CHAPTER

1

Severe COVID-19 Infection

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CASE PRESENTATION

A 37-year-old male patient without any previous medical history was admitted to emergency department with difficulty in breathing for the last few hours; he also reported high grade fever, sore throat and generalized weakness for last 3–4 days. On evaluation, he was febrile (101°F), tachypnoic, using his accessory muscle for breathing and his oxygen saturation was 84%. He was a chronic smoker and using 2 packs/day. He was immediately started with oxygen using nonrebreathing mask. A rapid antigen testing was positive for Covid-19 infection. Blood investigations were sent immediately along with C-reactive protein (CRP), D-dimer and a chest X-ray was done. His oxygen saturation did not improve and he remained tachypnic. He was supported with noninvasive ventilation with increasing oxygen and ventilatory support, however, he remained hypoxemic and his work of breathing remained high with subcostal retraction. His arterial blood gases showed mixed respiratory failure (pH 7.12, $PaCO_2$ 59, PaO_2 54). He was started with Remdesivir and steroids. He was electively intubated and mechanically ventilated. In the next few hours his oxygenation did not improve in spite of increasing positive end expiratory pressure (PEEP) and keeping fraction of inspired oxygen FiO_2 1.0. He required small dose norepinephrine infusion (0.05 µg/kg/min) to maintain his blood pressure after adequate fluid administration. His blood gases further worsened with PaO_2: FiO_2 48, hypercapnea despite ventilator rate of 28, with plateau pressure 42. In the last 2 hours his urine output started falling and his lactate levels were 4.1 mmol/L.

Q. How Adequate Oxygenation can be Maintained and what other Strategies should be followed to Optimize this Patient?

The clinical spectrum of patients with Covid-19 infection ranges from no symptoms to critical illness. However, clinical condition of patient may overlap and may change over time. The patients with severe illness present with SpO_2 <94% on room air, arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) <300 mm Hg, a respiratory rate >30 breaths/min, or lung infiltrates >50%. However, these patients may further worsen and nearly 5% of all covid infected patients become critical and require ICU admission.[1] These patients may develop respiratory failure, distributive shock, and/or involvement of other organs leading to multiple organ dysfunction. Patients aged ≥65 years or who are having bronchial asthma or chronic respiratory disease, malignancy, cardiovascular disease, chronic renal or hepatic disease, diabetes, advanced or untreated HIV infection, obesity, pregnancy, cigarette smoking or post-transplant are at higher risk for progressing to severe or critical disease.[2] Almost two-thirds of the patients admitted in ICU develop acute hypoxemic respiratory

failure. All the patients who require oxygen therapy above 6–8 L/min to achieve oxygen saturation around 90–92%, or develop respiratory failure, shock, acute organ dysfunction and at risk of clinical deterioration should be admitted in ICU. Patients with hyperpyrexia, above 65 years of age, increased acute-phase reactants such as C–reactive protein and serum ferritin, lymphocytopenia, altered hepatic enzymes, increased D-dimer or acute kidney injury are prone for developing ARDS.[3]

ARDS is primarily non-cardiogenic inflammatory pulmonary edema, with reduced area of normal ventilation in lungs with reduced lung compliance and shunt effect. Berlin definition defines ARDS on the basis of degree of hypoxemia: Mild (200 mmHg < PaO_2/FIO_2 ≤300 mmHg), moderate (100 mmHg <PaO_2/FIO_2 ≤200 mmHg), and severe (PaO_2/FIO_2 ≤100 mmHg) along with radiographic severity, lung compliance (≤40 mL/cm H_2O), requirement of PEEP (positive end-expiratory pressure) ≥10 cm H_2O, and corrected expired volume per minute (≥10 L/min).[4] The COVID-19-induced ARDS patients have intense endothelial dysfunction and thromboinflammatory response. This may lead to abolition of hypoxic pulmonary vasoconstriction (HPV), severe pulmonary vasoconstriction and formation of micro or macrothrombus. These all contribute to increasing dead space, V/Q (ventilation/perfusion) mismatch leading to inadequate gas exchange and vasodilation.[5]

In patients admitted in ICU with severe gas exchange abnormalities modalities such as HFNO or NIV support may be required, however, patients with severe ARDS may require invasive mechanical ventilation or extracorporeal membrane oxygenation (venovenous ECMO) to maintain adequate gas exchange. Encouraging the non-intubated patients for prone position has been useful in improving the oxygenation if they tolerate proning for more than 3 hours continuously.

Patients with severe ARDS require several maneuvres for recruitment of collapsed alveoli which help in reducing elastance and improve compliance, such as incremental PEEP, other alveolar recruitment maneuvers, along with prone position. Prone positioning promotes alveolar recruitment, reduces ventilation/perfusion mismatch and reduces overinflated area in the lung and thus improves the oxygenation. Prone positioning should always be considered if not contraindicated in patients with PO_2/FiO_2 <150.[6]

The goal of mechanical ventilation in severely hypoxemic patients is to maintain a lung-protective strategy which includes a low tidal volume of 4 to 8 mL/kg predicted body weight (PBW) and restricting plateau pressure below 30 cm H_2O (Fig. 1.1). Two phenotypes of ARDS have been conceptualized in Covid patients, L (Low elastance) type and H (High elastance) type on the basis of responsiveness of PEEP and lung weight on CT scan. The "L type" patients having good pulmonary compliance, can be ventilated with higher tidal volumes (VT) (approximately 7–8 mL/kg of PBW) to avoid absorption atelectasis and hypercapnia. The application of lower PEEP (8–10 cm H_2O) help in preventing the blood flow away from the aerated pulmonary vasculature and thus reduces shunt effect. The H type may progress with worsening of inflammatory edema and self-induced lung injury (P-SILI) may further contribute to worsening. The lung protective ventilation strategy include tidal volume <6 mL/kg and high PEEP with a goal to keep driving pressure below 14 cm H_2O.[7] The prone position and alveolar recruitment strategies may improve oxygenation in refractory cases.

HEMODYNAMIC OPTIMIZATION AND SUPPORT

Myocardial dysfunction with hemodynamic instability is common in critically ill Covid-19 patients. Several factors may contribute including viral toxin, hypoxemia, acute inflammatory responses, increased thrombogenesis, endothelial injury, sympathetic overactivity,

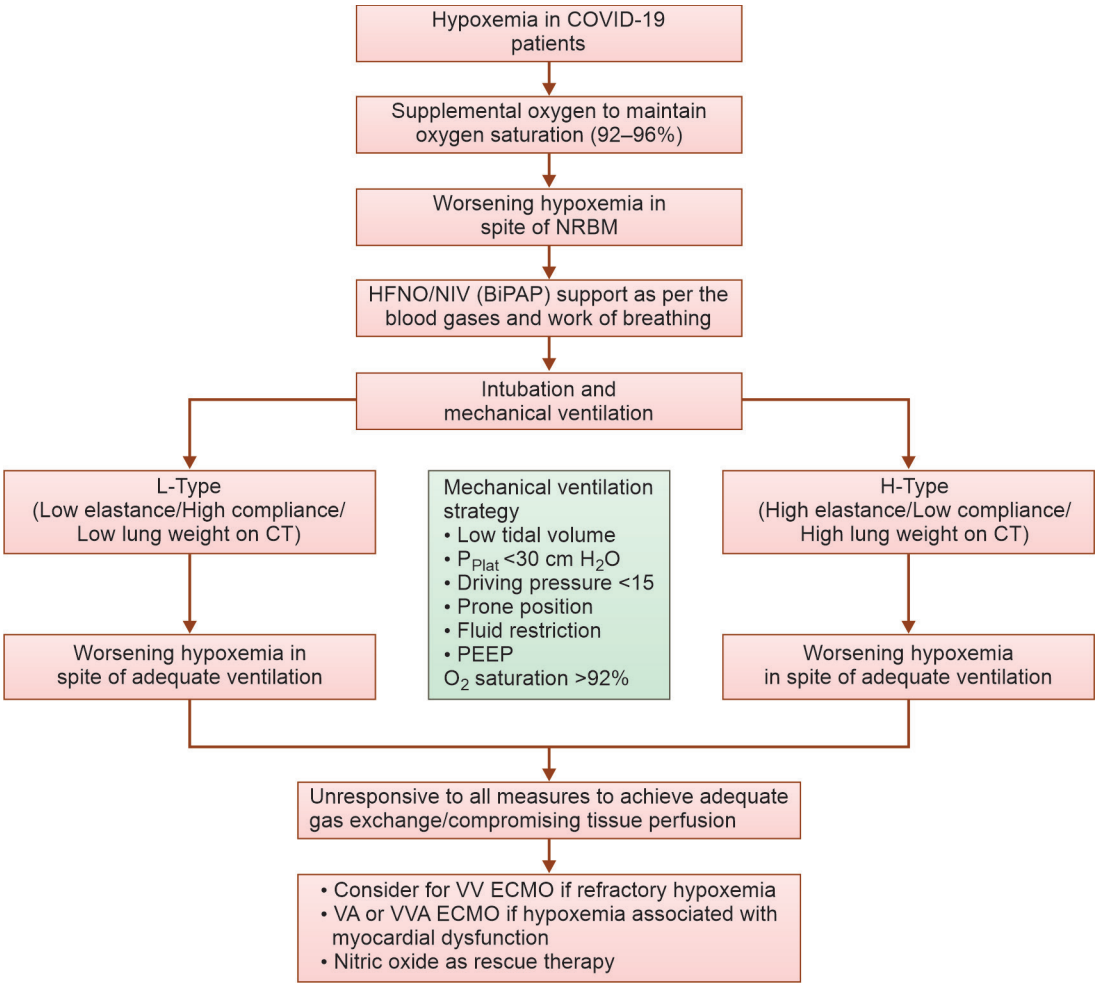

Fig. 1.1: Approach to a hypoxemic Covid-19 patient

myocarditis, vasoconstriction, supply–demand mismatch, poor respiratory reserve, and superadded infections. The various presentations include myocardial injury, arrhythmia, myocarditis with heart failure, arterial or venous thromboembolic event or acute coronary syndrome and cardiogenic shock.[8]

The shock and hemodynamic instability management strategy in severely ill COVID-19 patients include optimizing the blood pressure and cardiac output, thus maintaining tissue perfusion. COVID-induced lung injury and positive pressure ventilation may lead to hemodynamic instability. In addition to COVID-induced pulmonary inflammation, consolidation, microvascular thrombosis and vasoconstriction, hypoxemia and dead space ventilation increases right-ventricular (RV) afterload followed by RV dilatation. The reduction in LV filling due to septal shift may lead to reduction in cardiac output and hemodynamic instability.[9] An optimal fluid balance is important for survival, volume overload is associated with prolonged ICU stay and poor outcome. Whereas hypovolemia may lead to tissue hypoperfusion, thrombus formation and may worsen hypoxemia especially in COVID-19 patients. The various methods for assessment of fluid status include fluid challenge test by administering crystalloid fluid boluses and assess the dynamic indices such as cardiac index

and/or velocity–time integral (VTI). The change in pulse pressure variation (PPV) may be assessed by transiently increasing the tidal volume in deeply sedated ARDS patients. Advanced hemodynamic modalities with assessment of dynamic variable may be applied if fluid management is challenging.[10, 11]

COVID-19 induced myocardial depression may occur in severely affected patients and around 1% patients may develop fulminant myocarditis. Troponin levels, natriuretic peptide monitoring and echocardiography assessment may help in early detection of myocardial dysfunction. Echocardiography can be a useful tool in diagnosis and assessment of fluid responsiveness during shock management. If haemodynamic instability persists in spite of adequate fluid administration, norepinephrine infusion should be considered as first-line vasopressor. Norepinephrine infusion may also improve RV function in ARDS patients by improving arterial blood pressure and thus RV blood supply. Vasopressin infusion may be started as second-line vasopressor if adequate blood pressure is not achieved with norepinephrine alone. Dobutamine infusion may be initiated as inotropic agent in case of cardiac dysfunction with acute decompensated heart failure.

Prone positioning should be used in cases of refractory hypoxemia if there is no contraindication. The use of inhaled selective pulmonary vasodilators which help in improving the RV afterload and RV function and thus improve the haemodynamics.

Isolated ARDS or ARDS associated with severe myocardial dysfunction unresponsive to mechanical ventilation and high doses of vasoactive drugs may be considered for VV ECMO (isolated ARDS) or VA ECMO (associated with myocardial dysfunction). However, a hybrid ECMO (V-AV or V-VA) may be required to prevent upper body hypoxemia in worsening of ARDS with VA ECMO.

RENAL DYSFUNCTION AND MANAGEMENT

Besides respiratory failure, the other organ dysfunctions due to COVID-19 include heart and kidney. The incidence of acute kidney injury (AKI) in severe COVID-19 patient is around 6–7% but carries a very high mortality risk especially those patients who are having hematuria or proteinuria, underlying renal dysfunction or AKI as per AKIN (Acute Kidney Injury Network) criteria II or more.[12] COVID-19 associated AKI may occur possibly due to cytokine storm, organ crosstalk or due to infection. Cytokine-induced injury due to release of several mediators IL-6/IL-8/IL-10/IL-18, etc. leading to cytokine storm.[13] This may lead to increased vascular permeability and hypovolemia due to fluid shift and also cause myocardial dysfunction. This may lead to AKI and is labelled as cardiorenal syndrome Type I. Cytokines removal using extracorporeal therapies may be useful in COVID-19 patients who develop acute kidney injury. The other mechanism leading to AKI is organ crosstalk where one injured organ (alveoli in ARDS) may produce tubular injury. Hemodynamic instability may lead to AKI, whereas rhabdomyolysis, metabolic acidosis, and hyperkalemia further worsen the AKI in COVID-19 patients.

The management included the haemodynamic optimization, treatment of sepsis and other supportive measures such as correction of hyperkalemia and metabolic acidosis. The loop diuretics may be used in cases of volume overload. Patients who are unresponsive to medical management should be supported with renal replacement therapy (RRT). The indications for RRT for AKI in critically ill patients are similar in COVID-19 patients. CRRT may be preferred in critically ill patients with potential of haemodynamic instability. However, sustained low-efficiency dialysis (SLED) can also be performed in critically ill patients. The selection of therapy depends upon several factors including cost, expertise and availability of resources as

well as reduction of exposure risk. The most common anticoagulation used during CRRT is regional citrate, however, due to risk of circuit thrombosis in COVID-19 patients or if patient is already on heparin, anticoagulation should be achieved with nonfractioned heparin.

METABOLIC DERANGEMENTS

The most common comorbidities encountered during COVID-19 infection are diabetes, hypertension, and cardiovascular diseases (CVD). Patients having diabetic are more often associated with severe COVID-19 infection. Blood sugar monitoring is essential throughout the ICU course, especially those patients who are receiving steroid. The poor blood sugar management is associated with increased morbidity and mortality (Table 1.1).[14]

Table 1.1: Blood glucose management

Regular monitoring of blood glucose level in severe COVID-19 patients
Maintaining pH, electrolytes and checking plasma glucose level
Use of intravenous insulin infusion in severe COVID-19 cases (ARDS and shock) to achieve adequate glycemic control Target blood glucose level: 110–180 mg%

OTHER MANAGEMENT

Remdesivir is most important antiviral therapy at present in severe Covid-19 infection. This is basically a prodrug and inhibits viral RNA polymerases after metabolizing to an analogue of adenosine triphosphate. The use of Remdesivir is associated with reduced mortality and length of hospital stay. The drug is administered intravenously (200 mg IV on day one and 100 mg IV daily 5–10 days). Recently the combination of lopinavir/ritonavir alongwith interferon beta-1b and ribavirin has shown reduced hospital stay and clinical improvement in severely ill COVID-19 patients.[15]

Corticosteroids have shown mortality benefit in COVID-19 patients requiring oxygen or mechanical ventilation. The dose of steroids in COVID-19:[16]

- Methylprednisolone 0.5 mg/kg I/V twice a day for 5 days or
- Dexamethasone 6 mg I/V once daily for 10 days or
- Dexamethasone 20 mg I/V once daily for 5 days and then 10 mg once daily for next 5 days.

Drugs with **Immunomodulation** potential such as tocilizumab, sarilumab, anakinra, reparixin, interferon-α etc. have been used for improving outcomes in COVID-19 patients. Tocilizumab administration has shown the reduction in mechanical ventilation days and decrease in serum IL-6 level. The maximum benefits may be achieved with the early use of Tocilizumab in ICU patients prior to intubation. This potential benefit is possibly related to high levels of IL-6, D-dimer, C-reactive protein, LDH, and ferritin.[17] However, recent randomized trial did not support the benefit with the use of tocilizumab in COVID-19 patients.

ANTICOAGULATION MANAGEMENT

COVID-19 infection induces the thromboinflammatory response with thrombus formation due to multiple factors such as endothelial damage, inflammation, inappropriate fibrinolysis, reduction of natural anticoagulants, and activation of coagulation factors. These patients have higher incidence of deep venous thrombosis and pulmonary embolism. So pharmacologic venous thromboembolism (VTE) prophylaxis should be used in all hospitalized COVID-19

patients if not contraindicated.[18] The anticoagulation regimens may be modified in obese patients, patients with severe thrombocytopenia or deteriorating renal function. What remains to be confirmed is the real role of therapeutic anticoagulation in these patients. The dose of enoxaparin for therapeutic anticoagulation in high risk category is 1 mg/kg twice daily or unfractionated heparin infusion may be given targeting aPTT 60–80 seconds. In the low risk category group, enoxaparin 40 mg once daily dose should be administered.[19]

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