

# Basic Critical Care for Management of COVID-19 Patients: Position Paper of the Indian Society of Critical Care Medicine, Part II

Deven Juneja<sup>1</sup>, Raymond D Savio<sup>2</sup>, Shrikanth Srinivasan<sup>3</sup>, Rahul A Pandit<sup>4</sup>, Suresh Ramasubban<sup>5</sup>, Pavan K Reddy<sup>6</sup>, Manoj K Singh<sup>7</sup>, Palepu BN Gopal<sup>8</sup>, Dhruva Chaudhry<sup>9</sup>, Deepak Govil<sup>10</sup>, Subhal B Dixit<sup>11</sup>, Srinivas Samavedam<sup>12</sup>

## ABSTRACT

In a resource-limited country like India, rationing of scarce critical care resources might be required to ensure appropriate delivery of care to the critically ill patients suffering from COVID-19 infection. Most of these patients require critical care support because of respiratory failure or presence of multiorgan dysfunction syndrome. As there is no pharmacological therapy available, respiratory support in the form of supplemental oxygen, noninvasive ventilation, and invasive mechanical ventilation remains mainstay of care in intensive care units. As there is still dearth of direct evidence, most of the data are extrapolated from the experience gained from the management of general critical care patients.

**Keywords:** Acute respiratory distress syndrome, Antibiotics, COVID-19, Critical care, SARS-CoV-2, Sepsis, Thromboprophylaxis, Venous thromboembolic.

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## INTRODUCTION

The management of COVID-19 has perplexed us and has left us with several uncertainties. In this position paper—part II, we attempt to address basic issues regarding use of antibiotics, management of sepsis, acute respiratory distress syndrome (ARDS), and thromboprophylaxis. Details on basic critical care, antiviral therapy, and role of steroids are discussed in part I. To aid in understanding the level of evidence, the recommendations were accorded as per the Grading of Recommendations Assessment, Development and Evaluation (GRADE) basic approaches and rules.<sup>1</sup> In the absence of direct clinical evidence, grade of useful practice point (UPP) was awarded, by consensus of the working group based on clinical experience and expertise.<sup>1</sup> As the literature emerges, these recommendations may change and hence, frequent updates may be required.

## ROLE OF PROPHYLACTIC/EMPIRIC ANTIBIOTICS

Secondary infections or coinfections are uncommon, especially in the early phase, in patients with COVID-19 infections. Hence, routine use of antibiotics is not indicated. However, use of antibiotics may be justified in specific subgroup of patients admitted in intensive care units (ICUs).

### When to Start Prophylactic/Empiric Antibiotics

#### Recommendations

- Start empiric antibiotics in patients who have hypoxemic respiratory failure needing mechanical ventilation in COVID-19 patients (UPP).
- Do not start prophylactic antibiotics to prevent pneumonia in COVID-19 patients (UPP).

#### Rationale

The rationale for antibiotic therapy in COVID-19 is based on experience with influenza infections where the incidence of bacterial coinfection is reported in 11–35% of patients.<sup>2</sup> The exact

<sup>1</sup>Institute of Critical Care Medicine, Max Super Speciality Hospital, New Delhi, India

<sup>2</sup>Department of Critical Care Medicine, Apollo Hospitals, Chennai, Tamil Nadu, India

<sup>3</sup>Department of Critical Care Medicine, Manipal Hospitals, New Delhi, India

<sup>4</sup>Department of Intensive Care, Fortis Hospital, Mulund, Mumbai, Maharashtra, India

<sup>5</sup>Department of Critical Care, Apollo Gleneagles Hospital, Kolkata, West Bengal, India

<sup>6</sup>Department of Critical Care, CARE-Banjara, Hyderabad, Telangana, India

<sup>7</sup>Department of Critical Care, Apollo Hospitals International Limited, Ahmedabad, Gujarat, India

<sup>8</sup>Department of Critical Care, Continental Hospital, Hyderabad, Telangana, India

<sup>9</sup>Department of Pulmonary and Critical Care, Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, Rohtak, Haryana, India

<sup>10</sup>Institute of Critical Care and Anesthesia, Medanta: The Medicity, Gurugram, Haryana, India

<sup>11</sup>Department of Critical Care Medicine, Sanjeevan and MJM Hospital, Pune, Maharashtra, India

<sup>12</sup>Department of Critical Care, Virinchi Hospital, Hyderabad, Telangana, India

**Corresponding Author:** Deven Juneja, Institute of Critical Care Medicine, Max Super Speciality Hospital, New Delhi, India, Phone: +91 9818290380, e-mail: devenjuneja@gmail.com

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incidence of bacterial coinfection or secondary bacterial infections in COVID-19 patients is unknown. However, incidence of documented bacterial infections appears much lower than in influenza.<sup>3,4</sup> Secondary bacterial infections from COVID-19 cases in Wuhan were reported in 15% but the incidence was higher among non-survivors.<sup>5</sup> Zhou et al. showed that 50% of non-survivors had a secondary bacterial infection in a study of 191 patients.<sup>6</sup>

A recent meta-analysis of 3,834 patients showed that the rate of secondary bacterial infection was only 7% in hospitalized patients but increased to 14% among patients admitted in ICU.<sup>7</sup>

Given the uncertainty of incidence of cobacterial infection, difficulty in differentiating from viral and bacterial pathogen and high mortality in severe cases, empiric antibiotics should be considered in severe cases (hypoxemic respiratory failure requiring mechanical ventilation) of suspected or confirmed COVID-19.

Antibiotics should not be given prophylactically for preventing pneumonia. However, empiric treatment for bacterial pneumonia may be considered in cases of new fever, after defervescence, with new consolidation on chest imaging. Reevaluate the need to continue antibiotic therapy daily. Serial procalcitonin may be helpful in early identification of superinfection and initiation of empirical antibiotic pending culture results. Further studies need to be conducted to substantiate this practice.

### Which Antibiotic to Start and Duration of Therapy

#### Recommendations

- $\beta$ -lactam antibiotics may be added as first line in patients with severe COVID-19 infection (UPP).
- Atypical coverage may be added where appropriate (UPP).
- Antibiotic treatment duration should not exceed 5 to 7 days in most cases (UPP).

#### Rationale

As there is no direct evidence from patients with COVID-19, antibiotic prescription may follow the community-acquired pneumonia (CAP) guidelines<sup>8</sup> and should be reserved for patients with severe manifestation.  $\beta$ -lactam antibiotics maybe the first choice of antibiotic and macrolides may be added for atypical coverage. Methicillin-resistant *Staphylococcus aureus* (MRSA) or antipseudomonal coverage should be added only if there is a history of previous such infection.<sup>8</sup> Results from meta-analysis with around 10,000 critically ill patients with CAP showed a significant mortality benefit with  $\beta$ -lactam and macrolide combination as compared with non-macrolide containing therapies.<sup>9</sup> However, macrolides and quinolones should be avoided in patients taking chloroquine or hydroxychloroquine, as they may prolong QT interval on electrocardiogram. In such patients, atypical coverage may be provided with doxycycline. Antibiotic treatment duration should not exceed 5–7 days in most cases, as generally recommended for CAP.<sup>8</sup> Standard measures to prevent infection and antibiotic prescription should be followed (Table 1).

Use of steroids and IL6 blockers in severe cases make patients more prone to nosocomial infections. Appropriate preventive, diagnostic, and therapeutic measures need to be taken in such patients and local antibiogram should be followed for the choice of antibiotics.

**Table 1:** Points to be considered for starting appropriate antibiotics

**Thorax CT:** For a more exact determination of the typical infiltrate associated with bacterial lower respiratory tract infection as opposed to the typical glass ground opacities seen in COVID-19.

**Microbiological tests:** Blood cultures, urinary antigens (*Pneumococcal* and *Legionella*) and bronchoalveolar lavage (BAL) (limited by aerosol generation risk in COVID-19) should be obtained before starting antibiotics.

**Inflammatory biomarkers:** C-reactive protein and procalcitonin should be measured.

**Reevaluation and de-escalation:** Antibiotic treatment should be rapidly reevaluated and stopped as soon as possible if the probability of bacterial superinfection is considered low.

## MANAGEMENT OF SEPSIS

Patients with COVID-19 infection may present with signs and symptoms of sepsis/septic shock. Apart from this viral sepsis, these patients are also at risk of developing secondary bacterial and fungal infection which may further lead to secondary sepsis.

### Fluid Resuscitation

#### Recommendations

- To assess fluid responsiveness, dynamic parameters like stroke volume variation (SVV), and stroke volume change with passive leg raising (PLR), should be preferred over static parameters (UPP).
- Conservative fluid management therapy should be preferred over liberal fluid resuscitation (UPP).
- For patients with shock, crystalloids should be preferred over colloids for acute resuscitation (UPP).
- Routine use of albumin should be avoided for initial acute resuscitation (UPP).
- Balanced solutions should be preferred over unbalanced crystalloids for acute resuscitation (UPP).

#### Rationale

Despite several research publications on general management principles, there is no direct evidence regarding fluid therapy in managing sepsis/septic shock secondary to COVID-19 infection. The data have to be extrapolated from experience gathered from managing critically ill patients in general.

Dynamic variables like SVV, pulse pressure variation (PPV), and stroke volume change with PLR or fluid challenge have been found to be better in predicting fluid responsiveness as compared to static parameters like central venous pressure (CVP) and mean arterial pressure (MAP). In a large meta-analysis of 13 randomized control trials (RCTs), including 1,652 patients, the use of dynamic parameters during fluid resuscitation was reported to reduce mortality, ICU length of stay, and duration of mechanical ventilation.<sup>10</sup> Among the dynamic parameters, PLR has been shown to have better accuracy in predicting fluid responsiveness than PPV and SVV.<sup>11</sup>

Even though serum lactate level is a non-specific marker, the use of lactate clearance as compared to central venous oxygen saturation (ScVO<sub>2</sub>) to guide fluid resuscitation has been shown to reduce mortality, length of stay in hospital, and duration of mechanical ventilation.<sup>12</sup> Assessing capillary refill testing (CRT) every 30 minutes has also shown to reduce mortality in the

ANDROMEDA-SHOCK trial, although the difference was not statistically significant.<sup>13</sup>

As most of the patients with severe COVID-19 infection develop ARDS, conservative fluid therapy may be beneficial. A meta-analysis of 9 RCTs with 637 patients reported no significant difference in mortality or other serious events in sepsis patients receiving conservative or liberal fluid resuscitation.<sup>14</sup>

The use of colloids in critically ill patients has shown to offer no benefit over crystalloids in a large meta-analysis of 69 RCTs including 30,020 patients. Use of albumin as against crystalloids offers no mortality benefit as shown in a meta-analysis involving 20 RCTs with 13,047 patients.<sup>15</sup> Considering the cost, limited availability, and adverse-effect profile of colloids, crystalloids should be the preferred solution.<sup>15</sup>

Among the crystalloids, there is growing evidence in favor of balanced solutions, especially when a large volume is required for resuscitation. Though a large meta-analysis of 21 RCTs with 20,213 patients comparing balanced crystalloids with 0.9% saline for resuscitation of critically ill reported no statistically significant difference in hospital mortality or acute kidney injury, there was a trend toward improved outcome when balanced solutions were used.<sup>16</sup>

## Vasopressors

### Recommendations

- In patients with shock, not responding to fluid therapy, noradrenaline should be used as the first-line agent (UPP).
- Adrenaline or vasopressin may be used in case of non-availability of noradrenaline (UPP).
- Vasopressin may be added as a second-line agent, in patients with shock refractory to noradrenaline therapy (UPP).
- Dopamine should be avoided because of increased risk of arrhythmias (UPP).
- In patients with cardiac dysfunction, dobutamine may be added in shock refractory to fluid resuscitation and noradrenaline (UPP).

### Rationale

Noradrenaline is the most widely studied agent for the management of septic shock in general critical care. A large meta-analysis of 28 RCTs including 3,497 patients proved its role as the best first-line vasopressor.<sup>17</sup> Vasopressin or adrenaline may be used in case of non-availability of noradrenaline, on case to case basis depending on the presence of contraindications for each agent. Dopamine is not favored because of increased risk of arrhythmias.<sup>18</sup> In view of risk of arrhythmias, vasopressin may be added as a second-line agent, in patients with refractory shock not responding to noradrenaline.<sup>19</sup> However, risk of digital ischemia should be kept in mind.<sup>19</sup>

## Steroids

### Recommendations

- In patients with septic shock refractory to vasopressor therapy, low-dose corticosteroid therapy may be used (GRADE IIIB).

### Rationale

Evidence from critically ill patients suggest that use of low-dose corticosteroids may lead to early resolution of shock, and reduce the length of stay in hospital and ICU, without having any effect on mortality and serious adverse events.<sup>20,21</sup> Hence, use of steroids may be justified in COVID-19 patients with refractory

septic shock. The most commonly recommended regimen is of intravenous hydrocortisone 200 mg/day either as a continuous infusion or divided in 6 hourly doses. Patients already receiving dexamethasone should be switched over to hydrocortisone.

## Biomarkers

### Recommendations

- High white blood cell (WBC) counts may suggest secondary infection or a more severe disease (UPP).
- C-reactive protein (CRP) levels should be measured at the time of hospital admission for early risk assessment and prioritization of high-risk patients (GRADE IIB).
- Procalcitonin levels should be measured at the time of ICU admission for early risk assessment and prioritization of high-risk patients (GRADE IIB).
- Repeat procalcitonin levels may be helpful in detecting secondary infections and in monitoring progression of severity of bacterial infection (GRADE IIA).

### Rationale

Measurement of WBC count is one of the routinely performed tests in ICU. Its utility remains unproven in COVID-19 patients as it is non-specific and may be raised after corticosteroid use or from a secondary infection. White blood cell counts remain within normal range in most observations of COVID-19 patients with no underlying secondary infection.<sup>22-24</sup>

A meta-analysis of 5,350 patients showed that high CRP levels were associated with poor outcomes in hospitalized patients with COVID-19 infection. C-reactive protein levels correlated with severity of COVID-19 infection and need for ICU care, but were not associated with increased mortality.<sup>25</sup> C-reactive protein is a non-specific acute phase reactant and its levels may be high in patients with severe COVID-19 infection even without bacterial coinfection.<sup>26</sup> Moreover, the CRP levels may fall rapidly after tocilizumab use, further compromising its utility in the diagnosis of secondary infections secondary to immune-suppression caused by tocilizumab.<sup>27</sup> Hence, raised CRP may indicate severe COVID-19 infection, but is a less reliable marker of secondary bacterial infection.

Procalcitonin may prove to be another valuable tool in the management of critically ill COVID-19 patients and may aid in early identification of patients at low risk for bacterial coinfection and adverse outcome.<sup>6,23</sup> Recent data suggest that serum procalcitonin levels are <0.5 µg/L in >96% of patients with low disease severity and these patients have good clinical outcome. Levels above 0.5 µg/L correlate with a more severe disease or secondary bacterial infection. As per a recent meta-analysis, procalcitonin levels above 0.5 µg/L in COVID-19 patients, correlated with 5 times higher risk of severe infection.<sup>28</sup>

## MANAGEMENT OF ARDS

Severe ARDS and hypoxemic respiratory failure have been shown to be the major cause of mortality in COVID-19. As there is no promising pharmacological therapy, respiratory support in the form of supplemental oxygen, noninvasive ventilation (NIV), and invasive mechanical ventilation (IMV) remains mainstay of care in ICU. Earlier reports suggested that many patients who were intubated had difficult weaning and higher mortality.<sup>29</sup> The strategy of low or high threshold for intubation depends on many factors like population, resources, manpower, and burden on healthcare

system. In a country like India, we need to consider the utility of noninvasive ventilatory techniques wherever applicable, with proper aerosol precautions.

## Oxygen Therapy

### Recommendations

- Supplemental oxygen should be initiated if peripheral oxygen saturation ( $\text{SpO}_2$ ) is  $<92\%$  (UPP).
- Supplemental oxygen therapy should be immediately initiated in patients with severe acute respiratory illness (SARI) and respiratory distress, hypoxemia or shock, and target oxygen saturation ( $\text{SpO}_2$ )  $>94\%$  (UPP).
- In patients with acute hypoxemic respiratory failure (AHRF) on oxygen, we suggest that  $\text{SpO}_2$  be maintained no higher than  $96\%$  (UPP).
- Recognize severe hypoxemic respiratory failure when a patient with respiratory distress is failing to respond to standard oxygen therapy and prepare to provide advanced oxygen/ventilatory support (UPP).

### Rationale

As there are no direct studies in COVID-19 patients, the recommendations are drawn from non-COVID literature. Hypoxemia, in critically ill patients has been shown to be associated with worse clinical outcomes.<sup>30</sup> On the contrary, a large meta-analysis of 25 RCTs with 16,037 patients reported that liberal oxygen therapy targeting  $\text{SpO}_2$  above  $96\%$  was associated with an increased risk of hospital mortality.<sup>31</sup> Hence, supplemental oxygen therapy should be initiated to maintain an  $\text{SpO}_2$  between  $92$  and  $96\%$ .<sup>32</sup>

## Noninvasive Ventilatory Techniques in COVID-19

### Recommendations

- High-flow nasal cannula (HFNC) or NIV should be considered in patients with AHRF not responding to conventional oxygen therapy (UPP).
- High-flow nasal cannula may be preferred over NIV in view of patient comfort and healthcare worker protection (UPP).
- If HFNC is unavailable, a trial of NIV may be given with close monitoring for worsening of respiratory failure (UPP).
- All aerosol-generating procedures should be performed in a negative pressure room (UPP).

### Rationale

High-flow nasal cannula can deliver up to  $100\%$   $\text{FiO}_2$  at flow rates of up to  $60$  L/minute. The heated and humidified oxygen may improve secretion clearance, decrease airway inflammation, and also decrease energy expenditure, particularly in the setting of AHRF. It provides approximately  $1$  cm  $\text{H}_2\text{O}$  of positive end-expiratory pressure (PEEP) for every  $10$  L/minute of flow delivered with closed mouth breathing.<sup>33</sup> Another advantage of HFNC is that it flushes nasopharynx and eliminates dead space providing a continuous flow of fresh gas at high-flow rates, thus improving breathing efficiency.<sup>34</sup> It enhances the tolerance and comfort of patient as compared to traditional high-flow oxygen mask or NIV as the interface is compact, loose, and comfortable while it permits uninterrupted vision, speech, and food intake.

Though NIV is the modality of choice for patients with acute hypercapnic respiratory failure and cardiogenic pulmonary edema

(CPE), it has never been shown to be consistently effective for AHRF and ARDS which are encountered in this pandemic. In severe ARDS, there is oxygenation deficit that requires high PEEP and stiff lungs that require high inspiratory pressure. Together these will create more leak and discomfort. It is difficult to achieve synchronization in a setting of tachypnea and high minute ventilation requirement. Bi-level positive airway pressure (BiPAP) could provide benefit beyond continuous positive airway pressure (CPAP) by providing some mechanical support for the work of breathing. However, this does carry a theoretical risk of possibly encouraging the patient to take excessively large breaths, thereby inducing lung damage. Hence, NIV should be considered for patients with underlying COPD with exacerbation, CPE, and those who are on home BiPAP therapy. Non-invasive techniques may also be indicated in case of unavailability of invasive ventilators.

The risk of bacterial contamination with HFNC has been shown to be similar to that of oxygen supplementation<sup>35</sup> and its use was also shown not to increase the risk of infection transmission to healthcare workers in SARS epidemic.<sup>36</sup> Studies reported that with HFNC, exhaled air mean distances increased from  $65$  to  $172$  mm when flow was increased from  $10$  to  $60$  L/minute, but still it was less as compared with NIV.<sup>37</sup> However, no clear increase in risk of infection transmission has been demonstrated with NIV use also.<sup>38,39</sup>

Droplet mask can be tried over HFNC interface to overcome the risk of aerosol dispersal. If NIV is used, helmet may be a good interface as it may significantly reduce exhaled air dispersion compared to face mask.<sup>40</sup> Non-invasive ventilation or HFNC should ideally be used in a room with at least  $12$  air exchanges per hour. For NIV, it is recommended to use dual limb circuit ventilator with exhalation viral/bacterial filter.

## When to Intubate

### Recommendations

- In adults with COVID-19 receiving NIV or HFNC, we recommend close monitoring for worsening of respiratory status, and early intubation in a controlled setting if worsening occurs (UPP).
- Endotracheal intubation should be performed by a trained and experienced provider using airborne precautions (UPP).

### Rationale

The Chinese Society of Anaesthesiology Task Force on Airway Management initially recommended endotracheal intubation for patients showing no improvement in respiratory distress, tachypnea (respiratory rate  $>30$ /minute), and poor oxygenation ( $\text{PaO}_2$  to  $\text{FiO}_2$  ratio  $<150$  mm Hg) after 2-hour HFNC or NIV.<sup>41,42</sup> Such early intubation was recommended as there may be rapid deterioration of patients with COVID-19 with silent hypoxemia and it takes time for preparation and performance of intubation. Both preintubation hypoxemia and absence of preoxygenation are associated with a much higher risk of cardiac arrest.

We need to avoid premature intubation but we lack the evidence to determine the exact time for intubation. The optimal time depends on the patient's severity of illness, anticipated deterioration, and coexisting conditions. Hypoxemia alone cannot be the indication for intubation. Other factors like increased work of breathing not relieved by noninvasive ventilatory techniques, agitation, altered mental status, and severe hemodynamic instability should also be considered. Sometimes intubation is

required to facilitate investigations or therapies that the patient would not otherwise tolerate because the patient cannot be positioned or transferred safely.

Patients who are hemodynamically unstable requiring vasopressor support, or with persistent tachypnea or thoracoabdominal asynchrony, and those with worsening oxygenation status on noninvasive ventilatory strategy should be assessed for need for IMV. Recently, the “ROX Index” was developed to help in the prediction of HFNC success or failure. It is calculated as  $\text{SpO}_2/\text{FiO}_2/\text{RR}$ . In a validation cohort of 191 patients, Roca et al. showed that ROX of  $<4.88$  at 12 hours yielded area under curve (AUC) of 0.759 predicting failure.<sup>43</sup>

## Strategies for IMV

### Recommendations

- Use low-tidal-volume ventilation (4–8 mL/kg of predicted body weight) (UPP).
- Target plateau pressure below 30 cm H<sub>2</sub>O (UPP).
- Higher PEEP strategy may not benefit all COVID-19 patients with ARDS, hence PEEP should be titrated as per patient’s characteristics and response to PEEP (UPP).
- Use prone ventilation for 12–16 hours vs no prone ventilation (UPP).
- Neuromuscular blocking (NMB) agents may be used for lung protective ventilation especially in first 24–48 hours after intubation (UPP).
- Venovenous extracorporeal membrane oxygenation (ECMO) should be considered in patients on IMV who have refractory hypoxemia despite optimization of ventilation and have undergone rescue therapies and proning (UPP).

### Rationale

Most guidance is based on our previous experience with ARDS and severe coronavirus disease (e.g., SARS, MERS, and COVID-19). A protective lung ventilation strategy is recommended. Lung protective ventilation strategy using low-tidal-volume, high PEEP, and maintaining plateau pressures  $<30$  cm H<sub>2</sub>O, have shown to reduce mortality in patients with ARDS.<sup>44–46</sup> Positive end-expiratory pressure above 10 cm H<sub>2</sub>O is arbitrarily considered as high.<sup>47</sup> Although direct evidence in COVID-19-induced ARDS (CARDS) is lacking, use of high PEEP is associated with increased risk of pneumothorax.<sup>47</sup> Early reports and expert opinions suggest that all COVID-19 patients may not benefit from high PEEP,<sup>48–50</sup> hence, PEEP should be titrated as per the patient’s characteristics and response to PEEP.

A recent meta-analysis of 9 RCTs with 2,129 non-COVID ARDS patients showed improved mortality when prone ventilation was used for  $>12$  hours.<sup>51</sup> Even though direct evidence is lacking, but early evidence suggests that it may be beneficial in patients with CARDS<sup>52</sup> and is increasingly being used in these patients.<sup>53</sup>

Intermittent boluses of NMB agents should be preferred over continuous for lung protective ventilation. However, continuous infusion may be required in patients with persistent ventilator dyssynchrony, needing ongoing deep sedation, prone ventilation, or persistently high plateau pressures.<sup>47</sup>

It is generally recommended to use recruitment maneuvers (RM) in severe ARDS patients on IMV who exhibit hypoxemia despite optimization of ventilation.<sup>47</sup> However, early data from COVID-19 patients suggest that lung recruitability may be poor in

these patients.<sup>50,54</sup> Hence, RM may be used cautiously depending on patient’s response and risk of barotrauma should be kept mind.

For those patients on IMV who have refractory hypoxemia despite optimization of ventilation and who have undergone rescue therapies and proning, venovenous ECMO should be considered, if available.<sup>47</sup> Extracorporeal membrane oxygenation is resource-intensive and requires experienced centers, healthcare workers, and infrastructure and therefore should be considered in carefully selected patients.

## Role of Steroids

### Recommendations

- In mechanically ventilated adults with CARDS, we suggest using systemic corticosteroids, over not using corticosteroids (GRADE IIB).

### Rationale

Steroid administration during replication phase (early) may promote viremia, and hence, is not recommended.<sup>55</sup> The RECOVERY trial demonstrated a mortality benefit using dexamethasone 6 mg daily for up to 10 days among hospitalized patients requiring supplemental oxygen or mechanical ventilation.<sup>56</sup>

## THROMBOPROPHYLAXIS IN COVID-19

COVID-19 is associated with endotheliitis, hypoxemia, hypercoagulable state, and immobility, which may all predispose to the development of thromboembolic complications.<sup>6,24,57,58</sup> More recent data and clinical experience suggest an increased prevalence of thrombosis and venous thromboembolic (VTE) events in COVID-19, especially in those with more severe disease.

Wide clinical experience has also reported increased incidence of arterial thrombosis—including large vessel occlusion and ischemic strokes,<sup>59</sup> increased invasive catheter clotting, and extracorporeal circuit clotting (continuous renal replacement therapy and ECMO circuits).<sup>60</sup> Postmortem studies have also documented pulmonary embolism (PE) and VTE. Postdischarge thromboembolic phenomenon and VTE have also been reported in COVID-19 patients.

## Coagulation Parameters Testing

### Recommendations

- We recommend testing coagulation parameters in all hospitalized COVID-19 patients at least once during admission (GRADE IA).
- We recommend testing platelet counts, prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, and D-dimer levels in patients admitted to the ICU (GRADE IIB).
- We recommend viscoelastic tests like thromboelastography (TEG) to decide on thromboprophylaxis in patients with increasing trends of D-dimers who have clinical risk of bleeding (e.g., low platelets, elevated aPTT) (GRADE IIC).

### Rationale

Guan et al. observed elevated D-dimers in 46% of patients in a series of 1,099 patients.<sup>57</sup> Tang et al. observed more prolonged PT (median 15.5 s vs 13.6 s), aPTT (median 44.8 s vs 41.2 s), and higher D-dimers (median 2,120 vs 610  $\mu\text{g/L}$ ) in non-survivors compared with survivors in a study of 183 cases of COVID-19 pneumonia.

Seventy-one percent of non-survivors had disseminated intravascular coagulation (DIC) (defined as a DIC score of  $\geq 5$ ) as compared with 0.6% of survivors.<sup>61</sup> Huang et al. reported median levels of 2,400  $\mu\text{g/L}$  in 13 patients admitted to ICU, and 500  $\mu\text{g/L}$  in 28 patients who did not.<sup>62</sup> D-dimers are a non-specific acute phase reactant which may be elevated in acute inflammatory illnesses, pneumonias, and other causes of sepsis and in patients in ICUs. But is unclear whether elevated D-dimer levels reflect inflammation or thrombosis or thrombolysis. Fibrinogen levels are also significantly elevated in COVID-19; Helms et al. reported a median level of 6.99 g/L (normal 2–4).<sup>60</sup>

Panigada et al. in a study of 24 ventilated COVID-19 patients studied coagulopathy using TEG and found that “reaction” (R) time was shortened (in 50%), consistent with increased early thrombin burst, clot formation time (K) was shortened (in 83%), consistent with increased fibrin generation, maximum amplitude (MA) was increased (in 83%), consistent with greater clot strength, and clot lysis at 30 minutes (LY30) was reduced (in 100%), consistent with reduced fibrinolysis.<sup>63</sup>

### Initiation and Titration of Anticoagulation

#### Recommendations

- We recommend initiating prophylactic dose low molecular weight heparin (LMWH) for all patients hospitalized with COVID-19, unless absolutely contraindicated (GRADE IA).
- We recommend initiation of intermediate dose LMWH for critically ill COVID-19 patients in ICU (GRADE IIB).
- We recommend therapeutic dose of LMWH (enoxaparin 60 mg SC BD or 1 mg/kg SC BD) in suspected or confirmed VTE or PE (GRADE IB).
- We recommend therapeutic dose of LMWH (enoxaparin 60 mg SC BD or 1 mg/kg SC BD) in COVID-19 patients who were already on therapeutic anticoagulation for other purposes (e.g., prosthetic valves/high CHAD-VASC scores/prior VTE or PE) (GRADE IB).
- We recommend equivalent unfractionated heparin instead of LMWH as a choice in patients with creatinine clearance  $< 15$  mL/minute or on renal replacement therapy (GRADE IA).
- We recommend escalating dose from prophylactic dose to intermediate or therapeutic dose of LMWH in COVID-19 patients, depending on risk assessment based on escalating D-dimer levels ( $> 6$  times upper limit of normal), prothrombotic profile on viscoelastic tests, underlying malignancy, sepsis-induced coagulopathy (SIC) score  $\geq 4$ , past history of VTE/PE (GRADE IIB).

#### Rationale

Lower limb deep vein thrombosis (DVT) were reported in 25% of patients in ICU by Cui et al.<sup>64</sup> In a Dutch study by Kloot et al., acute thrombosis was seen in 31% of ICU patients despite being on VTE prophylaxis.<sup>65</sup> Increased age and coagulopathy (PT increased by  $> 3$  s or aPTT increased by  $> 5$  s) were independent predictors of outcome. Despite 70% of patients receiving prophylactic heparin and 30% treatment-dose heparin on ICU admission, Helms et al. demonstrated PE in 17% of ICU COVID-19 patients. In comparison with a matched cohort of non-COVID-19 ARDS patients, thrombotic complications were 2.6 times and PE 6.2 times more likely in patients with COVID-19.<sup>60</sup> Similarly, Middeldorp et al. showed that despite receiving prophylactic LMWH, 39% of COVID-19 patients admitted to ICU had VTE, of which 24% had symptomatic VTE.<sup>66</sup>

Leonard-Lorant et al. performed pulmonary artery-phase CT in 106 of 1,696 suspected or proven COVID-19 patients.<sup>67</sup> Thirty-two patients (30%) were diagnosed with PE and the median D-Dimer level was 6,110  $\mu\text{g/L}$  among those with PE compared with 1,920  $\mu\text{g/L}$  among those without.

In the study by Tang et al., survival was superior in the subset of patients receiving prophylactic dose heparin who had a SIC score  $\geq 4$  and/or D-dimers  $> 3,000$   $\mu\text{g/L}$ .<sup>61</sup> As is apparent, the high incidence of VTE in critically ill COVID-19 patients despite prophylactic anticoagulation warrants consideration for higher doses of LMWH.<sup>60,65</sup> In a small study of 10 patients with increased dosing of prophylactic LMWH, D-dimer levels and hypercoagulability as assessed by viscoelastic tests were shown to improve.<sup>68</sup>

Heparin resistance, requiring of high doses of heparin to achieve a therapeutic aPTT or anti-factor Xa activity, may be a concern in acutely ill patients with COVID-19. A series of 15 COVID-19 patients in the ICU anticoagulated for VTE noted an extremely high requirement for unfractionated heparin (8 of 10 required  $> 35,000$  units/day).<sup>69</sup> It is postulated that since heparin is negatively charged and can interact with various positively charged plasma proteins, some of which behave like acute phase reactants and will compete for heparin binding, this could account for heparin resistance.

The impact of increased intensity of anticoagulation requires further evaluation. At present, there is no conclusive evidence that increasing the dose of LMWH thromboprophylaxis improves clinical outcomes or reduces the risk of VTE. But many expert centers recommend intermediate-dose thromboprophylaxis for critical care patients requiring high-flow oxygenation or mechanical ventilation.<sup>70</sup>

Some guidelines stratify the thrombosis risk using D-dimer thresholds of  $< 1,000$ , 1,000 to 3,000, and  $> 3,000$   $\mu\text{g/L}$  to identify patients who should receive standard-dose, intermediate-dose, and treatment-dose anticoagulation. Apart from increased D-dimer levels and fibrinogen levels, risk stratification may also be based on factors, such as disease severity, requirement of oxygen supplementation and ventilation, SIC score  $\geq 4$ , and a clinical suspicion of VTE (Table 2).<sup>71</sup>

### Anticoagulation at Discharge

#### Recommendations

- Extended home anticoagulation may be warranted in “high risk” COVID-19 patients after discharge (UPP).
- We recommend discharging COVID-19 patients with suspected or confirmed VTE or PE with home anticoagulation on therapeutic dose direct acting oral anticoagulants (DOACs) or LMWH for a minimum of 3 months (GRADE IB).

#### Rationale

LMWH has shorter duration of action than DOACs or vitamin K antagonists (VKA) and are preferred in the critically ill patients.

**Table 2:** Sepsis-induced coagulopathy (SIC) score

Category	Parameter	0 point	1 point	2 point
Prothrombin time	INR	$\leq 1.2$	$> 1.2$	$> 1.4$
Coagulation	Platelet count ( $\times 10^9/\text{L}$ )	$\geq 150$	$< 150$	$< 100$
Total SOFA	SOFA four items	0	1	$\geq 2$

The total sequential organ failure assessment (SOFA) is the sum of the four items (respiratory SOFA, cardiovascular SOFA, hepatic SOFA, and renal SOFA)

DOACs or VKA can interact with antiviral therapies that may be considered in selected COVID-19 patients. Hence, in patients receiving these prior to admission, switching to LMWH may be necessary. Although LMWH is recommended in patients who commence anticoagulation for suspected or proven VTE during their in-patient stay, it seems reasonable to switch to a DOAC on discharge.

Extended thromboprophylaxis on discharge can be considered if the patient is at high risk of VTE (e.g., past history of VTE, cancer, significantly reduced mobility, critical care admission, morbid obesity) and the risk of VTE is felt to outweigh the risk of bleeding. The nature and duration of thromboprophylaxis in patients recovering from COVID-19 pneumonia is not clear but a standard prophylactic dose of LMWH or DOAC for at least 1 to 2 weeks may be a reasonable approach.<sup>72-74</sup>

## CONCLUSION

While each one of the discussed entities have well-established evidence-based management protocols, whether the same can be extrapolated to the setting of COVID-19 remains dubious. Until better evidence emerges from the enormous database, the onus remains with the bedside intensivist to deliver care based on best judgment combined with available evidence.

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