Article published online: 2022-12-03

COVID 19: Airway Management and Pharmacological Strategies

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J Card Crit Care 2022;6:210–215.

Abstract

Coronavirus disease 2019 caused by severe acute respiratory syndrome coronavirus 2 has since resulted in more than 250 million cases worldwide and over 50 million deaths. Although treatment is mainly supportive, with oxygen therapy being the mainstay, various pharmacological treatment modalities have also been explored. In this review, we have evaluated the available evidence on airway management as well as medical management and highlighted the possible interventions that may be effective in care of critically ill patients.

Keywords
- airway management
- COVID-19
- Pharmacological strategies

Introduction

Coronavirus is an enveloped, single-stranded ribonucleic acid (RNA) virus, transmitted mainly via respiratory tract. The virus has tropism for respiratory tract, due to high expression of angiotensin-converting enzyme-2 (ACE-2) (its entry receptor) in multiple epithelial cells of airway and alveolar epithelial type II cells in lung parenchyma.[1,2] In severe cases, viral replication occurs in lower respiratory tract and manifests as pneumonia and acute respiratory distress syndrome (ARDS). Key mechanisms for multiorgan injury include direct viral toxicity, endothelial cell damage, thrombi inflammation, dysregulation of the immune response, and renin–angiotensin–aldosterone system.

The mechanism of virus invasion into the host is: attachment, penetration, biosynthesis, maturation, and release. After binding to the host cell receptors, the virus enters the host cells through endocytosis or membrane fusion and releases its contents. The viral messenger RNA enters the host nucleus and makes viral proteins. New viral particles are then produced and released.[2]

Coronavirus consists of four structural proteins: spikes, membrane, envelop, and nucleocapsid.[2] Spikes are composed of transmembrane trimetric glycoprotein protruding from the viral surface and determine the diversity of coronaviruses as well as host tropism.[2] After binding to the host protein, spike protein undergoes protease cleavage.

New Strains Especially Delta, Delta Plus, and Omicron...How Are They Different

Host Response

T cell responses are initiated by the antigen presenting cells (dendritic cells and macrophages). CD4+ T cells activate B cells to promote the production of virus-specific antibody, while CD8+ T cells can kill viral infected cells.[3] In severe cases, overactivation of innate immunity causes T cell lymphodepletion resulting in a dysregulated immune response and cytokine release syndrome (CRS).[3] Cytokines (interleukin [IL]-6, tumor necrosis factor-α, and IL-1) are elevated resulting in endothelial dysfunction, vascular damage, and metabolic dysregulation; thereby causing multiple organ damage.[3]

DOI https://doi.org/10.1055/s-0042-1759862.
ISSN 2457-0206.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Clinical Presentation

The clinical presentation varies from asymptomatic to severe respiratory failure and multiorgan dysfunction.[4,5] The most common symptoms include fever (98.6%), fatigue (69.6%), and dry cough.[4,5]

Classification

Mild: Majority (81%) of patients present with mild symptoms of an upper respiratory tract viral infection including dry cough, mild fever, nasal congestion, sore throat, headache, and malaise.[4,5]

Moderate: These patients present with cough, shortness of breath, and tachypnea.[4,5]

Severe: Patients may develop severe pneumonia, ARDS, sepsis, or septic shock. Clinical presentations include severe dyspnea, tachypnea (respiratory rate > 30/minute), respiratory distress, $SpO_2 \leq 93\%$, $PaO_2/FiO_2 < 300$, and/or $\geq 50\%$ lung infiltrates within 24 to 48 hours. Five percent of patients develop a critical disease with features of respiratory failure, cardiac injury, septic shock, or multiple organ dysfunction. Case–fatality rate for critical patients is 49% especially in presence of preexisting comorbidities like diabetes (7.3%), respiratory disease (6.5%), cardiovascular disease (10.5%), hypertension (6%), and oncological complications (5.6%). Patients without comorbidities have a lower case–fatality rate (0.9%).

Acute Respiratory Distress Syndrome

Severity of ARDS is graded according to PaO_2/FiO_2 values (severe: $\leq$ 100 mm Hg; moderate: 100–200 mm Hg; and mild: 200–300 mm Hg).[4,5] Chest imaging modalities like X-ray, computed tomography (CT) scan, and lung ultrasound can support the diagnosis. The most frequent finding on CT scan includes ground-glass opacity (86%), consolidation (29%), crazy paving (19%), bilateral disease distribution (76%), and peripheral disease distribution (33%).[6]

Extrapulmonary Manifestations

Sepsis and Septic Shock

Multiorgan dysfunction is a consequence of dysregulated host response to infection. Clinical signs include severe dyspnea, low oxygen saturation, reduced urine output, tachycardia, hypotension, cold extremities, skin mottling, and altered mentation.[4,5] Laboratory findings includes acidosis, high lactate, hyperbilirubinemia, thrombocytopenia, and evidence of coagulopathy.[4,5]

Renal Manifestations

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) directly infects the renal cells. Histopathological findings include acute tubular injury and obstruction in peritubular/glomerular capillary loops.[7,8] Most common renal manifestations include acute kidney injury, proteinuria, hematuria, electrolyte imbalance, and metabolic acidosis.[7,8] Proteinuria and hematuria is associated with a worse clinical course and higher mortality.[9]

Cardiovascular Manifestations

ACE-2 receptors have high expression in cardiovascular tissues including cardiac myocytes, fibroblasts, endothelial cells, and smooth-muscle cells causing direct viral injury. Clinical manifestations are heart failure (23–52%), acute cardiac injury (8–12%), arrhythmias (8.9–16.7%), new-onset atrial fibrillation/flutter, sinus tachycardia, sinus bradycardia, QTc prolongation, sudden cardiac death, and cardiomyopathy.[10]

Hematological Manifestations

A cardinal laboratory finding reported in 67 to 90% of coronavirus disease 2019 (COVID-19) patients is lymphopenia, a marker of impaired cellular immunity.[11] Thrombocytopenia (16.4–32.3%), leukocytosis, and neutrophilia are also present.[11] COVID-19-associated coagulopathy is marked by elevated D-dimer and fibrinogen, prolonged prothrombin time, and partial thromboplastin time.[11] This leads to thromboembolic complications, including myocardial infarction, ischemic stroke, deep vein thrombosis (DVT), and pulmonary embolism (PE). There can be increase in inflammatory markers including erythrocyte sedimentation rate, C-reactive protein, ferritin, IL-6, and lactate dehydrogenase.

Gastrointestinal Manifestations

Clinical presentations include anorexia (26.8%), nausea/vomiting (10.2%), diarrhea (12.5%), and abdominal pain (9.2%).[12] Laboratory markers affected are elevated hepatic transaminases (16.1–53%), elevated bilirubin, and low serum albumin.[12]

Neurological Manifestations

COVID-19-associated nervous system damage is caused by direct infection, hypoxic injury, and immune responses. Common neurological symptoms are: headache (16.8%), dizziness (13.1%), anosmia (79%), ageusia (1.7%), myalgia, and stroke (2.8%).[13]

Management

Methods of Oxygen Supplementation

Supplemental oxygen therapy should be initiated in presence of respiratory distress or any oxygen saturation (SpO_2) < 90%.[14] Oxygen therapy may range from simple noninvasive methods like nasal cannulas to invasive mechanical ventilation (IMV). Noninvasive ventilation (NIV) is an option in selected patients in early stages with milder acute hypoxemic respiratory failure.[15] For critically ill patients, the oxygen index needs to be closely monitored and switched to mechanical ventilation if required.

Noninvasive methods

Nasal prongs/cannulae are useful in patients requiring minimal oxygen supplementation or as a step-down method in patients being weaned from high-flow oxygen therapy. Nasal cannulas cause a higher dispersion of droplets than other

Table 1 Comparison of various types of oxygen therapy devices[18]

Delivery system	Flow of oxygen (L/min)	Delivered FiO_2 (%)
Nasal cannula	0.5–4	22–40
Face mask	5–10	40–60
Venturi mask	Variable (depending on required FiO_2)	24–50
Reservoir mask	10–15	60–90

systems.[16] Air dispersion from low-flow nasal cannulae can reach greater than 1 m away, a distance which, although less than that of an uncovered cough, produces a constant rate of dispersal.[16] The nasal cannula, if used, must be positioned well inside the nostrils and a surgical mask should be used over it covering the patient's mouth and nose to prevent dispersion of droplets while coughing, reducing the dispersion distance and levels of virus-infected bioaerosol while coughing.[17]

Face masks with an oxygen flow of 5 L/min, venturi mask up to 60% FiO_2, or oxygen masks with reservoir bag up to 15 L/min are recommended to escalate oxygen (►**Table 1**).

High-flow nasal cannula (HFNC): HFNC delivers high-flow humidified oxygen via nasal cannula. It is effective in improving oxygenation but increases bioaerosol dispersion due to high flow. Leung et al compared the use of HFNC at 60 L/min and oxygen mask at 8 L/min in intensive care unit patients. There was no significant difference in bacterial counts in the air sample and settling plates at a distance of 0.4 and 1.5 m from patients between these two oxygen devices at 1, 2, and 5 days of incubation.[18,19] Placing a surgical mask over HFNC may further reduce aerosol dispersion.

Hyperbaric oxygen therapy (HBOT): HBOT consists of exposure to 100% oxygen under increased atmospheric pressure (up to 2.4 atm). It improves recovery from infection if administered at an early stage of onset of desaturation. Elevated partial pressure allows oxygen to penetrate the tissues rapidly and in higher concentration. Accentuated supply of oxygen preserves cellular metabolism and improves mitochondrial function. It alters the balance between glycolysis and mitochondrial respiration, possibly countering the effect of viral infection on cellular caloristasis network and improving hypoxia in COVID-19 patients. A few limitations of HBOT are that it occupies significant space with a limited number of bed settings per chamber. HBOT has been successfully used at 200 kPa to treat severely ill COVID patients.[20]

For patients with $SpO_2 < 90\%$ and/or showing signs of respiratory distress with above treatment strategies, noninvasive support (continuous positive airway pressure [CPAP]/bilevel positive airway pressure) can be administered. Early use of CPAP may delay or alleviate the need for IMV. NIV is planned according to $PaCO_2$ values. Suggested initial settings are CPAP 10 cm H_2O and FiO_2 titrated to achieve target SpO_2 of 92 to 96%, except in the presence of acute or acute on chronic type 2 respiratory failure, where target SpO_2 is 88 to 92%.

Invasive Mechanical Ventilation

Absence of clinical improvement with NIV (worsening of hypoxemia) mandates IMV. Delay in endotracheal (ET) intubation by prolonged use of NIV is associated with higher mortality rate.[5,21]

Bag and mask ventilation should be avoided to prevent high aerosol generation. Clamping of the ET tube is recommended before insertion and heat and moisture exchange filters should be used at the inlet of ventilator tube to reduce droplet dispersion during intubation and mechanical ventilation. Periodical verification of the ET cuff pressure (25–30 cm H_2O) is advised. ET tube should be suctioned using a closed suction circuit to minimize droplet dispersion and loss of positive end-expiratory pressure (PEEP), which can worsen atelectasis.

Lung preserving ventilatory strategies are employed to minimize ventilator-associated lung injury and to improve survival. Tidal volume of 4 to 8 mL/kg and plateau pressure < 30 cm of H_2O are targeted. Higher PEEP can decrease the requirement for high FiO_2 by improving gas exchange, whereas too high a PEEP may lead to lung overdistension and hemodynamic instability.

Prone Positioning

For spontaneously breathing patients, prone position is used when FiO_2 of 0.28 fails to achieve SpO_2 of 94 to 95%.[14] Awake patients may be able to turn themselves prone without any special assistance, but may not tolerate long period in prone position. To minimize the time spent in supine position, patients on basic respiratory support can be advised to alternate supine positioning with prone, left, and right lateral decubitus positioning.[22]

Prone position improves oxygenation in mechanically ventilated patients with moderate to severe ARDS and is recommended for 12 to 16 hours/day.[23] It can be repeated until PaO_2/FiO_2 ratio ≥ 150 mm Hg is achieved using PEEP $\leq$ 10 cm H_2O and $FiO_2 \leq 0.60$ for at least 4 hours in supine position. Early application of prone position in patients with severe ARDS resulted in decreased mortality.[23]

Appropriate measures taken to minimize or avoid complications associated with prone positioning like pressure ulcers, periorbital edema, corneal damage, injury to brachial plexus, and difficulty in cannulation.

Extubation

Extubation should not be hastened in these patients as failed extubations (up to 60%) have been reported in the first 24 to 48 hours.[24]

Extracorporeal Membrane Oxygenation

Extracorporeal membrane oxygenation (ECMO) has developed from being used as a "rescue therapy" to become an accepted treatment option for patients with severe ARDS. It is considered as a last resort when all ventilator strategies fail to improve patient's condition. It replaces the cardiopulmonary function partially or completely to deliver oxygen supply to the organs and strive for time to treat the primary disease.[25,26]

Venovenous ECMO provides respiratory support in patients with severe ARDS, refractory to optimal ventilator management.[26,27] Venoarterial ECMO is usually reserved for those who also have accompanying right ventricular dysfunction due to severe ARDS or pulmonary emboli, persistent malignant arrhythmias, acute myocardial infarction, or acute myocarditis.[28]

Patients with severe ARDS with $PaO_2/FiO_2 < 60$ mm Hg for > 6 hours, $PaO_2/FiO_2 < 50$ mm Hg for 3 hours, or pH < 7.20 with $PaCO_2 > 80$ mm Hg for 6 hours in spite of optimal ventilation strategies, neuromuscular blockade, appropriate PEEP, and prone positioning can be considered for ECMO. Patients with disseminated malignancy, multiorgan failure, and severe acute neurological injury are not considered for ECMO.[28] The use of ECMO in COVID-19 has been associated with variable recovery rates.[29–32]

Hemorrhage and coagulopathy are the most common complications with ECMO. DVT and PE have also been reported. COVID-19-induced thrombosis combined with ECMO will place the patient at a greater risk of coagulopathy.[33]

Medical Management

Azithromycin

Azithromycin is a broad spectrum macrolide antibiotic which decreases viral entry into the host cells. It also has immunomodulatory effects, including upregulation of the innate immune response against viral antigens and inhibition of production of several cytokines (including IL-1 and IL-6) involved in severe systemic hyperinflammation seen in patients with severe COVID-19. It also helps in preventing or treating superimposed secondary bacterial infections, as there is an increased incidence of anaerobic bacterial infections by commensal lung anaerobes in COVID patients. The recommended dosage is 500 mg once daily for 5 to 7 days.

Anticoagulant Therapy

Aspirin

SARS-CoV-2 leads to multiple organ failure via formation of microthrombi. Aspirin has antithrombotic, anti-inflammatory, and analgesic effects, and hence is used as potential adjunctive therapy in COVID patients. Low-dose aspirin is recommended for prevention of cardiovascular morbidity in COVID patients. The anti-inflammatory effects of aspirin are more prominent at higher doses.

Heparin

Patients who meet the diagnostic criteria of sepsis-induced coagulopathy can benefit from anticoagulant therapy. Increase in D-dimer and prothrombin levels along with a decrease in fibrinogen has been associated with a lower survival rate. Patients with elevated D-dimer (> 6 upper limit of normal), an indirect marker of coagulation activation also benefit from anticoagulant therapy. Heparin also has anti-inflammatory and antiviral properties. Additionally, patients with severe COVID infections are confined to bed rest for a prolonged duration, and need prophylaxis for DVT, for which low molecular weight heparin (LMWH) is indicated. Patients with severe COVID-19 need to undergo analysis of D-dimer, prothrombin time, and platelet count at admission, followed by serial assessment. All patients should be put on prophylactic LMWH therapy, unless contraindicated.

Corticosteroids

COVID-19 leads to a cytokine storm, caused by dysregulated host immune response resulting in a surge in cytokine levels including C-reactive protein, IL-1, and IL-6. The use of systemic corticosteroids is aimed at curbing this hyperinflammatory response. Corticosteroids have potent anti-inflammatory and antifibrotic properties, reducing systemic and pulmonary inflammation. In COVID patients with ARDS, methylprednisolone 1 to 2 g/day intravenously for 5 to 7 days reduced the mortality to 46%, as compared with 61.8% in patients who did not receive steroids. Improvement in clinical symptoms such as fever and hypoxia, and a shortened disease course has also been reported in patients who received methylprednisolone.

Dexamethasone is a long-acting corticosteroid with potent anti-inflammatory action, as well as low mineralocorticoid activity. Optimal dosage is 0.2 to 0.4 mg/kg for 5 to 7 days. Administration of dexamethasone was associated with increased ventilator-free days and lower Sequential Organ Failure Assessment (SOFA) score. There was no increase in the rate of secondary infections, and hyperglycemia was seen to be the major adverse effect. Some studies have found decreased viral clearance in patients receiving corticosteroids, especially if used in the early phase of the disease. The Surviving Sepsis guidelines do not recommend the routine use of systemic corticosteroids, and suggest its use in the sicker population of COVID-19 with ARDS.

Secondary fungal infections have been reported with COVID-19, which may occur due to immune dysregulation caused by the host response to the virus, and added immunosuppressive effects of steroids and monoclonal antibodies. Some life-threatening cases of rhinocerebral mucormycosis and invasive pulmonary aspergillosis have been reported.

Monoclonal Antibodies

Cytokine storm, also known as the CRS, is the main pathophysiological hallmark of COVID-19. This is associated with high levels of IL-1, IL-6, and C-reactive protein. IL-6 is one of the main modulators of this response, and hence is a potential target for therapeutic intervention. Tocilizumab is a humanized monoclonal antibody which antagonizes IL-6 by competitively blocking its attachment to the IL-6 receptor. The recommended dose is a single dose of 400 mg. This dose can be repeated after 24 hours. Luo and colleagues found that in 67% of the patients IL-6 levels increased sharply immediately after administration of tocilizumab but decreased thereafter. Administration of tocilizumab resulted in a remarkable improvement in clinical symptoms, with the temperature returning to normal on the first day postadministration in all patients, lowered oxygen requirements, and resolution of CT abnormalities.

Tocilizumab decreased the incidence of invasive ventilation and death as compared with patients receiving standard

care. In addition, the maximal benefit was documented in patients with a PaO_2/FiO_2 ratio < 150 mm Hg, implying that benefit would be greater in patients at a higher risk of need for mechanical ventilation. The only major concern was higher incidence of secondary infections, with 24 (13%) of 179 patients being treated with tocilizumab diagnosed with new infections, versus 14 (4%) of 365 patients treated with standard of care alone ($p < 0.0001$). Known side effects of the drug are thrombocytopenia and hepatotoxicity, hence it is not recommended if liver enzymes are deranged to levels more than five times the normal values.

Convalescent Plasma Therapy

Convalescent plasma has antibodies r from patients who have recovered from an infection. A case series from China reported a decrease in viral load, improvement in SOFA score, fall in body temperature, and gradual resolution of lung opacities on CT scan within 10 to 12 days of administration of plasma to patients with COVID-19. Neutralizing antibody levels increased rapidly, clinical symptoms improved significantly, and oxyhemoglobin saturation increased within 3 days. Radiological examination showed varying degrees of correction of lung lesions within 7 days. The viral load was undetectable posttransfusion in 7 patients who had previous viremia. No significant adverse effects were observed.

The proposed mechanism of this therapy is suppression of viremia by enhancement of host humoral immunity. An in vivo trial highlighted that convalescent plasma increased free viral clearance, blocked new infections, and also caused acceleration of infected cell clearance. Viremia peaks during first week of infection, and is followed by the active host immune response and recovery, hence, maximal beneficial effects would be seen when plasma is administered early in the course of the disease. A recent study investigating the effectiveness of convalescent plasma in treatment of moderate COVID reported no reduction in progression to severe COVID-19 and mortality.[34]

Remdesivir

Remdesivir exhibits broad spectrum antiviral activity by inhibiting the incorporation of adenosine triphosphate into RNA chain, causing delayed termination of RNA chain during viral replication. This effectively results in the inhibition of RNA-dependent RNA polymerase. The recommended dose is 200 mg intravenously on day 1, followed by 100 mg intravenously daily for 4 days.

Grein et al[35] reported clinical improvement in 68% patients even with a single dose, despite inclusion of severely ill and critical patients. Hundred percent of patients with mild symptoms and 71% with moderate symptoms showed improved recovery with remdesivir. A recent meta-analysis[36] showed significant improvement in 28-day recovery in remdesivir group. A 5-day regimen gave similar outcomes but fewer adverse drug reactions as compared with a 10-day regimen. However, Wang et al[37] found no significant difference in time to clinical improvement within 28 days, and in the 28-day mortality with administration of remdesivir. They also found no significant difference in outcome between patients receiving remdesivir early (within 10 days of onset of symptoms) or later in the course of the disease.[37]

Favipiravir

Favipiravir is an antiviral drug which gets phosphorylated intracellularly and is incorporated into the nascent viral RNA, inhibiting viral replication.[38] Recommended dosage is 1,800 mg orally 12 hourly on day 1, followed by 800 mg orally twice daily for up to 14 days. A study conducted in China by Cai et al[39] found that patients receiving favipiravir had a shorter viral clearance time and significant improvement in chest imaging. A meta-analysis including 1,798 studies found significant radiological and clinical improvement following favipiravir.[40] However, there was no difference in terms of virological clearance and oxygen requirements.

Ivermectin

Ivermectin is an antiparasitic drug with low cost and a safe therapeutic profile. It has been used in the treatment of COVID due to its antiviral and anti-inflammatory activities. Ivermectin has shown a significant reduction in mortality with a standard dose of 0.2 to 0.4 mg/kg.[41] Early use in the course of disease may also reduce progression to severe disease.[42] However, there have been conflicting reports on usefulness of ivermectin in COVID-19 patients.[43]

Vitamin Therapy

Vitamins A to E are known to have immunomodulatory, antioxidant, and antimicrobial activities and are given as a part of immunonutrition. Oxidative stress is one of the main pathological mechanisms of COVID, and vitamin supplementation has been shown to reduce production of superoxides and peroxides. Jovic et al highlighted the beneficial role of vitamins in preventative or supportive therapy of COVID-like respiratory illness.[44]

Conclusion

The world is challenged by the ongoing pandemic. Newer therapies are evolving and need thorough evidence-based evaluation. Pharmacological agents and airway interventions are essential for saving lives of critically ill COVID-19 patients.

Conflict of Interest
None declared.

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