GUIDELINES

Critical Care for COVID-19 Affected Patients: Updated Position Statement of the Indian Society of Critical Care Medicine

Yatin Mehta[1], Dhruva Chaudhry[2], OC Abraham[3], Jose Chacko[4], Jigeeshu Divatia[5], Bharat Jagiasi[6], Arindam Kar[7], GC Khilnani[8], Bhuvana Krishna[9], Prashant Kumar[10], RK Mani[11], BK Rao[12], Pawan K Singh[13], Sanjeev Singh[14], Pavan Tiwary[15], Chand Wattal[16], Deepak Govil[17], Subhal Dixit[18], Srinivas Samavedam[19]

Abstract

The management of coronavirus disease-2019 (COVID-19) is witnessing a change as we learn more about the pathophysiology and the severity of the disease. Several randomized controlled trials (RCTs) and meta-analysis have been published over the last few months. Several interventions and therapies which showed promise in the initial days of the pandemic have subsequently failed to show benefit in well-designed trials. Understanding of the methods of oxygen delivery and ventilation have also evolved over the past few months. The Indian Society of Critical Care Medicine (ISCCM) has reviewed the evidence that has emerged since the publication of its position statement in May and has put together an addendum of updated evidence.

Keywords: Convalescent plasma, COVID-19, SARS-CoV-2.

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Oxygenation and Ventilation

Hypoxemia is the most common indication for hospitalization of coronavirus disease-2019 (COVID-19) patients. Conventional oxygen therapy may not be sufficient among moderately and severely ill patients. Options for such patients include high-flow nasal cannula (HFNC), noninvasive ventilation (NIV), invasive ventilation, and extracorporeal membrane oxygenation (ECMO). High-flow nasal cannula seems to result in more ventilator-free days compared to NIV among non-COVID-19 patients.[1]

Prone positioning has been successfully used for managing hypoxemic respiratory failure. Awake proning is a concept that has emerged during the pandemic and has widely been used.[2,3] Small case series have shown reduced intubation rates with the awake proning strategy.

Indian Society of Critical Care Medicine (ISCCM) position—revised take home points:

- Close monitoring is required for hypoxemic patients (BPS).
- High-flow nasal cannula may be preferred over NIV (SR, MQE).
- In the absence of HFNC, a closely monitored trial of NIV can be given to hemodynamically stable hypoxemic patients (SR, LQE).
- Awake proning can be tried in hypoxemic patients in whom intubation is not otherwise indicated (SR, MQE).
- Awake proning may not be used as a rescue therapy for refractory hypoxemia to avoid invasive ventilation (SR, MQE).

Extracorporeal Membrane Oxygenation

ECMO has been suggested by the WHO in its guidance document issued in March. The current evidence for ECMO as a treatment modality for severe COVID-19 is equivocal.[3] Advanced age,

[1]Department of Critical Care and Anesthesiology, Medanta: The Medicity, Gurugram, Haryana, India

[2,13]Department of Pulmonary and Critical Care, Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, Rohtak, Haryana, India

[3]Infectious Disease Medicine, Christian Medical College, Vellore, Tamil Nadu, India

[4]Critical Care Medicine, Narayana Hrudyala, Bengaluru, Karnataka, India

[5]Critical Care and Anesthesia, Tata Memorial Centre, Homi Bhabha National Institute, Mumbai, Maharashtra, India

[6]Department of Critical Care, Reliance Hospital, Navi Mumbai, Maharashtra, India

[7]CK Birla Hospitals, Gurugram, Haryana, India; CMRI Institute of Critical Care, Kolkata, West Bengal, India; Indian Society of Critical Care Medicine; European Society of Intensive Care Medicine

[8]Department of Pulmonary, Critical Care and Sleep Medicine, PSRI Hospital, New Delhi, India

[9]Department of Critical Care Medicine, St. John's Hospital, Bengaluru, Karnataka, India

[10]Department of Anaesthesiology, Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, Rohtak, Haryana, India

[11]Critical Care and Pulmonology, Batra Hospital and Medical Research Centre, New Delhi, India

[12]Department of Critical Care and Emergency Medicine, Sir Ganga Ram Hospital, New Delhi, India

[14]Amrita Institute of Medical Sciences, Ernakulam, Kerala, India; Amrita Hospitals, Faridabad, Haryana, India

[15]All India Institute of Medical Sciences, New Delhi, India

[16]Clinical Microbiology and Immunology, Sir Ganga Ram Hospital, New Delhi, India

[17]Institute of Critical Care and Anesthesiology, Medanta: The Medicity, Gurugram, Haryana, India

comorbidities, and lymphopenia seem to be determinants of adverse outcome with ECMO. Results seem to be better with the use of ECMO, in the context of a cytokine storm.[2] The Extracorporeal Life Support Organization (ELSO) has released a consensus document on the use of ECMO for COVID-19.[4] Indications and contraindications for the use of ECMO have been listed in this guideline. The guideline recommends ECMO to be offered in experienced centers rather than compromise existing infrastructure in non-ECMO centers.

Indian Society of Critical Care Medicine Position—revised take home points:

- ECMO is an option for patients with refractory hypoxemia (WR, LQE).
- It is preferable to offer ECMO as per standard indications (SR, MQE).
- Centers well-versed and experienced in ECMO should be utilized for ECMO during COVID-19 pandemic (SR, LQE).

Corticosteroids

The potent anti-inflammatory effects of corticosteroids make them an attractive option for blunting the inflammatory response associated with COVID-19. The RECOVERY trial demonstrated a survival benefit among hypoxemic patients treated with dexamethasone (6 mg/day for 10 days or till hospital discharge). The CODEX RCT[5] was a multicenter open-label randomized controlled trial (RCT), evaluating the benefit of using dexamethasone in moderate-to-severe COVID-19-related acute respiratory distress syndrome (ARDS). The primary endpoint was ventilator-free days at 28 days, which was found to be significantly better in the dexamethasone group. The REMAP-CAP COVID-19 study[6] and the CAPE-COVID trial[7] evaluated the effect of hydrocortisone among patients requiring cardiovascular and respiratory organ support. Both the studies failed to show any superiority for hydrocortisone over standard therapy. The MET COVID trial[8] evaluated the effect of methylprednisolone among patients hospitalized for COVID-19. The intervention was used for patients requiring oxygen supplementation. The primary outcome was 28-day mortality which was not influenced by the intervention. A meta-analysis published in JAMA, from the WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, found that in critically ill COVID-19 patients, administration of corticosteroids was associated with reduced mortality.[9] The evidence was strongest for the use of dexamethasone (0.64, 95% CI, 0.50–0.82; $p < 0.001$), since it involved largest number of patients (3 trials, 1,282 patients, and 527 deaths), as compared to the hydrocortisone (0.69, 95% CI, 0.43–1.12; $p = 0.13$, 3 trials, 374 patients) or methylprednisolone (0.91, 95% CI, 0.29–2.87; $p = 0.87$ and 1 trial, 47 patients).

Indian Society of Critical Care Medicine Position—updated take home points:

- Dexamethasone is recommended for COVID-19 patients requiring oxygen (SR, HQE).
- Intravenous route is recommended (SR, HQE).
- Hydrocortisone and methylprednisolone are not as effective (SR, MQE).
- Non-hypoxemic patients may not benefit from dexamethasone (SR, HQE).

Effective doses of steroids have to be understood and followed during prescription.

[18]Department of Critical Care Medicine, Sanjeevan and MJM Hospital, Pune, Maharashtra, India

[19]Department of Critical Care, Virinchi Hospital, Hyderabad, Telangana, India

Corresponding Author: Dhruva Chaudhry, Department of Pulmonary and Critical Care, Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, Rohtak, Haryana, India, Phone: +91 9991101616, e-mail: dhruvachaudhary@yahoo.co.in

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Drug	*Dose (mg)*
Hydrocortisone	20
Cortisone acetate	25
Prednisone	5
Prednisolone	5
Deflazacort	6
Methylprednisolone	4
Dexamethasone	0.75
Betamethasone	0.75
Triamcinolone	4
Beclometasone	0.75

Pharmacological Treatment

Chemoprophylaxis

At present, no agent has been proven to be effective for pre-exposure prophylaxis against COVID-19. Several agents including hydroxychloroquine (HCQ), ivermectin, tenofovir plus emtricitabine, vitamin C, vitamin D, and zinc have been studied or are under investigation with no demonstrable benefit. Similarly, no drug has been shown to be effective for post-exposure prophylaxis either. Boulware et al. could not demonstrate a reduction in symptomatic disease with the use of hydroxychloroquine sulfate (HCQS) as post-exposure prophylaxis.[10]

Indian Society of Critical Care Medicine Position—Revised take home points

- No single agent or a combination of agents can be recommended for either pre- or post-exposure prophylaxis against COVID-19 (SR, HQE).

Therapy

Several RCTs evaluating therapy for COVID-19 have been initiated and some have been published.

Azithromycin was one of the first drugs to be used for the treatment of COVID-19. Furtado et al.[11] evaluated the effect of adding azithromycin to standard therapy that included HCQS as part of the COALITION II study. This was an open-label RCT across 57 Brazilian centers that enrolled 447 patients over a 2-month period. The authors could not demonstrate a treatment benefit with the addition of azithromycin. However, the incidence of adverse events was not increased.

Chloroquine and HCQS have been evaluated in multiple studies (including RCTs) for both safety and efficacy. Rosenberg et al.[12] in a large RCT among hospitalized patients could not show a decrease in 28-day mortality with the use of HCQS. Median hospital stay was, in fact, longer in the HCQS group. In addition, large retrospective observational studies do not show benefit with HCQS. The ongoing RECOVERY trial[11] ended the HCQS arm on June 5, after an independent data monitoring committee could not find a beneficial effect with HCQS.

Ivermectin, of late, has been proposed as a therapeutic option for COVID-19 in view of its ability to inhibit the replication of SARS-CoV-2 virus in cell cultures. The only RCT evaluating ivermectin compared to a combination of ivermectin (200 µg/kg) with doxycycline to a combination of HCQS and azithromycin.[13] In this small study of 181 patients, a single dose of ivermectin combined with doxycycline did not fare better than a combination of HCQS and azithromycin.

Lopinavir/ritonavir combination was known to be effective against SARS-CoV. Several RCTs[14–16] evaluating the combination have failed to show a clinical benefit among moderately to severely ill COVID-19 patients.

Remdesivir inhibits viral replication through premature termination of RNA transcription. In a multinational RCT of remdesivir vs placebo for severe COVID-19,[17] the authors demonstrated a significant reduction in the time to recovery. The benefit was clearest in the group requiring oxygen. However, the benefit was not obvious in those requiring HFNC/NIV. Recovery was also not better among those who were on invasive ventilation or ECMO. In a study which excluded patients needing invasive ventilation or ECMO, or having MOF, clinical improvement was no different among those who received remdesivir.[18] A 10-day course of remdesivir was not found to be superior to a 5-day course in an RCT.[19] A network meta-analysis of use of remdesivir in moderately to severely ill patients (2,049 patients) confirmed these findings.[9] A large trial in moderately ill COVID-19 596 patients, compared the efficacy of 5 or 10 days of remdesivir treatment compared with standard care on clinical status. There was no difference in outcomes after a 5- vs 10-day course of remdesivir and though the patients who received a 5-day course of remdesivir had statistically better outcomes at 11 days, the clinical significance of this finding was uncertain.[9]

Indian Society of Critical Care Medicine Position—Revised take home points:

(i) No drug can be recommended for chemoprophylaxis.

- Azithromycin cannot be recommended as a standard treatment modality (SR, HQE).
- Lopinavir/ritonavir cannot be recommended for moderate-to-severe cases (SR, HQE).
- HCQS either alone or with azithromycin cannot be recommended as standard treatment (SR, ERS NEHQE).
- Ivermectin cannot be recommended as a standard treatment modality (WR, MQE).
- A 5-day course remdesivir is recommended as standard treatment for all patients requiring oxygen (SR, HQE).
- Remdesivir can also be tried among patients requiring HFNC/NIV/invasive ventilation/ECMO with less predictable results (WR, MQE).
- Extended course of remdesivir cannot be recommended as a standard treatment modality (SR, HQE).

Immunomodulatory Therapies

IL-6 Inhibitors

Increased cytokine release as evidenced by increased levels of IL-6, c reactive protein (CRP), D-dimer, and ferritin may be responsible for the severity of SARS-CoV-2 infection. Two classes of IL-6 inhibitors are available, which could have theoretical benefit in the setting of raised IL-6 levels. These are the anti-IL6 receptor monoclonal antibodies (sarilumab, tocilizumab) and anti-IL6 monoclonal antibodies (siltuximab). The most widely used molecule in India is tocilizumab. The industry sponsored COVACTA phase 3 trial[20] evaluating the effect of tocilizumab on clinical improvement did not show a significant benefit in terms of need for invasive ventilation and intensive care. Observational[21] and retrospective[22] studies did show a benefit.

Indian Society of Critical Care Medicine Position—Updated take home point:

- There is no strong evidence to recommend the use of tocilizumab as standard treatment for COVID-19 (WR, LQE).

Interferons (Alfa and Beta)

Interferons are cytokines with antiviral properties. Previous studies during the MERS-CoV and SARS outbreaks have failed to show benefit. A double-blind placebo-controlled trial[23] evaluating interferon-beta 1a demonstrated a quicker recovery to ambulation among a cohort of 50 patients. Another similar small study[24] using a subcutaneous formulation failed to show a clinical benefit.

Indian Society of Critical Care Medicine Position—New

- Interferon therapy cannot be recommended as a standard therapy based on current evidence (SR, LQE).

Antithrombotic Therapy

COVID-19 is associated with inflammation and a prothrombotic state. This state is characterized by increased D-dimer values. Patients hospitalized in intensive care units seem to have a higher incidence of venous thromboembolism (VTE). The incidence ranges from 16 to 69%.[25–27] Data regarding benefit from monitoring coagulation markers and treating with anticoagulants are scanty. The WHO has provided some answers in its interim guidance.[28,29] The Society of Thrombosis and Haemostasis Research has also issued guidelines for the initiation of treatment, drug dosing, and duration of pharmacological VTE prophylaxis in COVID-19 patients.

Indian Society of Critical Care Medicine Position—Updated take home points:

- All patients with COVID-19 should be considered to be at high risk of VTE (SR, MQE).
- Standard prophylactic dose of unfractionated or low molecular weight heparin is recommended for all hospitalized patients (SR, HQE).
- Extended prophylaxis should be considered after hospital discharge (45 days) (SR, WQE).
- Suspected pulmonary thromboembolism (PTE) should be treated as PTE (SR, VLQE).

Convalescent Plasma Therapy

Plasma from donors who have recovered from COVID-19 may contain antibodies, which could have antiviral and anti-inflammatory properties. This was demonstrated to be feasible and safe.[30] The first RCT on convalescent plasma therapy (CPT) for COVID-19[31] was terminated early due to the clearance of the

pandemic in China. Just over 100 patients completed the study. Negative PCR results on repeat testing were reported in a higher number of patients treated with convalescent plasma.[32,33] Disease severity and 28-day survival, however, did not differ.

Indian Society of Critical Care Medicine Position—New take home point:

- There are insufficient data either to recommend in favor or against CPT for COVID-19 (SR, LQE).

There are insufficient data either to recommend in favor or against CPT for COVID-19. However, units planning to use CPT are advised to follow stringent donor and recipient selection criteria.

Donor Selection

Evidence of COVID-19 documented by a laboratory test either by a diagnostic test (e.g., nasopharyngeal swab) at the time of illness or

A positive serological test for SARS-CoV-2 antibodies after recovery.

Complete resolution of symptoms at least 14 days prior to donation.

Male donors, or female donors who have not been pregnant, or female donors who have been tested since their most recent pregnancy and results interpreted as negative for HLA antibodies.

When measurement of neutralizing antibody titers is available, neutralizing antibody titers of at least 1:160 is recommended.

A titer of 1:80 may be considered acceptable if an alternative matched unit is not available.

Recipient Criteria

Laboratory confirmed COVID-19:

- Severe or immediately life-threatening COVID-19.Severe disease is defined as one or more of the following:
- Dyspnea.
- Tachypnea ≥30/minute.
- Blood oxygen saturation ≤93%.
- PaO_2/FiO_2 <300.
- Lung infiltrates >50% within 24–48 hours.

The life-threatening disease is defined as one or more of the following:

- Respiratory failure.
- Septic shock.
- Multiple organ dysfunction.

Cytokine Storm

The cytokine storm is an acute hyperinflammatory response that has been implicated in severe forms of COVID-19. Mehta et al.[34] have described the syndrome in detail. They have drawn an analogy with secondary hemophagocytic lymphohistiocytosis. Corticosteroids, heparin, convalescent plasma, IL-6 inhibitors, and extracorporeal removal have been proposed as possible therapeutic strategies against cytokine storm.

Indian Society of Critical Care Medicine Position—New take home points:

- The cytokine storm has a definite clinical and biochemical pattern (SR, HQE).
- Multiple strategies may be used in combination to manage this complication (SR, HQE).

Cardiopulmonary Resuscitation during COVID-19

The American Heart Association (AHA) issued interim guidelines for CPR during the pandemic. The guideline acknowledged the increased risk of exposure to healthcare workers and the fact that performing CPR involves numerous aerosol-generating procedures. CPR also involves numerous professionals working in close proximity. The guideline emphasized on PPE use, limiting the number of personnel involved, and using mechanical devices for CPR where possible. Contrary to usual recommendation, the AHA recommends pausing chest compressions for intubation.
Indian Society of Critical Care Medicine Position:

- CPR should be initiated as per clinical requirement (SR, LQE).
- All rescuers should don full PPE (SR, HQE).
- Number of personnel should be limited (BPS).
- Guidelines issued by the AHA need to be understood and all code blue teams should have reorientation regarding the same (SR, LQE).
- CPR may be tried in prone position if patient is already prone, if already intubated, guided by invasive arterial blood pressure monitoring and or $ETCO_2$ monitoring (SR, VLQE).
- Defibrillation in prone patients can be done with pads positioned anterior-posteriorly, or in bi-axillary regions (SR, LQE).

Discharge Criteria

The WHO has updated the criteria for discharge of the patients from isolation.[29,35] The WHO mentions that this guidance applies to all categories of patients irrespective of disease severity and location of treatment. The updated de-isolation guidelines are based on the symptom-free interval. The Ministry of Health and Family Welfare (MOHFW) has also made similar recommendations[32,36] for discharge of patients with moderate COVID-19. For severe cases, the MOHFW recommends discharge only after symptom resolution and one negative PCR rest.

Indian Society of Critical Care Medicine Position—Updated take home points:

- Negative PCR is no longer mandatory for discharge of moderately sick patients from isolation.
- For mild to moderately symptomatic patients, a 3-day symptom-free period following a 10-day isolation after symptom onset is enough for de-isolation.
- For asymptomatic patients, 10 days after a positive test is enough for de-isolation.
- For severely symptomatic patients, one negative PCR test is enough to consider discharge from isolation.

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