617.2) was discovered in India. It also has a high transmission and reduced neutralization by post-vaccination serum. However, most of its variants are not resistant to monoclonal antibodies used against the virus.

Vaccines are still effective in reducing severe disease but have no protection against mild to moderate diseases.

Mode of Transmission

Aerosols are less than 5um, and droplets are more than 5um in size.

1. Aerosol transmission / airborne transmission (particles of less than 5 um size) spread is a risk for COVID 19, and that's the reason level 3 PPE is recommended for any procedure which can generate aerosol such as intubation, mechanical ventilation, CPR, tracheostomy, nebulization, suctioning of secretions, non-invasive ventilation such as BIPAP.
2. More Common mode is droplet (more than 5um size particles) transmission, which is settled on skin or fomites or mucous membrane or objects we touch when someone coughs or sneezes.
3. Some studies are saying intestinal infection too, and maybe that route may emerge too but not confirmed at this stage. It can be stable for up to 5 days or even seven days.[3,4]

How does COVID-19 escape Immunity & why the COVID-19 virus has limited neutralizing antibodies?

Neutralizing antibodies are directed against the receptor-binding motif located in the receptor-binding domain of the virus. These antibodies block the receptor-binding motif (RBM) of the COVID-19 virus to ACE-2 (Angiotensin Converting Enzyme-2), the viral receptor on target cells. The receptor-binding motif (RBM) comprises 70 amino acids and is the actual part of the RBD, which interacts with ACE-2. RBD of the virus had multiple epitopes and is located at the top of the virus's Spike (S) protein. This complex (S protein with RBD having RBM) is the virus's Achilles to bind with the target cell. Then this S protein is cleaved by furin & serine protease enabling the fusion of the viral & host cell membrane, a step needed for the viral RNA to enter into the host cells. This cleavage of the S protein may also be a target for neutralizing antibodies. Neutralizing antibodies against the COVID virus are produced at lower amounts and rapidly wane. Some patients become

Table 1: *Currently Designated Variants of Concerns (VOCs) by CDC*

WHO Label	Pango Lineage	GISAID Clade	Nexrstrain Clade	Additional amino acid changes	Earliest documented samples	Date of designation
Alpha	B.1.1.7	GRY	201(V1)	+S:484K +S:452R	UK Sep-2020	18/12/2020
Beta	B.1.351	GH501Y.V2	20H(V2)	+S:L18F	South Africa May-2020	18/12/2020
Gamma	P.1	GR/501Y.V3	20J(V3)	+S:681H	Brazil Nov-2020	11/01/2021
Delta	B.1,617.2	G/478K.V1	21A, 211, 21J	+S:417N +S:484K	India Oct-2020	VOC 11/05/2021
Omicron	B.1.1.529	GRA	21K, 21L, 21M	+S: R346K	Multiple countries Nov-2021	VOC 26/11/2021

negative for antibodies, and also some patients get reinfection within months.[5]

Normal RNA viruses are 25-50 nm in diameter, whereas COVID has 100nm. Other RNA viruses have 10000 genes in RNA, whereas COVID has 30000 genes and a very well-established proofreading system required for keeping the viral population viable based on genomic stability. Due to limited genomes, many other RNA viruses can't make complex surface proteins. Still, the COVID-19 virus has a much larger genetic material, which helps the virus to make complex RBD on S proteins and deceive the immune system. This also helps the virus escape the immune response by changing its antigens.

Receptor Binding Domain (RBD) sits on top of the spike (S) protein 20 nm long, making it away from the lipid bilayer. S proteins & the RBD at the top of S proteins are loosely fitted in the lipid bilayer membrane, which helps them move away. These S proteins & RBD are spaced at an ab interval of 25nm (unlike other viruses where proteins in the membrane are at 5nm distance & more compact).

These non-rigid S protein arrangements, which are lesser in number and are widely spaced, are inefficient in cross-linking with B-cells receptors or natural IgM antibodies required for complement activation and induction of long live plasma cells. This is one mechanism of how the COVID-19 virus can avoid potent neutralizing antibodies response by diluting its Achilles heel (RBD on S protein) in a sea of lipid & other proteins. Immune stimulation against other viruses is better when their immunon (epitomes/antigens on the surface) are spaced at 5-10 nm & are more in number. Both are needed for efficiently cross-linking with B-cell receptors & also being recognized by natural IgM for complement activation needed for long live plasma cells. It's a known fact that reducing the epitope density in a molecular structure increases tolerance & increasing the density increases immunogenicity. Hence, the epitome in low numbers in the COVID-19 virus may inhibit rather than activate B-cells.[4,5]

Variable results about the neutralizing antibodies response are also multifactorial: 1): lack of long-term follow-up. 2): miner symptoms when a virus is limited to the upper respiratory tract also have short-lived antibodies response. 3): lack of standardized methods used to measure these antibodies. Antibody production has an early short-lived plasma cells response followed by a second wave of antibodies produced by long live plasma cells. Hence, when antibodies are measured, they may fall in either phase and affect the titer. Also, the gold standard method to measure antibodies is by using an alive virus, which is not practical in many labs as it needs level 3 safety precautions. Instead of other such as ELISA or pseudotype neutralizing assay) which are useful but less meaningful than the standard gold test. Patient factors such as genetic variants in the innate immune system (especially interferon pathways) are also important for immune escape. Also, many COVID cases have impaired T cell response to the virus. Likely, T cells may also have a protective role against the virus. Non-neutralizing antibodies may also have some role in viral protection.[6]

Clinical Presentation of COVID-19

When to Suspect Covid-19:

1: Any sepsis without clear source OR any unexpected rapid deterioration in any patient, especially with code blue, etc. Patients admitted in ER or wards for some other reason may be in a career state when they present; hence, any unexpected deterioration down the track should alert us.

2: High CRP with normal CBC: Low platelet or low WCC should also suggest viral. This is due to the IL-6 related effect, one of the cytokines produced by this virus.

3: Any respiratory symptom (nasal, sinuses, throat, airways, or lung parenchyma). Even anosmia could be a symptom.

4: Travel or exposure history is very helpful, but its absence doesn't exclude it.

Use common sense. The above clues are important to keep in mind.

COVID & Respiratory Tract

Fever, flu-like symptoms, myalgia may be very severe but don't quantify the disease extent. Loss of smell and taste are common symptoms too. Interstitial pneumonitis & progressive disease with bilateral multilobar pneumonia are common lower respiratory tract involvement.

Lower Respiratory symptoms & signs:

1): Cough is lower respiratory tract symptoms (larynx to alveoli). So the presence of cough means the lower respiratory tract is getting involved.

2): Dyspnoea; it's less common in young people as the lungs have many reserves. Hence they don't get dyspnoea unless significant lung disease is there. Hence, the absence of dyspnoea or desaturation in a young person doesn't exclude lung involvement.

3): Pleuritic pain would mean pleura involvement which often happens after alveolar involvement or Pulmonary Embolism. Hence pleuritic pain is a serious symptom.

4): Crackles on auscultation means alveolar pathology.[4,5,6]

COVID & Hypoxia

High A-a gradient on ABG indicates an interstitial pathology, and nowadays, COVID-19 comes on top in the setting of acute infections.

Oxygen saturation: Normal O2 saturation doesn't exclude hypoxemia because unless PaO_2 drops below 60, oxygen saturation will stay at 95%. Saturation dropping below 95% means PaO_2 is below 60 mmHg as we need 60 mm Hg of PaO_2 for 95% Saturation. A young person's lungs can compensate a lot; hence normal saturation in someone with previously healthy lungs doesn't exclude lung involvement.

Increased A-a gradient and drop in PaO_2 is the first thing that would happen in pneumonia.[3,5,6]

Workup for COVID

Lab Tests:

CRP: unlike other viral infections that usually don't cause very high CRP, COVID cases often have high CRP due to IL-6 production (IL-6 is one of the major cytokines involved in the storm and disease progression). Hence rise in CRP is a poor prognostic factor.

Elevated D-Dimer with Relatively Normal PT & APTT: COVID causes increased clotting factors; hence, PT and APTT stay relatively normal despite the extensive thrombotic process. Hence normal PT & APTT in such cases doesn't exclude coagulopathy. A rise in D-Dimer is a poor prognostic factor. Also, tissue factor is produced in large quantities, and heparin (or LMWH) is the main anticoagulant that can work against tissue factors. Hence LMWH is the anticoagulant of choice (Heparin works too but increases the exposure of health care workers to patients due to the need for monitoring. Hence LMWH is a better choice over heparin).

Ferritin rises as a result of macrophages' response to COVID infection. High Ferritin is a poor prognostic factor.

Full Blood Count: Low platelet count, neutropenia & lymphopenia can be seen. Neutrophilia will usually indicate superadded bacterial infection.

PCR:

Positive PCR on the nasopharyngeal swab, Throat Swab, or sputum can confirm the infection. A negative PCR from the upper respiratory tract has only 70-80% sensitivity, so repeat PCR at least twice if strongly suspect. Sensitivity increases if it's done on lower respiratory secretions. Negative PCR doesn't exclude COVID-19 if there is strong suspicion. If PCR is negative but clinical suspicion is high, repeat the PCR, which should be repeated thrice with an interval of 2-3 days when suspicion is high.[5,6,7]

Radiological Investigations

Normal X-ray or HRCT in the early few days doesn't exclude lung involvement as radiological changes are a bit late to appear than clinical signs. HRCT has a sensitivity of 90% or above. HRCT after a few days of the onset of symptoms is a very sensitive test to do in such cases even if there are no clinical symptoms & also even if the chest X-ray is normal. HRCT may also show classic lung changes in cases where the PCR test is negative. Everyone who can afford & where available should have HRCT, especially when respiratory symptoms are present.

X-ray or HRCT showing bilateral interstitial changes, consolidation (s), ground-glass opacities. Sub pleural infiltrates classic findings, often multifocal and often bilateral. But can be unilateral and can be central as well. Classic bilateral interstitial acute pneumonitis changes without any reduction in lung volume are classic for viral pneumonia. If it's progressing to lobar pneumonia, it indicates progressive disease.[4,6,7,8]

Dengue Virus vs COVID: A Dilemma of Developing Countries

Dengue is a non-localizing fever with cytopenia, capillaries leakage, & capillary rupture with bleeding are the main issues. Dengue starts from blood and then goes to other organs. Consequences of capillary leakage are hypovolemia, hypotension, haemoconcentration & third spacing of the fluid in body cavities. In contrast, COVID starts from the upper & lower respiratory tract first and then spreads to the blood and other organs. Hence lungs are the main focus. Covid produces a lot of cytokines as well, affecting the clotting system, CRP, etc.

- Dengue is transmitted by mosquito bites (not through droplets). Hence mosquito exposure may be there in Dengue. COVID is a droplet infection.
- COVID classically starts as a flu-like illness (no rigors in early-stage, and fever gradually builds up in the next 2-3 days). Dengue causes high-grade fever to start with shivering (rigors like malaria) as Dengue is a blood infection at the start & the patient had multiple temperature spikes in 24 hours. Usually, the temperature doesn't settle down in b/w major spikes.
- Dengue doesn't affect the taste or smell & doesn't usually cause a sore throat. COVID does.
- Dengue doesn't make clots & hence clotting tests or D-Dimer are not high in an uncomplicated Dengue. Instead, it causes bleeding and capillary leakage (hence pleural effusions, ascites, and skin edema). Uncomplicated COVID usually doesn't bleed and doesn't cause capillary leakage syndrome

but makes clots and affects clotting tests & D-Dimer.

- Dengue affects the upper abdomen more (like persistent vomiting, liver involvement, and hepatomegaly). COVID mostly gives flue-like symptoms and focuses mainly on the lungs (cough, oxygen drop, dyspnoea, chest pain). In contrast, Dengue comes to the lungs when it's complicated like ARDS (lungs are usually not involved to start with as Dengue is blood infections which later settles to organs in complicated phase).
- Dengue causes severe bones and abdominal pain caused by capillary blockage and ischemia. It's also called bone-breaking fever. Pain can be as worse as that of a fractured bone. COVID generally causes more muscle aches and pains or chest pain.
- Blood counts (platelets & neutrophils) often drop in Dengue. However, Haemoconcentration (high hematocrit) due to plasma leakage is seen in Dengue but usually not in Covid. COVID can cause thrombocytopenia too.
- Dengue usually doesn't cause very high CRP. Covid does cause high CRP-like bacterial infections due to IL-6 production as part of cytokines production. COVID also causes high Ferritin, LDH, D-dimers & IL-6.
- Whereas COVID classically affects lungs first and then the rest of the body and causes peripheral (subpleural) opacities on HRCT or X-ray. Dengue doesn't cause peripheral (sub-pleural) lung involvement on X-ray or HRCT. It causes more like ARDS picture and lungs are involved as a complication, not as a starting organ.
- Testing for viral antigens (NS1 etc., for Dengue) & viral PCR can confirm too. For COVID, PCR may be negative in patients with lungs, but upper airways are spared. Hence PCR negatively doesn't exclude COVID in patients with classic lung involvement.
- Treatment is mainly supportive for both, but Dexamethasone is recommended when COVID involves lungs or other organs, whereas it's not recommended for Dengue. Ramedesivir for early COVID infection is also used. IL-6 blockers can be used for severe COVID with cytokines storm, severe lung involvement, organ involvement, or pre-ventilator stage.
- Certainly, both can co-exist, especially in Pakistan during this time. Tests and clinical judgment should help.[3,6,7,9]

Treatment of COVID-19

Since the COVID-19 pandemic, several trials and studies have been conducted, including previously used drugs for other indications and new novel therapies. Success remains somewhat variable. Vaccination against SARS-CoV-2 significantly impacts case numbers, hospitalizations, and deaths in more affluent countries, but poorer populations remain vulnerable due to limitations in access to vaccinations. COVID-19 infection can be asymptomatic but symptomatic disease ranges from mild to severe [Table II].

Asymptomatic Disease:

A meta-analysis indicated an overall estimate of 31% of asymptomatic disease in screened populations with prediction intervals ranging between 26 – 37%[1]. Other systematic reviews found that between 14 – 25% of people remained asymptomatic throughout the infection.[10,11] Whole cohort testing, for example, in the Diamond Princess Cruise ship found an asymptomatic proportion (among all infected cases) of 17.9% (95% CI: 15.5 – 20.2%).12.

Symptomatic Disease

Among symptomatic individuals, most people develop the only mild disease (40%) without evidence of viral pneumonia/hypoxia or moderate disease (40%) with clinical signs of pneumonia (fever, cough, dyspnea, fast breathing) but no signs of severe pneumonia, including SpO2 >90% on room air. Approximately ~15% develop a severe disease requiring oxygen support with less than 90% oxygen saturation on room air, signs of pneumonia, and severe respiratory distress. 5% of individuals have a critical symptomatic disease requiring life-sustaining treatment with multiple complications. These complications include respiratory failure requiring ventilatory support, acute respiratory distress syndrome (ARDS), sepsis and septic shock, thromboembolism, or multi-organ failure, including acute kidney injury (AKI) requiring kidney replacement therapy and cardiac injury[4]. One can imagine that these proportions will vary according to therapeutic interventions, surveillance strategies, demographics, vaccination rates in the community, and evolving SARS-CoV-2 variants.

Implementation of appropriate infection control and prevention measures

The universal use of the mask is required in health care facilities (wearing a mask at all times except when eating or drinking) for all people, including staff, patients, visitors, service providers, and others[13] as well as rational and proper use of all personal protective equipment (PPE).[13]

Treatment of mild COVID-19: symptomatic treatment

Mild disease is characterized by fever, malaise, cough,

and upper respiratory symptoms without dyspnea. Patients with the mild disease should be isolated to contain virus transmission. In most cases, this can be done at home (self-isolation). Symptomatic treatment with antipyretics (paracetamol) for fever and pain is reco mmended. Non-steroidal anti-inflammatories (NSAIDs) can be given if required. Appropriate nutrition and rehydration are important components of symptomatic management of mild COVID-19. Patients should be counseled about the symptoms and signs indicative of complications that prompt urgent medical care. Antibiotics or prophylaxis is not recommended in patients with mild disease.

Treatment of moderate COVID-19: pneumonia treatment

All patients should be isolated to prevent the transmission of the virus. In non-hospitalized patients, pulse oximetry monitoring at home is suggested, along with appropriate education, counseling, and follow-up. Antibiotics should not be prescribed as a default unless there is clinical suspicion of a bacterial infection. A recent systematic review of hospitalized patients reported only 8% experiencing bacterial/fungal co-infection during hospital admission.[14] In geriatric patients, particularly those in long-term care facilities, children under five years of age, and if a diagnosis is uncertain, empirical antibiotics for community-acquired pneumonia should be considered.[15,16] Venous thromboembolism prophylaxis with low molecular heparin or unfractionated heparin is recommended for all hospitalized patients.

The optimal approach to the treatment of COVID-19 is evolving, and the therapeutics used will vary depending on local availability in different countries.

Dexamethasone

Trial data suggest a mortality benefit with Dexamethasone for those on supplemental oxygen or ventilatory support, dose 6 mg daily for ten days or until discharge. Similarly, mortality benefit is shown with adjunctive Tocilizumab or baricitinib and a possible clinical benefit with Ramdesivir (especially for patients on low-flow supplemental oxygen). Trial data suggest that Dexamethasone improves mortality in patients on non-invasive oxygen supplementation. A recent meta-analysis that included over 1700 critically ill patients with COVID-19 patients demonstrated glucocorticoids reduced 28-day mortality.[17,18]

Baricitinib

Baricitinib is a Janus Kinase (JAK) inhibitor that has been used for the treatment of rheumatoid arthritis. Apart from immuno-modulatory effects, it is thought to have an antiviral effect as it interferes with viral entry. Baricitinib is an option for patients requiring high-flow oxygen or non-invasive ventilation and for selected patients who are on low-flow oxygen but are progressing toward needing higher levels of respiratory support despite the initiation of Dexamethasone[19,20] Baricitinib is also a reasonable alternative to Tocilizumab if it is not available. The dose is 4 mg orally once daily for up to 14 days. The dose is reduced in patients with renal insufficiency and is not recommended if the estimated glomerular filtration rate (eGFR) is <15 mL/min per 1.73 m^2.

Remdesivir for treatment of moderate to severe COVID-19 infection

Remdesivir is a nucleotide analog that inhibits SARS-CoV-2 RNA polymerase causing premature termination of RNA transcription. It has shown in vitro activity against SARS-CoV-2. Remdesivir is recommended in adults aged ≥ 18 years, or aged ≥ 12 and < 18 years of age weighing ≥ 40 kg hospitalized with confirmed SARS-CoV2 with oxygen saturation (SpO_2) ≤ 92% on room air and requiring supplemental oxygen and evidence of pneumonia.[21-23] Side effects include nausea, vomiting, and transaminase elevations. It is not recommended in patients requiring intubation.

Dosage: For adults and children aged ≥ 12 years and weighing ≥40 kg

- For patients requiring mechanical ventilation - 200mg IV on day one then 100mg intravenously daily for a total 10-day course.
- For patients not requiring mechanical ventilation - 200mg IV on day one then 100mg daily for a total 5-day course (a further four days of 100mg daily).
- If the patient does not demonstrate clinical improvement, treatment may be extended by up to a further five days, i.e., up to a total of 10 days.

Contraindications

- Hypersensitivity to any component of the product
- Pediatric patients weighing less than 40kg
- Renal impairment - remdesivir is not recommended in patients with eGFR < 30mL/min unless the potential benefit outweighs the potential risk
- Hepatic impairment – do not use in patients with ALT ≥ five times the upper limit of normal (ULN). Discontinue therapy in patients who develop ALT > five times ULN or ALT elevation accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or INR
- Co-administration of remdesivir and chloroquine phosphate or hydroxychloroquine sulfate is not recommended as it may result in the reduced antiviral activity of remdesivir

Use of monoclonal antibodies

Monoclonal antibodies targeting the spike protein of SARS-CoV-2 are one of the first-line COVID-19-specific treatment options for symptomatic outpatients with risk factors for severe disease.[24-26] These agents are expensive, have limited availability, require parenteral administration, and must be given early in the course of illness.

Casirivimab-imdevimab

In phase 3 randomized controlled trial with mild to moderate COVID-19 and one or more risk factors for severe disease, combination Casirivimab-imdevimab, at two different doses (1200 and 2400 mg total doses) administered intravenously within seven days of symptom onset was compared with placebo. At 29 days, there was a reduction in the combined outcome of hospitalization and death among those treated with both doses of Casirivimab-imdevimab compared with placebo.[27,29]

Sotrovimab

Sotrovimab is considered for non-hospitalized patients with mild to moderate COVID-19 (e.g., not requiring supplemental oxygen or, if on chronic supplemental oxygen, without an increased oxygen requirement) who have certain risk factors for severe disease, e.g., age >65 years, obesity, chronic kidney disease, cardiovascular disease, diabetes, immunosuppression, chronic lung disease, etc.

Sotrovimab is given as a single intravenous infusion (500 mg). In a randomized clinical trial of non-hospitalized adults with early, mild to moderate COVID-19 and one or more risk factors for severe disease as mentioned above, Sotrovimab (500 mg) was administered within five days of illness onset was compared with placebo.[30,31] According to an interim analysis that included 583 participants, Sotrovimab reduced the combined rates of hospitalization and death at 29 days compared with placebo (1 versus 7.2 percent; 85 percent relative risk [RR] reduction, 97% CI 44-96). The rate of adverse events was similar in both groups. Sotrovimab is expected to maintain efficacy against the Omicron variant.

Thromboprophylaxis

Enoxaparin 40mg daily if CrCl >30ml/min is recommended for VTE prophylaxis. Alternatively, Heparin 5000 units Q8H can also be used, especially if CrCl <30ml/min or enoxaparin is unavailable. It is recommended that all hospitalized patients are at higher risk of venous thromboembolism (VTE).[32]

Management of severe COVID-19

Hypoxemia (oxygen saturation <94% on room air) or the need for ventilatory support are indicators of severe disease. Supplemental oxygen should be given to all patients with emergency signs during resuscitation to target SpO2 >94% and >90% in patients without emergency signs. SpO2 >92 – 95% should be aimed for in pregnant females. Dexamethasone should be given to all patients with hypoxemia.

Methods of delivery of oxygen

1) Nasal cannula for flow rates up to 5 L/min
2) Venturi mask for flow rates 6 – 10 L/min
3) Face mask with reservoir bag for flow rates between 10 – 15 L/min

Positioning: Awake-prone positioning may help optimize oxygenation, ease a sense of breathlessness and reduce energy expenditure.[33,34]

Empirical Antibiotics

Based on local epidemiology and clinical judgment, empirical antibiotics to treat all possible pathogens (usually ceftriaxone and azithromycin) should be given as soon as possible. Ideally, blood cultures should be obtained before the commencement of antibiotics. Empiric antibiotics should be de-escalated as soon as possible based on microbiology and clinical judgment. Duration is generally 5 – 7 days.[35]

Monitoring and Investigations

The application of timely, effective, and safe supportive therapies is the cornerstone of therapy for patients who develop severe manifestations of COVID-19. Hospitalized patients with COVID-19 require regular monitoring of vital signs (including pulse oximetry). Hematology/biochemistry laboratory testing, ECG, and chest imaging should be performed at admission and clinically indicated to monitor for complications, such as ARDS, acute liver injury, acute kidney injury, acute cardiac injury, disseminated intravascular coagulation (DIC), and shock. Monitor patients with COVID-19 for signs or symptoms suggestive of venous or arterial thromboembolism. After resuscitation and stabilization of the pregnant woman, fetal well-being should be monitored based on gestational age, maternal clinical status (e.g., hypoxia), and fetal conditions.

Management of critical COVID-19: acute respiratory distress syndrome (ARDS)

High Flow Nasal Oxygen (HFNO)

High flow nasal oxygen may reduce the need for intubation compared to standard oxygen therapy.[36,37] Patients with type 1 respiratory failure, hemodynamic instability, multi-organ failure, or abnormal mental status should not receive HFNO or non-invasive ventilation (NIV). These patients should be cared for in a monitored environment to perform intubation in case of patient deterioration. Adult HFNO systems can deliver 60 L/min of gas flow and FiO2 up to 1.0.

Non-invasive ventilation (NIV), including CPAP and BiPAP

NIV guidelines make no recommendation on use in hypoxemic respiratory failure. Exceptions are cardiogenic pulmonary edema, postoperative respiratory failure, early NIV for immunocompromised patients, or pandemic viral illness (referring to SARS and pandemic influenza).[38] ARDS usually results from ventilation-perfusion mismatch or shunt and requires mechanical ventilation.[39] Risks include delayed intubation, large tidal volumes, and injurious transpulmonary pressures.

Mechanical Ventilation

If mechanical ventilation is required, it is strongly recommended to have lower tidal volumes (4 – 8 mL/kg predicted body weight) and lower inspiratory pressures (plateau pressure < 30cm H20).[40] Initially, tidal volume is aimed at 6 mL/kg but can be increased to 8 mL/kg if undesirable side effects develop (e.g., pH <7.15, dyssynchrony).

Management of critical COVID-19: septic shock

Vasopressors are required in case of a shock to maintain mean arterial pressure (MAP) > 65 mm Hg without hypovolemia. Norepinephrine is considered a first-line treatment in adult patients. Other vasopressors, e.g., epinephrine or vasopressin, can be added to achieve the MAP target. Dobutamine should be considered if signs of poor perfusion and cardiac dysfunction persist despite achieving MAP target with fluids and vasopressors.

Monitoring and preventing complications in hospitalized and critically ill patients with COVD-19

Sings and symptoms of thromboembolism such as stroke, deep venous thrombosis (DVT), pulmonary embolism (PE), or acute coronary syndrome (ACS) should be monitored and appropriately managed. In hospitalized patients without established indication for therapeutic dose anticoagulation, standard thromboprophylaxis dose should be administered (enoxaparin, unfractionated heparin, tinzaparin, dalteparin, or fondaparinux).[40]

Complications of COVID-19

The clinical features of COVID-19 infection are variable. Among the symptomatic individuals, the symptoms vary from mild to severe. The Chinese Centre for Disease Control and Prevention report showed that 80% of confirmed cases of COVID-19 only had mild symptoms, 15% presented with severe disease, while only 5% of the patients were critically ill with respiratory failure or multi-organ dysfunction.[41,42] Recent data has suggested that up to one-third of patients remain asymptomatic throughout their illness.[41]

The common presenting features of COVID-19 infection include fever, sore throat, cough, myalgia, headache, nausea and vomiting, diarrhea, loss of smell or taste, and dyspnoea[43,44] Increasing age, multiple comorbidities, lower socio-economic background, male sex, and Black and South Asian ethnicities are usually risk factors for severe disease[42,43] Several complications of COVID-19 have also been described [Table III & IV].

Thromboembolism and coagulopathy:

Venous thromboembolism (VTE) such as deep vein thrombosis (DVT) and pulmonary embolism (PE) are relatively common among hospitalized patients with COVID-19, especially in patients requiring intensive care treatment.[45] Less commonly, cases of arterial thrombosis presenting as acute ischaemic strokes, acute limb ischemia, and acute myocardial infarction have also been described.[46] The pathogenesis of hypercoagulability state in COVID-19 is not fully clear. Endothelial injury, complement activation, changes in circulating prothrombotic factors, coagulation abnormalities, stasis and immobilization, critical illness, cytokine storm, and severe inflammatory response have all been implicated.[47,48] Older age and elevated D-dimer level are the most common risk factors for VTE in COVID-19 patients. Male sex, obesity, intensive care admission, mechanical ventilation, and elevated white cell count are the other contributing factors.[49,50]

The American Society of Haematology 2021 guidelines suggest prophylactic anticoagulation with low molecular weight (LMW) or unfractionated heparin for patients with COVID-19 related acute or critical illness who do not have suspected or confirmed VTE. Patients on the-

Table 2: *Selection of COVID-19-specific therapy in adults who have severe disease requiring oxygen supplementation (adapted from the update:*

Low-flow oxygen	High flow oxygen or NIV	Mechanical ventilation
1) Dexamethasone 2) Remdesivir 3) Add Baricitinib or Tocilizumab if increasing oxygen requirement despite Dexamethasone significantly elevated inflammatory markers or hospitalization within 96 hours	1) Dexamethasone 2) With or without Remdesivir 3) Add Baricitinib or Tocilizumab if within 24-48 hours of the onset of ICU-level care and within 96 hours of hospitalization	1) Dexamethasone 2) If within 24-48 hours of the onset of ICU-level care and within 96 hours of hospitalization, add Tocilizumab

rapeutic anticoagulation for other indications such as stroke prevention in atrial fibrillation should continue the higher dose unless contraindicated.[51] There is currently insufficient data regarding therapeutic anticoagulation for COVID-19. Patients with confirmed or highly suspected thromboembolic events should be treated with therapeutic anticoagulation similar to patients without COVID-19. LMWH, unfractionated heparin, direct oral anticoagulants, and warfarin are all reasonable options. Anticoagulation therapy is recommended for a minimum of 3 months.[52]

Acute kidney injury and renal complications:

Acute kidney injury (AKI) can complicate up to 20% of patients admitted to the hospital with COVID-19. The mortality rate of patients with AKI can be higher than 50%, pointing towards a more severe disease.[53] The pathogenesis of COVID-19 related AKI is unclear. Hemodynamic changes, cytokine release, and direct tubular toxicity are thought to be underlying mechanisms. Old age, diabetes, hypertension, pre-existing chronic kidney disease, renal transplant, and history of tumor are the common risk factors.[54] Management of COVID-19 related AKI is similar to non-COVID-19 critically ill patients, including initiation of renal replacement therapy where needed. Less common renal complications include collapsing focal segmental glomerulosclerosis (FSGS), thrombotic microangiopathy, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, anti-glomerular basement membrane antibody disease, and IgA nephropathy.[55,56]

Hepatic and gastrointestinal complications:

Gastrointestinal complications are common in patients admitted to the hospital with COVID-19. In one report from Wuhan, China, acute gastrointestinal complications were seen in 85% of critically ill patients with a mortality rate of almost 50%.[57] The exact cause for the high incidence of gastrointestinal complications in COVID-19 patients is unclear. Elevated liver transaminases, acute liver injury, ischaemic hepatitis, acute acalculous cholecystitis, acute pancreatitis, ileus, acute pseudo-obstruction, and mesenteric ischemia have all been reported complications of severe COVID-19 infection.[58] Mesenteric ischemia is the most severe gastrointestinal complication with a reported incidence of 4% and mortality rate of 40%, primarily within the immediate postoperative period.[59] Direct damage to the gastrointestinal tract by viral invasion and microvascular coagulopathy is thought to be the possible underlying pathophysiological mechanisms.[60]

Neurological complications:

A wide range of neurological complications has been reported in patients with severe COVID-19 infections. The most observed complications are delirium and encephalopathy, ischaemic stroke, intracranial hemorrhage, and cranial venous thrombosis. Rare complications include Guillain-Barre syndrome, peripheral neuropathies, meningoencephalitis, encephalitis, acute disseminated encephalomyelitis, seizures, and acute hemorrhagic necrotizing encephalopathy.[46,61,62,63] Direct neurological damage from virus invasion, hypoxemia-induced neurological injury, dysregulation of the reninangiotensin system, and immune dysfunction are thought to be the possible underlying aetiologies.[64] One hospitalized cohort from Wuhan in China shows over 34% of people experiencing anxiety symptoms and 28% experiencing symptoms of depression.[19] An observational case series from France found that 65% of people with COVID-19 in ICUs showed signs of confusion (or delirium), and 69% experienced agitation[11]. Delirium, in particular, has been associated with increased mortality risk in the context of COVID-19.[21]

Cardiac complications:

Multiple cardiac manifestations have been associated with COVID-19. Cardiac complications have been reported in 14% of hospitalized patients, with a mortality rate of nearly 10%.[65] Elevated troponin level and myocardial injury, inflammatory myocarditis, heart failure, cardiac arrhythmias, acute coronary syndrome, myocardial infarction, stress (Takotsubo), cardiomyopathy, sudden death have been reported.[66]

Respiratory complications:

Respiratory complications remain the primary cause of mortality and morbidity in COVID-19 patients. Pneumonia is the most common feature of severe infection, typically presenting with fever, cough, dyspnea, leucopenia, lymphocytopenia, and bilateral infiltrates on radiological imaging.[67] Severe hypoxia needing high flow oxygen therapy or respiratory support on intensive care unit can develop within 5 to 6 days of initial presentation, with up to 20% progressing to develop acute respiratory distress syndrome (ARDS) associated with high mortality.68

Long COVID and post-acute COVID syndrome:

The World Health Organization defines post-COVID syndrome (long COVID) as a condition that occurs in people with a history of probable or confirmed SARS-CoV-2 infection, usually occurring three months from the onset of symptoms, and lasting for at least two months, that cannot be explained by an alternative diagnosis.[69] A recent meta-analysis showed that 63.2% of patients had at least one post-COVID-19 symptom at 30 days, 71.9% at 60 days, and 45.9% at more than 90 days after the acute illness. Fatigue and dyspnea were the commonest symptoms affecting up to 60% of patients. Other post-COVID-19 symptoms included cough (20-25%), anosmia (10-20%), ageusia (15-20%)

or joint pain (15-20%).[70]

COVID & Thyroid:

Patients with COVID-19 are more likely to get post-viral thyroiditis. The subacute thyroiditis manifests as painful neck/goiter followed by mild thyrotoxicosis, then hypothyroidism, usually reverting to normal in a few weeks to months. The diagnosis carries a good prognosis. Remember to check thyroid antibodies and monitor thyroid function tests.

Interpret thyroid hormone levels in COVID-19 patients with caution. Typical alterations include slightly high fT4, slightly low or low normal fT3, and slightly low TSH (like sick euthyroid syndrome). These results are likely to be due to COVID-19 rather than thyrotoxicosis. Also, drugs used for COVID-19 like steroids, HCQ, and heparin are all known to give abnormal thyroid function test results.[7,54,55]

Vaccine related complications:

Vaccine-related side effects are relatively common but are predominantly mild and self-limiting, mostly within forty-eight hours. The most common adverse reactions include fever, myalgia, pain at the injection site, fatigue, headache, and ipsilateral axillary lymph node enlargement. The rare but potentially fatal side effects associated with different types of COVID-19 vaccines are summarized below.[49,62,66]

BNT162b2 (Pfizer-BioNTech)

- Anaphylaxis
- Myocarditis and pericarditis, mainly in male adolescents and young adults

mRNA-1273 (Moderna)

- Anaphylaxis
- Myocarditis and pericarditis, mainly in male adolescents and young adults

Ad26.COV2.S (Janssen/Johnson & Johnson)

- Thrombosis with thrombocytopenia
- Guillain-Barre syndrome

ChAdOx1 nCoV-19/AZD1222 (Oxford, Astra-Zeneca, and the Serum Institute of India)

- Thrombosis with thrombocytopenia

There is insufficient data on the vaccine-related severe adverse effects for other vaccines, including NVX-CoV2373 (Novavax), Ad5-based COVID-19 vaccine (CanSino Biologics), Gam-COVID-Vac/Sputnik V, WIV04 and HB02 (Sinopharm), and CoronaVac (Sinovac).

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Table 3: *Complications of COVID-19 infection*

Coagulopathy and thromboembolism	Deep vein thrombosis Pulmonary embolism Ischaemic strokes Acute limb ischemia Acute myocardial infarction
Renal	Acute kidney injury Collapsing focal segmental glomerulosclerosis (FSGS) Thrombotic microangiopathy Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis Anti-glomerular basement membrane antibody disease IgA nephropathy
Hepatic and gastrointestinal	Elevated liver transaminases Acute liver injury Ischaemic hepatitis Acute acalculous cholecystitis Acute pancreatitis Ileus and acute pseudo-obstruction Mesenteric ischemia
Neurological	Delirium and encephalopathy Ischaemic stroke Intracranial hemorrhage Cranial venous thrombosis Guillain-Barre syndrome Peripheral neuropathies Meningoencephalitis and encephalitis Acute disseminated encephalomyelitis Seizures Acute hemorrhagic necrotizing encephalopathy
Cardiac	Elevated troponin level and myocardial injury Inflammatory myocarditis, Heart failure Cardiac arrhythmias Acute coronary syndrome and myocardial infarction Stress (Takotsubo) cardiomyopathy Sudden death
Respiratory	Pneumonia Acute respiratory distress syndrome (ARDS)
Post-COVID syndrome	Fatigue Dyspnoea Cough Anosmia Ageusia Joint pain

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Table 4: *Complications of COVID-19 Vaccination*

Common and mild	**Fever** **Myalgia** **Pain at the injection site** **Fatigue** **Headache** **Ipsilateral axillary lymph node enlargement**
Rare and serious	**BNT162b2 (Pfizer-BioNTech)** • Anaphylaxis • Myocarditis and pericarditis, mainly in male adolescents and young adults **mRNA-1273 (Moderna)** • Anaphylaxis • Myocarditis and pericarditis, mainly in male adolescents and young adults **Ad26.COV2.S (Janssen/Johnson & Johnson)** • Thrombosis with thrombocytopenia • Guillain-Barre syndrome **ChAdOx1 nCoV-19/AZD1222 (Oxford, AstraZeneca, and the Serum Institute of India)** • Thrombosis with thrombocytopenia

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