Article title: Current Challenges in the Management of Critically Ill COVID-19 Patients: The Effect of Critical Illness Myopathy

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Preprint statement: This article is a preprint and has not been peer-reviewed, under consideration and submitted to ScienceOpen Preprints for open peer review.

DOI: 10.14293/S2199-1006.1.SOR-.PPW3KYM.v1

Preprint first posted online: 09 January 2021

Keywords: Coronavirus, Covid-19, Critical Illness Myopathy, Inflammation, Glycemic control, Respiratory therapy

BACKGROUND

At the time of this review, we are still in the depths of the COVID-19 pandemic. Although most infections are mild and self-limiting, patients who develop severe COVID-19 infections have a high mortality risk. A recent meta-analysis of 10,150 patients showed a mortality rate of 41.6% among COVID-19 patients admitted to the ICU.¹ In comparison, the mortality rate among ICU patients with other causes of viral pneumonia is 22%¹, and the total ICU mortality rate for all illnesses is 10-29% depending on illness severity and comorbidities². Given the lack of curative treatment options and the length of time required for vaccine development, there is a dire need for further investigation of illness complications and supportive care techniques for patients with COVID-19.

This review will focus on the impact of Critical Illness Myopathy and Polyneuropathy (CIMPN) on COVID-19 patient outcomes. CIMPN is a condition commonly acquired in ICU settings as a result of severe illness. Studies have shown that ICU patients who received mechanical ventilation for at least 4-7 days experience CIMPN at a rate of 25-33%. In patients experiencing acute respiratory distress (ARDS), that number climbs to 60%³. In CIMPN, complex inflammatory and biochemical interactions cause damage to muscles and nerves, which further weakens already-distressed patients. CIMPN mainly affects proximal limb musculature and respiratory muscles, which make it a possible contributor to failed respiratory therapy in critically ill COVID-19 patients.

PURPOSE

Many critically ill patients with COVID-19 never wean from respiratory support. The purpose of this literature review is to shine light on a possible complication of critical illness that may be contributing to the poor outcomes of critically ill COVID-19 patients.

METHODS

A systematic review of the literature was conducted using three primary electronic databases: PubMed, EMBASE, and ResearchGate. Articles were selected based on their relevance to COVID-19, CIMPN, and respiratory therapy. Information from these articles was analyzed in order to form a hypothesis on how CIMPN may be contributing to treatment failure in COVID-19 patients.

PATHOPHYSIOLOGY

The clinical features of COVID-19, the disease caused by the virus SARS-CoV-2, are largely caused by the body's inflammatory response to viral infection. A "cytokine storm" produced by the body during infection causes microvascular damage, leading to pulmonary edema and respiratory distress.⁴ Similarly, damage to microvasculature is implicated in the pathophysiology

of CIMP. In CIMP, it is hypothesized that leaky microvasculature in nerves and muscles causes localized edema that leads to ischemia and decreased delivery of nutrients. There is overlap in the identified cytokine profiles that contribute to both severe COVID-19 infections and the development of CIMP. Shepherd et al identified IL-1 and TNF-alpha as the main drivers of microvascular damage in CIMP.³ IL-1 and TNF-alpha in turn upregulate IL-6, which drives production of acute phase reactants. Some well known acute phase reactants include c-reactive protein, fibrinogen, and ferritin. According to Henry et al, elevated levels of IL-6, IL-10, and serum ferritin have been identified as strong indicators of severe infection in COVID-19 patients.⁵ This interaction of inflammatory mediators found in both CIMP and severe COVID-19 cases suggests that two separate disease processes may be simultaneously contributing to respiratory failure via pulmonary edema and respiratory muscle failure.

In addition to generalized inflammation, the TGF-beta/MAPK pathway has been specifically identified as a driver of muscle damage in CIMP. Activation of the MAPK cascade by TGF-beta in muscle cells alters transcription, reducing expression of the contractile filament myosin and transmembrane sodium channels necessary for excitation/contraction coupling.⁶ This signaling cascade also activates proteasomes that break down muscle filaments, causing apoptotic muscular atrophy.

Fig. 2: TGF-beta and muscle damage in CIMP

Interestingly, hyperglycemia is the only known modifiable factor that contributes to the development of CIMP.³ One study showed that patients with poor glycemic control in an intensive care setting had a higher incidence of CIMP with an odds ratio of 2.6.⁷ As previously mentioned, edema caused by microvascular damage results in decreased delivery of glucose and

other nutrients to nerve and muscle cells. Elevated blood glucose in turn, along with hypoalbuminemia, further contributes to edema, perpetuating the cycle of muscle damage. The fact that blood glucose levels are easily modified with diet and insulin administration make it an important consideration for the management of critically ill COVID-19 patients. This becomes especially important when considering diabetic patients, who already have a predisposition for both hyperglycemia and severe COVID-19 infections.⁸

Fig. 1: Contributors to the development of critical illness myopathy and polyneuropathy

CONCLUSIONS

CIMPN is a common complication of critical illness that contributes to muscular and respiratory failure. It's close association with severe inflammation and ARDS makes it a likely contributor to respiratory failure experienced by critically ill COVID-19 patients. The research analyzed in this literature review suggest that glycemic control should be an important consideration in the management of COVID-19 patients. This becomes especially important for diabetic patients, who are already predisposed to high blood glucose levels. Additionally, future clinical drug trials may seek to assess the usefulness of TGF-beta inhibitors in the treatment of critical COVID-19 patients. Inhibition of TGF-beta would hypothetically have the two-fold effect of slowing development of CIMPN and reducing suppression of CD8⁺ T-cells, which are the immune system's most powerful weapon against viral infections.

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