

Review Article

COVID 19 - Concerns for the Intensive Care Physician- A Review

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Article History

Received: 13.02.2021

Accepted: 27.02.2021

Published: 06.03.2021

Journal homepage:

<https://www.easpublisher.com>

Quick Response Code



Abstract: COVID-19 is most well-known for causing respiratory pathology. It can also result in other organ involvement. These include thrombotic complications like myocardial infarction and stroke. Cardiac arrhythmias, acute kidney injury, gastrointestinal symptoms, hepatocellular injury, pancreatitis, neurologic disorders including demyelination, endocrine issues like hyperglycemia and ketosis have been reported. Individually and in combination, these can add to mortality and morbidity. This review is primarily focussing on the potential life threatening problems that physicians can encounter during the course of COVID 19 patients' stay in intensive care unit. Electronic literature search was done to study COVID-19 and its pathophysiology, different organ involvement other than lungs, ICU management and mortality. The search engines used to conduct the electronic literature searches were PubMed, PubMed Central, Google Scholar and CAS. A combination of keywords was used to make the searches such as COVID-19 AND (Pathology OR Pathophysiology OR Complications OR Organ failure OR Intensive care OR Risk factors OR Mortality). The articles published in English language between the years 2019 and 2020 were considered in the review. Few cross references of previous years were also reviewed and included. The findings of these studies were synthesized into a narrative review.

Keywords: COVID-19, Pathophysiology, Complications, Organ failure, Intensive care, Risk factors, Mortality.

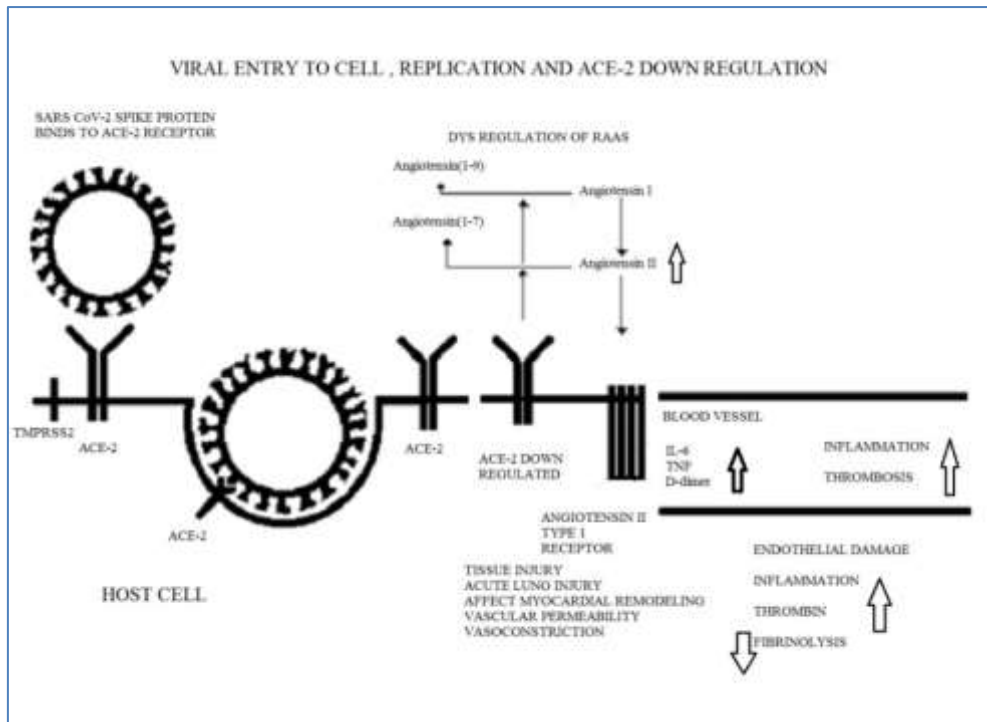
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INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is the third coronavirus infection in two decades, after Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) [1]. The COVID-19 pandemic has seen a surge of patients with Acute Respiratory Distress Syndrome (ARDS) in intensive care units across the globe. In the initial stage of the pandemic, mortality was high due to pneumonia, ARDS and respiratory failure. COVID-19 is most well-known for causing respiratory pathology. It can also result in other organ involvement.

PATHOPHYSIOLOGY

SARS-CoV-2 virus has receptor recognition capability similar to other virulent corona viruses such as SARS-CoV, responsible for the SARS epidemic of 2003 [2-4]. The virus' spike protein facilitates its entry into target cells. The spike subunit of SARS-CoV and SARS-CoV-2 engage ACE2 (Angiotensin Converting Enzyme 2) as an entry receptor (Fig1). Mechanisms that lead to multi-organ injury due SARS-CoV-2 infection include direct viral toxicity, endothelial cell damage and thromboinflammation, dysregulation of both the immune system and the renin-angiotensin-aldosterone system (RAAS) (Fig.1).



ACE 2 expression has been reported in histopathological studies in renal [5, 7] myocardial [5, 8], neurologic [5], pharyngeal [5] and gastrointestinal [9] tissues. Viral RNA was isolated less commonly from urine and blood [6].

Expression of ACE2 and TMPRSS2 (Transmembrane Protease Serine 2) was seen in lung alveolar epithelial type II cells, nasal goblet secretory cells, cholangiocytes, colonocytes, esophageal keratinocytes, gastrointestinal epithelial cells, pancreatic β -cells, and renal proximal tubules and podocytes [5, 10].

Endothelial cell damage and thrombosis

Endothelial cell damage by ACE2-mediated entry of SARS-CoV-2, leading to inflammation and progress to a prothrombotic state are the proposed pathophysiological mechanisms of COVID-19 [11-13]. Arterial and venous endothelium of several organs [11, 14] has ACE2 protein receptors as explained earlier.

Dysregulation of the immune response

Cytokine release syndrome, characterised by dysregulated immune response (over activation of immunity) is the hallmark of severe COVID-19 [15]. High serum inflammatory markers such as ESR (Erythrocyte Sedimentation Rate), C-reactive protein, LDH (Lactate Dehydrogenase), ferritin, D-dimer and fibrinogen are associated with severe disease and mortality in patients [16-18].

In about 30% of intensive care patients in China [19] and Netherlands [20], thrombotic complications were reported. Acute myocardial infarction (MI), acute limb ischemia and stroke were

noted in studies from the USA, Italy and France [21-24].

High rates of thromboembolic events were reported in critically ill patients with COVID-19 (17–22%), despite their having received prophylactic anticoagulation [22, 25, 26].

Severe COVID leads to more inflammation, endothelial damage and activation of prothrombotic state than other viral illnesses [27, 28].

Respiratory system

COVID -19 infections can cause problems ranging from mild upper respiratory tract symptoms to life-threatening viral pneumonia [29]. Patients with severe Covid-19 progressively become hypoxemic requiring ICU admission and mechanical ventilatory support.

Chest CT imaging of patients with pneumonia has shown peripheral lung ground-glass opacities fulfilling the Berlin criteria for ARDS [30].

Progressive respiratory failure is the primary cause of death in severe disease. In a small autopsy case series, it was found that microthrombosis of alveolar capillaries and vascular angiogenesis distinguished the pulmonary pathophysiology of Covid-19 from that of equally severe influenza virus infection [11].

Cardiovascular system

Cardiovascular effects include myocardial injury, Acute Coronary Syndrome (ACS), cardiomyopathy, arrhythmia and cardiogenic shock. The pathophysiology is probably multifactorial. Cardiac

myocytes, fibroblasts, endothelial cells and smooth-muscle cells [31] have high expression of ACE2, which can facilitate virus attachment.

Causes of myocardial damage, not specific to COVID-19, include severe ischemia or MI in patients with pre-existing coronary artery disease, Takotsubo, tachycardia-induced cardiomyopathy and myocardial stunning.

Renal system

Renal dysfunction (Acute Kidney Injury) is common with COVID-19 and is associated with mortality [32, 33]. Patho physiologically SARS-CoV-2 may directly infect renal cells, which is a possibility supported by histopathology findings and the presence of ACE2 receptors [34]. Histopathological findings include prominent acute tubular injury, diffuse erythrocyte aggregation and obstruction in peritubular and glomerular capillary loops [5, 7]. Viral inclusion particles in glomerular capillary endothelial cells suggest that micro vascular dysfunction is secondary to endothelial damage [13]. As in the case of other influenza viruses, cytokine storm [35] adds insult to injury.

Other etiologies of AKI, including ARDS, rhabdomyolysis, volume depletion and interstitial nephritis also need to be considered [36].

Gastro Intestinal Tract (GIT) and hepato biliary system

In 14–53% of critically ill COVID-19 patients, hepatocellular injury is seen [16, 37]. Transaminitis was usually less than five times the upper limit of normal.

Direct damage to the bile duct can be caused by this virus as it can bind to ACE2 on cholangiocytes [38]. Hyper inflammation with cytokine storm and hypoxia are other potential causes of hepatocellular damage [39]. Drug-induced transaminitis, secondary to the usage of Remdesivir, Lopinavir and Tocilizumab was also reported [39, 40].

Endocrine and metabolic effects

A wide spectrum of abnormalities including worsening hyperglycemia, euglycemic ketosis, and classic diabetic ketoacidosis were seen. In a retrospective study from China, of 658 patients hospitalized with COVID-19, 6.4% were presented with ketosis [41]. Studies from China and Italy demonstrated an association of underlying diabetes with severe illness and death [42, 43].

A more severe disease course was noted in diabetics, which may be attributable to hyperglycemia and ketosis. High cytokine levels may lead to impairment in pancreatic β -cell function and lead to apoptosis, which can contribute to insulin deficiency

[44]. ACE2 expression has been reported in the endocrine pancreas [45, 46].

Similar with SARS-CoV, direct binding of SARS-CoV-2 to ACE2 on β -cells might contribute to insulin deficiency and hyperglycemia [45]. Severe pancreatitis was also reported. Obesity [47] and diabetes [48] are risk factors for severe illness.

Nervous system

About 6% incidence of stroke [23, 49] is reported with severe COVID-19. Guillain-Barré syndrome has also been reported in some patients [50, 51]. Meningoencephalitis [52], Posterior Reversible Encephalopathy Syndrome (PRES) [53] and acute necrotizing encephalopathy have been described in case reports [54, 55].

Coronavirus that causes MERS have known neuroinvasive and neurotropic abilities [56, 57]. SARS-CoV-2 may access the central nervous system via the nasal mucosa, lamina cribrosa, and olfactory bulb. This can lead to meningoencephalitis.

Cytokine storm with its proinflammatory and prothrombotic cascade affects brain vasculature and the blood–brain barrier (often seen in severe cases).

INTENSIVE CARE MANAGEMENT

Airway and Breathing

COVID-19 patients requiring ICU admission are usually very hypoxic, needing some form of ventilator assistance. Approximately 5% of the patients who contract COVID-19 require admission to ICUs [58]. During the initial phase of the pandemic, most of the hypoxic patients were intubated early and Non Invasive modalities like HFNC (High Flow Nasal Cannula) and NIV (Non Invasive Ventilation) were not considered due to concerns of infection spread (aerosols). The concerns about aerosol dispersion had led to calls for early intubation [59]. With time, more evidence has emerged about the safety of Non Invasive Ventilation. With experience, physicians realized that mortality of invasively ventilated patients was high and it was not easy to extubate many of these patients.

Among patients with COVID-19 with ARDS, Gattinoni *et al.* [60-62] have described an “L” phenotype (for low elastance) in patients who demonstrated relatively preserved respiratory system compliance of > 50 mL/cm H₂O with focal areas of ground-glass opacity on CT scanning. In contrast, low compliance (“H” phenotype—for high elastance), is typically seen in non-COVID-19 patients with ARDS.

A number of studies have compared HFNC with NIV and mask oxygen. HFNC has been shown to be more comfortable and better tolerated [63]. Surviving Sepsis/Society of Critical Care Medicine guideline [64] advocates it as a first-line approach.

Patients on Non Invasive modalities will require very close monitoring in ICU. Patients who are rapidly deteriorating due to worsening hypoxemia, hypercarbia and acidosis will require invasive ventilator support.

Currently there are no studies addressing mechanical ventilation strategies in COVID-19 patients. Mechanically ventilated patients with COVID-19 should be managed similar to other patients with acute respiratory failure in the ICU [64]. A strong recommendation is to use low Tidal Volume (VT: 4–8 mL/kg predicted body weight) when ventilating patients.

While mechanical ventilation is a potentially life-saving intervention, it can worsen lung injury and ventilator-induced lung injury (VILI) can contribute to multiorgan failure in patients with ARDS [65]. One of the main ventilator strategies to minimize VILI is low VT ventilation.

Circulation and hemodynamics

Hemodynamic monitoring and support for COVID -19 patients should be similar to any other critical patient in ICU. The prognosis of patients with COVID-19 with shock has not been systematically reported. In a study of 150 patients from 2 hospitals in Wuhan, China, shock was a major reason for death in 40%, and partly be due to fulminant myocarditis[66].

Patients with shock will need dynamic parameters like skin temperature, capillary refilling time and/or serum lactate measurement over static parameters in order to assess fluid responsiveness [64]. For the acute resuscitation of adults with COVID-19 with shock, a conservative over a liberal fluid strategy is recommended (based on data extrapolated from critically ill patients with sepsis or ARDS).

After adequate fluid resuscitation, for adults with COVID-19 and shock, Norepinephrine is recommended as the first-line vasoactive agent. Vasopressin can be added as a second-line agent, along with titrating Norepinephrine dose, if target mean arterial pressure (MAP of 60–65 mmHg) cannot be achieved by Norepinephrine alone[64].

For patients in shock with evidence of cardiac dysfunction and persistent hypo perfusion, despite fluid resuscitation and norepinephrine, adding dobutamine should be considered over increasing norepinephrine dose [64]. Low-dose corticosteroid therapy is recommended for refractory shock [64].

Microvascular thrombosis and ischaemia

COVID -19 infection is known to produce microvascular thrombosis and ischaemia. Peripheral ischaemia involving digits and limbs are reported. Shock with hypo perfusion along with vasopressors will

add to the problem .Critical care physicians should be vigilant about this dreaded complication [67].

Renal

Severe COVID-19 pneumonia patients can develop Acute Kidney Injury due to multiple reasons. Apart from the direct insult of the virus on kidneys, other causes like rhabdomyolysis, volume depletion and interstitial nephritis need to be considered. Due to severe pneumonia and ARDS, clinicians tend to adopt a conservative fluid strategy which in turn can worsen renal function. Hemodynamic instability and sepsis will adversely affect renal function and increase the recovery time and mortality [32, 33]. ICU team needs to take a cautious approach to prevent intravascular volume depletion and maintain hemodynamic stability. Cytokine storm [35] adds to kidney injury.

The care strategy for patients with COVID-19 in the ICU remains mainly supportive. With high incidence of kidney involvement in COVID-19, it is important to support kidney function with all possible treatment options.

Following KDIGO supportive care guideline (e.g., avoidance of nephrotoxins, regular monitoring of serum creatinine and urine output, consideration of haemodynamic monitoring) in critically ill patients with kidney involvement is likely to reduce the occurrence and severity of AKI in COVID-19 [68].

If conservative management fails, Renal Replacement Therapy (RRT) should be considered in patients with volume overload, especially those with refractory hypoxemia. Other indications for RRT are oliguria, hyperkalemia, acidosis and azotaemia. Continuous RRT (CRRT) is the preferred modality in haemodynamically unstable patients with COVID-19 [69].

Gastro Intestinal Tract (GIT) and hepatobiliary system

Apart from direct viral invasion and damage to GIT causing nausea, vomiting and diarrhoea, potentially lethal complication like mesenteric ischemia can happen with severe COVID -19 infections. Histopathological evidence of diffuse endothelial inflammation in the submucosal vessels of the small intestine from patients with COVID-19 and mesenteric ischemia suggests microvascular small-bowel injury [13]. Unexplained lactic acidosis and diarrhoea should arouse high index of suspicion.

Even though incidence of GI bleed was not reported higher than in general ICU population, it is a potential complication which needs specific attention, since most ICU patients with COVID -19 will be on high dose anticoagulation and steroids. Hemodynamic instability and shock will add to the risk of GI bleed.

Viral invasion and injury to biliary tree and hepatocellular damage has been documented in critically ill patients [18]. Transaminitis, secondary to anti-viral drugs (Remdesivir) and Tocilizumab also need to be monitored closely.

Pancreatitis is another dreaded complication seen associated with COVID-19 infection. Symptoms can range from mild to potentially life threatening disease.

Nervous system

Acute incidence of stroke is seen in COVID-19 [23, 49]. It is important to watch for neurological deterioration in severe COVID-19 pneumonia patients requiring invasive mechanical ventilator support. Most of these patients will require deep sedation and Neuro Muscular Blocking agents to facilitate ventilation. This in turn will make motor assessment impossible. Meningoencephalitis [52], hemorrhagic posterior reversible encephalopathy syndrome [53] and acute necrotizing encephalopathy, including the brainstem and basal ganglia, have been described in case reports [54, 55]. Some of these neurological complications alone can lead to fatal outcome. Other neurological sequelae of critical illness are neuropathy and myopathy (high incidence is expected due to requirement of Neuro Muscular Blocking agents and Steroids) which in turn can delay the weaning from mechanical ventilation.

Endocrine and metabolic effects

A wide spectrum of abnormalities of glucose metabolism is seen in patients with COVID-19, including worsening hyperglycemia, euglycemic ketosis and classic diabetic ketoacidosis [41]. Glycemic control can further worsen by critical illness and steroid use. Such patients in the ICU will require continuous Insulin infusions and hourly blood glucose monitoring. Fluid management can become challenging as fluid overload can worsen hypoxemia. Adrenal insufficiency has to be kept in mind as most hypoxic patients will need steroids for longer period (Watch after 'taper and stop').

Sepsis

Secondary infection and sepsis is a challenge for patients who require invasive mechanical ventilator support. Most of these patients will need prolonged stay in ICU and ventilation. Periodic surveillance cultures and appropriate antibiotics are recommended. Incidence of sepsis is further increased by usage of steroids and Tocilizumab. If treating team initiates empiric antimicrobials, they should assess for de-escalation daily, and re-evaluate the duration of therapy and spectrum of coverage based on the microbiology results and the patient's clinical status.

Cytokine storm syndrome

Cytokine storm syndrome is a hyper inflammatory state that is characterized by fulminant multi-organ failure and elevation of cytokine levels.

Severely ill patients with COVID-19 may have an extreme immune response leading to severe respiratory failure. In such cases, inhibition of Interleukin 6 (IL-6) may help attenuate the cytokine release syndrome by reducing cytokine concentration and acute phase reactant production [70].

Tocilizumab is a humanized immunoglobulin that functions in the immune response and blocks IL-6 receptor binding to IL-6. It has been approved for CRS and other inflammatory conditions related to IL-6 related inflammation. It has been used on experimental basis [71].

This study published recently provides strong evidence that Tocilizumab might prevent intubation and death in adults with severe COVID-19 pneumonia. These findings are also in agreement with emerging evidence that, in the setting of COVID-19-induced cytokine storm, immunosuppressive treatments might be most helpful earlier in the disease, before florid respiratory failure [72].

Other supportive care

Other supportive care includes anti-viral, anti-coagulation, thromboprophylaxis, steroids and stress ulcer prophylaxis. Feeding and nutritional support is another area of importance in critical patients with COVID -19 since most of these patients are hyper catabolic.

CONCLUSION

Beyond the life-threatening pulmonary complications of SARS-CoV-2, the widespread other organ-specific pathology of COVID-19 are increasingly being recognized. Some of these are potentially life threatening by itself. It is important for the treating team to understand that COVID-19 is a multisystem disease akin to vasculitic disorders and anticipate possible complications and plan the treatment accordingly.

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Cite this article: Padmakumar V Arayamparambil & Deepa C Velayudhan (2021). COVID 19 - Concerns for the Intensive Care Physician- A Review. *EAS J Anesthesiol Crit Care*, 3(2), 10-17.