REVIEW ARTICLE

Cytokine Storm in Novel Coronavirus Disease (COVID-19): Expert Management Considerations

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ABSTRACT

Aim/objective/introduction: Cytokine storm or cytokine release syndrome (CRS) is inevitable in severe and critically ill patients with novel coronavirus disease-2019 (COVID-19). This review aimed to discuss current therapeutic options for the management of CRS in COVID-19.

Background: Cytokine storm is caused by the colossal release of proinflammatory cytokines [e.g., IL (interleukin)-2, IL-6, IL-8 TNF (tumor necrosis factor)-α, etc.] causing dysregulated, hyperimmune response. This immunopathogenesis leads to acute lung injury and acute respiratory distress syndrome (ARDS). Targeting cytokine storm with the therapies that are already available in India with the support of published guidelines and consensus can assist in achieving a better outcome in COVID-19.

Review results: We predominantly included published guidelines or consensus recommendations about the management of cytokine storm in COVID-19. From the existing literature evidence, it is observed that among the currently available agents, low-dose corticosteroids and heparin can be beneficial in managing cytokine storm. The use of serine protease inhibitors such as ulinastatin has been advised by some experts. Though therapies such as high-dose vitamin C and interleukin-6 inhibitors (e.g., tocilizumab) have been advised, the evidence regarding their use for cytokine storm in COVID-19 is limited. Therapies such as Janus kinase inhibitors (JAK) inhibitors and Neurokinin-1 receptor (NK-1) antagonists are still in research. Besides, pharmaceutical treatments, use of blood purification strategies, and convalescent plasma may be life-saving options in some of the critically ill COVID-19 patients. For these therapies, there is a need to generate further evidence to substantiate their use in CRS management.

Conclusion: Current management of COVID-19 is preventive and supportive. Different therapies can be used to prevent and treat the cytokine storm. More research is needed for further supporting the use of these treatments in COVID-19.

Keywords: Acute respiratory distress syndrome, Coronavirus, COVID-19, Cytokine storm, Immunosuppressants.

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BACKGROUND

Novel coronavirus disease-2019 [COVID-19/severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)] is a pandemic that has affected more than 1.7 million individuals globally and caused more than 110,000 deaths.[1] India has over 8,900 diagnosed cases, with more than 330 deaths attributed to COVID-19.[2] Though the majority of patients with COVID-19 develop a mild infection, nearly 14% develop severe disease requiring hospitalization and 5% need intensive care.[3] Severe disease is characterized by the development of complications such as acute respiratory disease syndrome (ARDS), sepsis and septic shock, multiorgan failure, including acute kidney injury (AKI) and cardiac injury.[4] With pathogenic coronaviruses, rapid virus replication with massive inflammatory cell infiltration and elevated proinflammatory cytokine/chemokine responses have been reported. This results in acute lung injury (ALI) and ARDS.[5] Accumulating evidence suggests that a subgroup of patients with severe COVID-19 might develop a cytokine storm syndrome.[6] The cytokine storm is thought to be the reason for rapid multiorgan failure. Therefore, modulation of the immune response or suppression of overreactive cytokine production may prove crucial in severe cases.[6,7] In this review, we discussed the pathogenesis and consequences of cytokine storm along with current therapeutic approaches and recommendations for its management in patients with COVID-19 infection.

REVIEW RESULTS

Pathogenesis and Consequences of Cytokine Storm

Although complete pathology of SARS-CoV-2 has not been fully understood, viral and host factors appear to play a vital role in

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this infection. Li and colleagues discussed the innate and adaptive immune response to SARS-CoV-2 in detail. Immunopathogenesis in response to the out-of-control immune response underlies the COVID-19 infection.[8] A fundamental understanding of COVID-19 is the biphasic immune response. During the incubation and mild stages, a specific adaptive immune response is required to eliminate the virus and to preclude disease progression to severe stages. In the later stages of the COVID-19 infection, the cytokine release syndrome (CRS) causes more severe disease.[9] A cytokine profile in COVID-19 is characterized by increased interleukin (IL)-2, IL-6, IL-7, granulocyte colony-stimulating factor (GCS-F), interferon-γ

(INF-γ) inducible protein 10, monocyte chemoattractant protein 1 (MCP-1), macrophage inflammatory protein 1-α (MIP 1-α), and tumor necrosis factor-α (TNF-α).[6] This cytokine profile resembles closely with secondary hemophagocytic lymphohistiocytosis (sHLH). Secondary hemophagocytic lymphohistiocytosis is usually triggered by viral infections and characterized by unremitting fever, pulmonary involvement (ARDS), cytopenias, and increased ferritin.[6]

Channappanavar and Perlman have described in depth the cause and consequences of CRS. The cause of CRS may include rapid viral replication, infection of the airway and/or alveolar epithelial cells, delayed INF response, and accumulation of inflammatory monocyte-macrophages and neutrophils in the lungs. The consequences of CRS include epithelial and endothelial cell apoptosis and vascular leakage causing alveolar edema and hypoxia, suboptimal T-cell response leading to uncontrolled inflammatory response, accumulation of alternatively activated macrophages and altered tissue homeostasis, ARDS leading to pulmonary fibrosis, and eventually death.[5]

In the histopathological examination of pulmonary lesions, along with nonspecific inflammatory responses (e.g., edema, inflammatory cell infiltration), other findings of the immunopathogenic response included severe exfoliation of alveolar epithelial cells, alveolar septal widening, damage to alveolar septa, and alveolar space infiltration. These findings indicate that the inflammatory response plays an important role throughout the course of COVID-19 infection.[7] Another supporting evidence is from a study in Wuhan, China. In assessing 150 cases of COVID-19, Ruan et al. identified age, the presence of underlying diseases, the presence of secondary infection, and elevated inflammatory indicators in the blood as predictors of mortality. They further concluded that COVID-19 death might be due to virus-activated "cytokine storm syndrome" or fulminant myocarditis.[10]

In addition to the inflammatory response, derangements in coagulation parameters have been identified. Raised D-dimer levels, higher levels of fibrin degradation products, and prolonged prothrombin time increase mortality risk. Compared to survivors, disseminated intravascular coagulation (DIC) was reported in a significantly higher proportion of nonsurvivors.[11] These data indicate that in addition to the inflammatory response, the coagulation and fibrotic response is seen in COVID-19 contributing to the fibroproliferative lung disease.[12]

Also, some investigators indicated that all patients with severe COVID-19 should be screened for hyperinflammation using laboratory trends like increasing ferritin, decreasing platelets, etc. HScore is an important tool that may help to discriminate patients with CRS. For calculating Hscore, please refer http://saintantoine.aphp.fr/score/.[13] The HScore incorporates nine parameters as shown in Table 1. Therefore, abolishing or minimizing the cytokine storm in COVID-19 can be helpful in improving the outcomes in severe cases.

Cytokine Storm: Current Therapeutic Strategies

Cytokine storm is a well-established clinical condition that is characterized by significant proinflammatory cytokine release leading to a dysregulated and hyperactive immune response causing organ dysfunction. Numerous investigators suggested targeting cytokine storm syndrome in severely ill patients with human coronavirus infection.[5,6] A report from China identified a cytokine storm being common in elderly patients with COVID-19. Amidst the antiviral and supportive treatment for COVID-19, immune modulation may become necessary in severe stages of

Table 1: Parameters evaluated using HScore

Known underlying immunodepression	Yes/no
Maximal temperature (°C)	<38.4, 38.4–39.4, and >39.4
Hepatomegaly	Yes/no/unknown
Splenomegaly	Yes/no/unknown
Lower hemoglobin level (g/dL)	≤9.2 or >9.2/unknown
Lower Leukocytes count (cells/mm³)	≤5,000 or >5,000/unknown
Lower platelets count (cells/mm³)	≤110,000 or >110,000/unknown
Higher ferritin level (ng/mL)	<2,000, 2,000–6,000, or >6,000/unknown
Higher triglyceride level (mmol/L)	<1.5, 1.5–4, or >4/unknown
Higher SGOT/ASAT level (UI/L)	<30 or ≥30/unknown
Lower fibrinogen level (g/L)	≤2.5 or >2.5/unknown
Hemophagocytosis features on bone marrow aspirate	Yes/no/unknown

Table 2: Possible therapeutic agents for cytokine storm in COVID-19

Category	Molecules
Currently available therapeutic options in India	Corticosteroids
	Vitamin C
	Heparin: unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH)
	Serine protease inhibitor: ulinastatin
	Convalescent plasma
	Blood purification systems
	IL-6 inhibitors: tocilizumab
	JAK inhibitors: baricitinib
Other drugs	IL-6 inhibitors: sarilumab, TZLS-501
	NK-1 antagonist: tradipitant

the disease.[14] Table 2 enumerates the therapies targeted toward CRS, which are discussed briefly in the below sections.

Corticosteroids

A small retrospective study from China in 201 patients reported lower mortality with the use of steroids in patients of COVID-19 with ARDS.[15] In patients with septic shock, the use of steroids can lower mortality and lead to a faster resolution of the shock.[16] The 2020 guidelines from the Society of Critical Care Medicine and the European Society of Intensive Care Medicine suggest the use of systemic corticosteroids in a low dose and for a short period in mechanically ventilated COVID-19 patients with ARDS.[17] It is being identified that low-dose steroids are being used in several patients across different countries in the management of COVID-19.[18] Though no current clinical studies are available for the use of steroids in a cytokine storm, the expert consensus from the Shanghai Medical Association recommends caution with the use of corticosteroids in COVID-19.[19] A systematic review also finds that current evidence is weak but suggests that low-dose steroids may be beneficial in

SARS-CoV infections (not specific to COVID-19).[20] In the past, the use of intravenous steroid in MERS-CoV and SARS-CoV resulted in a significant increased risk of mortality.[18] We consider that steroids if at all used must be used for 3–6 days only in critically ill COVID-19 patients based on clinical judgment with adequate monitoring of respiratory functions and pneumonia worsening on X-ray.

Vitamin C

Vitamin C through its actions on oxidative stress and inflammation, immune cell function, and epigenetic immunologic modifications has shown efficacy in patients of sepsis with ARDS. Recently, the CITRIS-ALI trial, which was a randomized, double-blind, placebo-controlled, multicenter trial, evaluated patients with sepsis and ARDS (n = 167). Compared to placebo, intravenous infusion of vitamin C (50 mg/kg in dextrose 5% in water over 96 hours) was associated with significantly lower 28-day mortality (29.8% vs 46.3%, $p = 0.03$).[21] The expert consensus Shanghai Medical Association recommends that 100–200 mg/kg intravenous vitamin C daily can lead to an improvement in the oxygenation index.[19]

Heparin

Apart from the anticoagulant effect, heparin has potential benefit in patients with COVID-19 with its anti-inflammatory properties. Inflammation and thrombin generation directly correlated in the immune-thrombosis bidirectional relationship theory, wherein heparin can reduce the inflammatory response by inhibiting thrombin formation. The direct anti-inflammatory properties of heparin are due to its ability to bind to inflammatory cytokines, inhibition of neutrophil chemotaxis, and leukocyte migration.[22] In a recent study, Tang and colleagues have shown the benefits of using heparin in terms of reduction in mortality in patients with SARS-CoV2. Use of heparin was most beneficial in patients with meeting the SIC (sepsis-induced coagulopathy) criteria of >4 and with markedly elevated D-dimer. The majority of the patients in the study received low-molecular-weight heparin (LMWH) and very few were on unfractionated heparin (UFH).[23] With emerging new evidence on the risk of venous thromboembolism (VTE) in seriously ill patients with COVID-19 and potential benefits of heparin (particularly LMWH) for its anti-inflammatory properties, the International Society on Thrombosis and Haemostasis (ISTH) has recommended thromboprophylaxis with LMWH for admitted patients with COVID-19 infection (including noncritically ill).[24]

Serine Protease Inhibitors

A recent observation from Hoffman et al. established that SARS-CoV-2 uses SARS-CoV receptor ACE2 for its entry in host cells. The host cell protease TMPRSS2 is necessary for SARS-CoV2 spike protein receptor priming for its effective attachment to the ACE2 receptor.[25] Zhou et al. demonstrated that viral spread and pathogenesis of SARS-CoV was effectively prevented by the serine protease inhibitor, Camostat.[26] Nafamostat is another serine protease inhibitor shown to inhibit the MERS-CoV S protein-mediated membrane fusion.[27] Given these observations, serine protease inhibitors seem to be potential therapeutic options in coronavirus infections.

In India, ulinastatin, a broad-spectrum serine protease inhibitor, is currently available for the treatment of severe sepsis and mild-to-severe acute pancreatitis. It is also effective for the treatment of ARDS as observed in various clinical studies. A recent meta-analysis of 33 randomized controlled trials (RCTs) involving 2,344 patients of ARDS showed that compared to conventional therapy, ulinastatin was superior in reducing mortality, ventilator-associated pneumonia, duration of mechanical ventilation, length of hospital stay, and increasing the patients' oxygenation index.[28] These effects were probably attributable to the effects of ulinastatin on serum inflammatory markers. The meta-analysis had also demonstrated a significant reduction in levels of TNF-α, IL-1β, IL-6, and IL-8.[28] The 2019 Shanghai Expert consensus recommends broad-spectrum serine protease inhibitors in the treatment of COVID-19. The consensus was based on the opinions of 30 experts representing the strongest medical force in the treatment of new-type coronavirus pneumonia in Shanghai. If lung lesion progresses, high doses of broad-spectrum protease inhibitor, ulinastatin, from 0.6 to 1 million U/day until lung radiographic improvement should be used. The consensus also recommended such treatment at a high dose of 1.6 million units, for the prevention and treatment of cytokine storm in COVID-19. Under mechanical ventilation, when the oxygenation index is greater than 300 mm Hg, the dose can be reduced to 1 million U/day.[19]

Considering the potential utility of serine protease inhibitors in severe and critically ill patients of COVID-19, the CamoCO-19 clinical trial (ClinicalTrials.gov Identifier: NCT04321096) is underway to examine the effect of Camostat mesylate (2 × 100 mg pills thrice daily for 5 days) on the clinical improvement of patients. Similarly, CLOCC trial (ClinicalTrials.gov Identifier: NCT04338906) is underway to establish the superiority of hydroxychloroquine—Camostat combination therapy to hydroxychloroquine—placebo in moderate COVID-19.

Convalescent Plasma

Convalescent plasma is an antibody-rich plasma collected from recovered COVID-19 patient, which is transfused to the sick patients. In a case series of five critically ill COVID-19 patients, transfusion with convalescent plasma with a SARS-CoV-2-specific antibody (IgG) binding titer greater than 1:1,000 and a neutralization titer greater than 40 resulted in negative viral load within 12 days. Acute respiratory distress syndrome resolved in four out of five patients on day 12 of transfusion. Among the five, three patients were discharged within 2 months from admission and two were in stable condition at 37 days after transfusion. This indicates convalescent plasma may be useful in clinical recovery critically ill patients.[29] The U.S. Food and Drugs Administration issued guidelines for use of investigational COVID-19 convalescent plasma. Criteria laid down for eligibility included laboratory-confirmed, severe (dyspnea, O_2 saturation ≤93%, respiratory rate ≥30 per minute, the partial pressure of arterial oxygen to fraction of inspired oxygen ratio <300 and lung infiltrates >50% within 24–48 hours) or life-threatening (respiratory failure, septic shock, multi-organ dysfunction) COVID-19 along with an informed consent provided by the patient or healthcare proxy.[30] However, logistical issues in terms of availability, the timing of administration of therapy, and consent from the recovering or recovered patients may limit its use.

Blood Purification Systems

Cytokine clearance can also be achieved using artificial-liver blood-purification (ALBP) systems. Methods such as plasma exchange, plasma absorption, and/or hemo or plasma filtration can be employed for cytokine clearance. From China, an Expert Consensus recommended ALBP therapy in the treatment of severe COVID-19 patients who exhibit cytokine storm. The indications for its use were a fivefold or higher level of proinflammatory cytokines such as IL-6 or an increase of more than onefold per day, rapid disease progression with more than 10% lung involvement on imaging,

and comorbidities requiring ALBP therapy.[31] Continuous renal replacement therapy (CRRT) and high-volume hemofiltration may be used particularly in patients with AKI for cytokine clearance.[32] CytoSorb is an extracorporeal cytokine adsorber designed to broadly reduce cytokine storm.[33] Though these therapies can be used in managing cytokine storm, the evidence of their use in COVID-19 patients is lacking.

IL-6 Inhibitors: Tocilizumab

An open-label, noncontrolled study (nonpeer-reviewed) from China in 21 severe COVID-19 patients who received a single dose of tocilizumab (400 mg IV infusion) reported improved oxygenation and normal lymphocyte counts. After a mean of 15.5 days of treatment, 19 patients were discharged, suggesting potential effectiveness of tocilizumab in severe cases of COVID-19.[34] Tocilizumab in COVID-19 pneumonia (TOCIVID) is phase 2 trial (ClinicalTrials. gov Identifier: NCT04317092) of tocilizumab (8 mg/kg (up to a maximum of 800 mg per dose), with an interval of 12 hours) in severe hospitalized COVID-19 patients with the primary outcome being the mortality rate at 30 days. Roche also announced the approval of phase III RCT of tocilizumab (COVACTA) in severe patients hospitalized with COVID-19 pneumonia.[35]

Clinical trials with sarilumab (ClinicalTrials.gov Identifier: NCT04327388, ClinicalTrials.gov Identifier: NCT04315298) in severe COVID-19 patients are initiated in the United States. An anti-interleukin-6 receptor monoclonal antibody TZLS-501 is currently under development.[34]

JAK Inhibitors: Baricitinib

AP2-associated protein kinase 1 (AAK1) is a key regulator in endocytosis of virus and interrupting this process can be helpful in treating infection such as SARS-CoV2. Baricitinib is a JAK inhibitor as well as an AAK1 inhibitor that interrupts the passage of the virus into cells and can help prevent virus infections.[36] Baricitinib in symptomatic patients infected by COVID-19 (BARI-COVID), a phase 3 trial (ClinicalTrials.gov Identifier: NCT04320277) of baricitinib (4 mg/day/orally) in mild to moderate COVID-19 infection, is underway.

Neurokinin-1 Antagonist: Tradipitant

Neurokinin-1 (NK-1) receptor is the principal receptor for the substance P. It is involved in neuroinflammatory processes that can result in serious lung injury following insults such as viral infections.[34] The ODYSSEY trial (ClinicalTrials.gov Identifier: NCT04326426) is currently recruiting patients with severe or critical COVID-19 infection to assess the efficacy of tradipitant (85 mg PO BID) with the primary outcome of normalization of fever and oxygen saturation by day 14.

Discussion

Considering the pathophysiology of cytokine storm in certain patients infected with coronavirus and its consequences leading to severe illness in the form of pneumonia, ARDS, and septic shock, it is very critical to have a comprehensive approach in such patients with the use of immunomodulatory drugs along with antiviral and standard supportive care. Among the available therapeutic options in India, we attempted to summarize the therapies that could be immediately considered for managing the cytokine storm in COVID-19 infection. There are certain crucial questions—when to initiate the immunomodulatory drugs? How to balance the benefit-risk profile? What patient profile is suitable for such therapies? Are these drugs immediately available in India? Among available options, which one is best? Though many therapies can possibly be used in managing cytokine storm, the evidence regarding their use is sparse. Furthermore, there is no uniform consensus with regard to the use of a specific class of drugs. We have enumerated current guidance and evidence from some of the published reports that have identified potential therapies for use in CRS in COVID-19 (Table 3). In our opinion, it is advisable to initiate these immunomodulatory therapies early in the course of the disease, i.e., at the stage of pneumonia to prevent possible cytokine storm and subsequent complications.

Among the available options, the WHO advised against the use of corticosteroids in management of COVID-19. However, the guideline did not discuss about the specific management of cytokine storm in COVID-19.[3] Suppression of the immune response with steroids can be associated with delayed virus clearance and systemic side effects like hyperglycemia, psychosis, etc.[41] But, a steroid such as methylprednisolone in a low dose for 3–6 days may be useful in patients with mechanical ventilation and refractory septic shock.[36] A systematic review from Russel et al. identified that low-dose corticosteroids can be helpful in cytokine storm in

Table 3: Summary of recommendations from major guidelines and consensus as well as published literature on use of therapeutic options for cytokine storm in COVID-19

Guideline/consensus/authors	Low-dose steroid	High-dose vitamin C	Serine protease inhibitor (e.g., ulinastatin)	Heparins (UFH, LMWH)	Other immunosuppressant (e.g., tocilizumab)	Blood purification system (e.g., CRRT)
WHO[3]	No	ND	ND	ND	ND	ND
SCCM and ESICM[17]	ND	ND	ND	ND	ND	ND
MOHFW, India[37]	ND	ND	ND	ND	ND	ND
ISCCM position statement[38]	No	ND	ND	ND	Yes	ND
Shanghai Medical Association consensus[19]	Yes	Yes	Yes	Yes	ND	ND
Ye et al.[39]	Yes*	ND	Yes	ND	Yes	Yes
Sun et al.[40]	No	ND	ND	ND	Yes	Yes
Russell et al.[20]	Yes	ND	ND	ND	No	ND
Jose and Manuel[12]	ND	ND	ND	Yes	ND	ND

*Steroid such as methylprednisolone to be used at 1–2 mg/kg/day for 3–5 days only. WHO, World Health Organization; SCCM and ESICM, Society of Critical Care Medicine and the European Society of Intensive Care Medicine; ISCCM, Indian Society of Critical Care Medicine; UFH, unfractionated heparin; LMWH, low-molecular-weight heparin; CRRT, continuous renal replacement therapy, ND: not discussed

SARS-CoV infection but not specific to COVID-19.[20] However, Sun et al. opined that steroids should not be used in the routine management of COVID-19 but may be prudently used in critically ill patients.[40] Therefore, the evidence is not clear to either accept or refuse the use of steroids in cytokine storm management.

Besides corticosteroids, various other specific immunosuppressive therapies can be used in treating cytokine storm. Specific IL-6 inhibitors such as tocilizumab can be useful in severe life-threatening CRS caused by chimeric antigen receptor T-cell (CART) immunotherapy. However, the use of tocilizumab cause even more profound immunosuppression than steroids, increasing the risk of sepsis, bacterial pneumonia, gastrointestinal perforation, and hepatotoxicity.[41] Evidence for use of tocilizumab is limited to a small single study from China. Therefore, there is a need to generate further evidence to support its use in the management of CRS in COVID-19.

Among the immunomodulating therapies, ulinastatin has a broad-spectrum protease inhibitory properties leading to inhibition of cytokines including IL-6. The drug is used commonly in China, Korea, Japan, including India for the management of sepsis and pancreatitis. The anti-inflammatory effects may be considered equivalent to those of steroids without significant suppression of the immune system.[39] A consensus document from China has recommended high-dose ulinastatin in the prevention and management of cytokine storm in patients with COVID-19.[19] Further, few of the experts also indicated the use of ulinastatin in cytokine storm.[39] However, there is a need to generate further evidence to prove its role in improving outcomes in COVID-19. Heparin including LMWH is one of the necessary treatments in CRS in COVID-19. Though they may be recommended for venous thromboprophylaxis, active use of LMWH in critically ill patients at increased risk of DIC can improve survival. It has been recommended by some of the experts in the management of COVID-19. The use of blood purification systems and convalescent plasma has been suggested but the evidence with their use is limited.

Further Research

COVID-19 is expanding in India and globally with varying mortality rates. It is emphasized that patients with severe ARDS, septic shock, or cytokine storm should be recognized early. The institution of the discussed treatments holds strong potential to alter the outcome of critically ill patients. Given heightened mortality with COVID-19 in certain comorbidities, early institutionalization of treatments to prevent and treat cytokine storm in COVID-19 is essential. Furthermore, publishing the data on the use of such treatments on an urgent basis is necessary to curb the mortality associated with this pandemic. We urge all physicians involved in the management of COVID-19 to identify, collect, and report the outcomes of patients with critically COVID-19 patients who have been managed with approved/off-label use of any of the therapies. This will not only bring out possibilities of benefits to the patients but to the world as a whole.

Conclusion

Novel coronavirus infection is a global pandemic that has affected more than a million population. In the absence of a therapeutic vaccine or drug, the management of COVID-19 is strictly based on preventive measures and supportive treatments. With increasing severity of the disease, CRS is expected in most of the patients who need to be identified and adequately treated. Currently, no clinical studies demonstrate the efficacy of a single agent in CRS, but investigators and experts in the field recommend a variety of therapies. In the Indian context, this article provided possible alternatives that can be considered in critically ill patients with COVID-19, which can possibly alter the outcome of the patients. Given the lack of concrete data, more evidence needs to be generated by the investigators to help combat this global pandemic.

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