## **Review Article**

## Intensive care management of patients with COVID-19

#### Anjan Trikha, Akhil Kant Singh, Puneet Khanna

Department of Anaesthesiology, Pain Medicine and Critical Care, All India Institute of Medical Sciences, New Delhi, India

#### Abstract

The COVID-19 pandemic originated in China in December 2019 and has since then, swept across the world. The last Influenza pandemic of 1918 happened before the advent of modern medicine. We have come a long way since then. But the pandemic has still caught us unprepared in many quarters. The review focuses on the management of critically ill COVID-19 patients and the various challenges faced by intensivists.

Keywords: COVID-19, critical care, India, severe acute respiratory illness

## Introduction

The COVID-19 pandemic has been sweeping the world since December 2019 and has resulted in almost four million infections and about a quarter of a million deaths.<sup>[1]</sup> This is the worst pandemic we have faced in living memory. As the SARS-CoV2 is a novel virus, it presents unique challenges to the healthcare community. These challenges are even more daunting in resource poor settings such as those found frequently in developing countries. The aim of this review is to provide a synopsis of the clinical presentation of COVID-19 and its intensive care management, associated infrastructure and staffing issues, research avenues, and hurdles. We place our experience of treating COVID-19 at the All India Institute of Medical Sciences, New Delhi within the context of the ongoing pandemic.

## Characteristics of Critically ill COVID-19 Patients

Data suggests that approximately 20% of infected cases require hospitalization, out of which around one-fourth (5%) require

Address for correspondence: Dr. Anjan Trikha, Room No. 6, Fourth Floor Porta Cabin, All India Institute of Medical Sciences, Ansari Nagar, New Delhi - 110 070, India. E-mail: anjantrikha@gmail.com

Access this article online		
Quick Response Code:	Website: www.joacp.org	
	DOI: 10.4103/joacp.JOACP_265_20	

intensive care management.<sup>[2]</sup> Case fatality ratio (CFR) varies around the world, and the 10 worst affected countries have a CFR ranging between 4 and 16%. The CFR is obviously affected by local resource availability and maybe higher in low resource settings.<sup>[3]</sup>

Older men with hypertension and/or diabetes are overrepresented in the cohort of patients requiring intensive care. Data from the United States,<sup>[4]</sup> Italy,<sup>[5]</sup> and China<sup>[6]</sup> corroborates this. Obesity is an independent predictor of disease severity.<sup>[7]</sup> Table 1 represents the prevalence of comorbidities in our ICU.

The most common symptoms at presentation are fever, cough, malaise, and breathlessness.<sup>[4,8-11]</sup> Some patients might develop hypoxaemia without demonstrating respiratory distress, a condition termed as "happy hypoxaemia."<sup>[12]</sup> Bilateral opacities may be seen on chest radiography and computed tomography (CT). CT may also show ground glass opacities and consolidation.

Course of the disease may be complicated by progression of viral pneumonia to acute respiratory distress syndrome (ARDS),

For reprints contact: WKHLRPMedknow\_reprints@wolterskluwer.com

How to cite this article: Trikha A, Singh AK, Khanna P. Intensive care management of patients with COVID-19. J Anaesthesiol Clin Pharmacol 2020;36:S29-38.

Submitted: 19-May-2020 Revised: 11-Jun-2020 Accepted: 13-Jun-2020 Published: 25-Jul-2020

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

myocardial injury, acute kidney injury, secondary infection, and sepsis/septic shock.<sup>[8-10,13]</sup> COVID-19 patients may sometimes present with neurological manifestations such as headache, hypogeusia/anosmia, acute cerebrovascular events, seizure, and ataxia. There is also some concern about the neurotropism of the SARS-CoV2 but more data is awaited to confirm the same.<sup>[14]</sup>

#### Cytokine storm/release syndrome

Cytokine release syndrome (CRS) refers to an overwhelming release of proinflammatory mediators by an overly activated immune system. CRS is known to be the basic immunopathology underlying pathological processes as varied as ARDS, sepsis, graft-versus-host disease, macrophage activation syndrome induced by rheumatic diseases, and primary and secondary hemophagocytic lymphohistiocytosis.<sup>[15]</sup> CRS has also been noted in patients receiving immunotherapies such as Chimeric Antigen Receptor T cell (CAR-T) cell therapies. A subgroup of patients with severe COVID-19 might have Secondary Hemophagocytic Lymphohistiocytosis (sHLH), a cytokine storm syndrome, characterized by a fulminant and fatal hypercytokinemia with multi-organ failure.<sup>[16]</sup> sHLH occurs in 3.7-4.3% of sepsis cases and is most commonly triggered by viral infections.<sup>[17]</sup> Clinical features of sHLH include unremitting fever, cytopenias, and hyperferritinaemia. Pulmonary involvement (including ARDS) occurs in approximately 50% of patients<sup>[18]</sup> having sHLH. sHLH usually presents in the second week of illness.<sup>[19]</sup>

#### Imaging

COVID-19 commonly presents as a viral pneumonia which may progress to acute lung injury and the features of ARDS. The reported CT imaging findings observed in early COVID-19 are bilateral multiple ground glass opacities with a peripheral or posterior distribution, predominantly in the lower lobes. Consolidation superimposed over ground glass opacities may also be seen. With disease progression, CT shows increase in the number and size of ground glass opacities leading to multifocal consolidations. Resolution is seen around week two and is marked by decrease in the number of consolidations and gradual clearing.<sup>[20]</sup>

Chest X-ray might be of little diagnostic value in the early stages of the disease. Less sensitive than CT, X-ray is often the

Table 1: AIIMS Unpublished data (23 <sup>rd</sup> May 2020)	
Total number of patients	224
Admitted to ICU	139
Hypertension	27%
Chronic Kidney disease	18%
On maintenance haemodialysis	6.9%
Diabetes Mellitus	18%

first imaging modality used in the ICU. Typically, normal in mild disease, findings are extensive 10–12 days in the disease course. Most common findings are ground glass opacities which are usually bilateral and peripheral [Image 1]. Chest X-rays are an inexpensive investigation to rule out other causes of hypoxia.

Lung ultrasound provides an alternate diagnostic modality sidestepping the concerns posed by CT such as logistic issues related to shifting a sick patient to the radiology suite, infection control and the radiation exposure. Lung ultrasound findings observed in COVID patients are B lines, thickened and/or irregular pleural lines and presence of subpleural consolidations. Lung ultrasound can not only be used to rule out other causes of SARI in the triage area but also can also aid decision making about treatment escalation/de-escalation by tracking the evolving disease process in the lungs.<sup>[21]</sup>

## Management of Acute Respiratory Failure

At our institution, all patients presenting with Severe Acute Respiratory illness (SARI) or Influenza like illness (ILI) are admitted in a holding area where they are tested for COVID and managed. If the test results are positive for COVID, they are transferred to the dedicated COVID hospital. If the test results are negative, they are transferred to the admitting unit. This works well in our setting and allows us to physically isolate suspected patients. This is in accordance with WHO guidance which suggests that any patient with severe acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath; AND requiring hospitalization) and in the absence of an alternative diagnosis that fully explains the clinical presentation be treated as a suspect.<sup>[22]</sup>



**Image 1:** Chest X ray AP view showing diffuse bilateral ground glass opacities. (Jai Prakash Narayan Apex Trauma Centre, All India Institute of Medical Sciences, New Delhi)

As we are still amid this evolving pandemic, specific clinical guidelines backed by robust data are lacking. Clinical practices are governed by what we already know about the management of acute respiratory illnesses.

Thus, all patients with SARI, testing positive for COVID-19 are admitted in our ICU. Patients who are hypoxic are started on oxygen therapy with face masks to target an oxygen saturation  $(SpO_2)$  of greater than 90%. For patients requiring low flow supplementation, nasal cannula is appropriate. Higher flows may be administered using a simple face mask, venturi device or non-rebreather mask. Risk of aerosolization increases with the use of higher flows.

#### Awake prone positioning

Deteriorating patients are asked to lie prone. Proning during invasive mechanical ventilation is advocated for ARDS and is almost the standard of care. Prone positioning during severe ARDS improved oxygenation and demonstrated a mortality benefit.<sup>[23]</sup> Awake proning works on the same principles and a small, single centre study has demonstrated improved oxygenation in COVID-19 patients.<sup>[24]</sup> We prone our awake patients for 2 h at a stretch or longer if they tolerate it and make them supine for 30 min. Avoiding awake proning immediately after meals and using prokinetics is prudent.

#### NIV and HFNC

If awake proning does not result in improvement in oxygenation and the patient deteriorates, the patient may be put on either High Flow Nasal Cannula (HFNC) or Non-Invasive Ventilation (NIV). It is important to understand that both modalities lead to increased aerosolization and consequently, increased risk to healthcare workers. However, it also delays tracheal intubation, which is associated with increased mortality. Another school of thought advocates against using these modalities at all in COVID-19 patients. This viewpoint must be weighed against the availability of resources, both material and human. Intubating all deteriorating patients might be feasible in a setting with adequate resources, but is not possible in a resource poor scenario and will result in an undue strain on ventilator demand in case of a surge.

At our institution, HFNC and NIV are important steps on the management ladder, though we prefer NIV over HFNC. The ERS/ATS guidelines recommend the use of NIV as a preventive strategy for avoiding intubation in hypoxaemic acute respiratory failure.<sup>[25,26]</sup> NIV and HFNC may be an option for mild to moderate ARDS (PaO<sub>2</sub>/FiO<sub>2</sub> > 100).

Helmet NIV has better acceptance than NIV by facemask. Using a helmet with double limb circuit and a good seal at the neck-helmet interface is a safe option in the COVID setting.<sup>[26,27]</sup> The use of a "helmet CPAP bundle" has been suggested to improve patient comfort and compliance with the helmet.<sup>[28]</sup> We start CPAP with the lowest effective pressures (5–10 cm of  $H_2O$ ). For HFNC, we start with low flow rates (20 L/min) and titrate according to the patient's requirement. This strategy allows us to mitigate the risk of aerosolization.

HFNC or NIV can also be combined with awake proning resulting in improved oxygenation. Early application of HFNC or NIV in a patient of moderate ARDS in prone position resulted in avoidance of intubation and improvement in oxygenation.<sup>[29]</sup> Presumably, these findings can be extrapolated to COVID-19 respiratory failure as well.

One of the drawbacks of using non-invasive modes of ventilation in pursuit of avoidance of intubation is the higher level of vigilance required on part of the healthcare personnel. Thus, patients on such modalities must be monitored closely with frequent blood gas analysis (every 2-3 h) to ensure safety. A low threshold for intubation should be maintained. Figure 1 provides the flow which we follow at our institution.

#### **Invasive ventilation**

Most COVID patients with severe ARDS will ultimately need invasive mechanical ventilation. Timing of intubation is important. If the patient is on NIV/HFNC, it is imperative that he/she is monitored closely for clinical and/or biochemical deterioration and intubation is not delayed as it is known to increase mortality. Intubation is known to have the highest risk of transmission due to aerosol generation.<sup>[30]</sup> It is important that certain pertinent points are kept in mind before performing intubation [Box 1].<sup>[31]</sup>

"Aerosol boxes" have been devised to prevent aerosol dissemination during endotracheal intubation.<sup>[32]</sup> In our experience, such boxes hinder arm movement and may actually delay intubation. We prefer to use a supra-normal dose of succinylcholine or rocuronium, and propofol as part of an RSI technique and intubate using the precautions mentioned previously.

The primary aim of ventilation strategy in a COVID patient is avoidance of ventilator induced lung injury (VILI). That means using a low tidal volume ventilation strategy as described by the ARDS Network.<sup>[33]</sup> We use tidal volumes 6 ml/kg predicted body weight (PBW) which targets a  $P_{plat} < 30$  cm  $H_2O$  with the prescribed PEEP. As is the practice in ARDS, ventilation is adjusted to keep driving pressure (DP =  $P_{plat}$  - PEEP) less than 15 cm $H_2O$ . Reports in the literature suggest that the COVID ARDS phenotype in the early stages of the disease is that with high lung compliance (L phenotype). Prone positioning has a proven benefit in ARDS and maybe especially beneficial in COVID-19 ARDS given the greater propensity of peripheral and dorsal areas of the lungs to be affected.<sup>[34]</sup> It is the logical next step when low tidal volume ventilation fails to improve the oxygenation. In our practice, we prone patients for a minimum of 16 h a day. Contraindications and complications remain the same as for any other ARDS case. Care should be taken to avoid venting of circuit to air which can be prevented by clamping it during disconnections. The PROSEVA trial demonstrated that the benefit from proning was accrued when it was done early rather than late.<sup>[23]</sup>

The decision to stop proning a patient must be individualized. PaO<sub>2</sub>/FiO<sub>2</sub> > 150 on FiO<sub>2</sub> < 0.6 and PEEP < 10 cm H<sub>2</sub>O for at least 4 h after the last prone session makes for a good candidate to cease prone positioning.

Neuromuscular blockade is not used routinely because of concerns for critical illness polyneuromyopathy. It should be used when there is refractory hypoxemia or patient ventilator dyssynchrony.

Veno-venous Extracorporeal Membrane Oxygenation (VV-ECMO) is reserved for the most severe form of COVID ARDS. Few centres perform ECMO on a regular basis, especially so in medium to low income countries as it is a resource intensive procedure. Experience from China has so far not demonstrated conclusive benefit from the use of ECMO in COVID patients.<sup>[35]</sup> In low resource settings, thought should be given to the dilemma of providing an advanced and expensive, yet unproven therapy to a few patients versus routine care to many patients. We do not provide ECMO as a routine therapy for COVID ARDS patients at our institution.

Figure 1 describes the treatment flow we follow at our institution.



Figure 1: Flow of COVID-19 patients according to oxygen requirements

#### Phenotypes of COVID ARDS

Marini and Gattinoni have speculated about the existence of a spectrum of lung pathophysiology in COVID ARDS (they call it CARDS).<sup>[36]</sup> They suggest that with the onset of disease symptoms, lungs retain good compliance (low elastance, low lung weight as estimated by CT scan and low response to PEEP; L phenotype). Many such patients stabilize at this stage, while some may transition to the H phenotype, characterized by high elastance (low compliance), extensive consolidations, high lung weight and high PEEP response. This transition can be caused by disease severity, host response, or suboptimal clinical management.

#### Liberation from ventilator

Assessment of readiness for weaning follows the standard protocols. Special considerations in COVID patients are to have a higher criterion for passing Spontaneous Breathing Trial. Instead of the usual 2 h, SBT can be performed for 4 h. Or a lower pressure support (0–5 cm  $H_2O$ ) can be provided during SBT. The rationale behind the altered SBT is that COVID patients are intubated for a longer duration than non-COVID patients and there is more volume of secretions and airway oedema.<sup>[5]</sup> Thus, there is a higher risk of weaning failure and re-intubation.

Extubation should be performed in an Airborne Infection Isolation Room (AIIR) with minimal personnel inside. PPEs should be donned as previously mentioned. The ventilator should be put in standby mode just before extubation, the circuit should be clamped, closed suctioning system should be engaged, and another suction catheter should be kept ready

Box 1: Important points to remember during intubation

Things to keep in mind

- An intubation checklist should be followed to avoid confusion
- The most qualified individual (e.g., anesthesiologist) should perform the intubation to decrease the number of attempts.
- If possible, the intubation should be performed in an Airborne Infection Isolation Room (AIIR).
- Minimum number of personnel should be in the room during the procedure.
- Personnel involved in intubation should be properly donned with Personnel Protective Equipment (PPE) which includes a fit tested N95 mask, eye protection, cap, gown, shoe covers and gloves.
- Preoxygenation should be performed using a 100% non-rebreather masks. Bag mask ventilation should be avoided to prevent aerosol generation. If the need for assisting ventilation is unavoidable, the mask should be replaced with a supraglottic device.
- An HME filter should be placed between the mask /supraglottic device and circuit.
- Rapid sequence induction (RSI) should be planned to decrease the apnoeic duration and to ensure complete paralysis at the time of intubation.
- Video-laryngoscope should be used to perform the intubation. This improves first pass success and allows distancing between the patient and the physician.

for aspirating the oral secretions. The endotracheal tube should be removed smoothly during inspiration and discarded immediately. We prefer to place our extubated patients on Helmet NIV with a CPAP of 5 cm  $H_2O$  for the first few hours.

#### Tracheostomy

A subset of patients (weaning failure, pulmonary toileting, neurological insult) may require a tracheostomy. Tracheostomy can also be a path to expedited weaning, and aid in fast-tracking patients to step down units, in scenarios where a surge overwhelms the critical care infrastructure.<sup>[37]</sup> Clinical guidelines suggest that either percutaneous or open approach is appropriate.<sup>[38-40]</sup> Availability of a flexible bronchoscope or the ability to sterilize it properly after use may be an issue. The recommended single use flexible bronchoscopes are either not widely available, or their price cannot be justified in low resource settings. Tracheostomy is second only to intubation as an aerosol generating procedure.<sup>[30]</sup> We prefer to perform tracheostomies in the operating room with full PPE in a completely paralysed patient. Apnoea is maintained from the time of opening the trachea to the inflation of the cuff after tracheostomy tube insertion to minimize aerosol generation.

## **Supportive Management**

#### Fluid management

We prefer to use a conservative fluid management strategy as is advised for any ARDS patient, unless the patient has sepsis or volume depletion secondary to gastrointestinal losses, fever, etc.<sup>[41]</sup> Management of COVID positive patients who have septic shock is similar to patients with septic shock due to other causes. In the recovering COVID patient on the ventilator, we prefer to keep them "dry" on the day before planned extubation. In our experience, it facilitates the weaning process.

#### Antibiotics

All our patients receive empirical broad-spectrum antibiotic coverage as it is common to have superimposed bacterial infection, especially in the presence of comorbidities. The specific antibiotic coverage can be tailored according to the local infectious disease epidemiology.<sup>[42]</sup> In the presence of local seasonal influenza, a neuraminidase inhibitor (e.g., oseltamivir) may be added.

#### **Corticosteroids**

Usage of systemic corticosteroids in Middle Eastern Respiratory Syndrome (MERS) resulted in increased viral shedding, delayed viral clearance, increased days on ventilator and mortality.<sup>[43-46]</sup> The World Health Organization (WHO), the Society for Critical Care Medicine (SCCM), and the Infectious Disease Society of America (IDSA) recommend against the routine use of systemic corticosteroids in all COVID-positive patients.<sup>[41,42,47]</sup> If the patient has underlying COPD or asthma, is in septic shock, or has severe ARDS; corticosteroids should be used.<sup>[41]</sup> Corticosteroids may also be used in severe COVID with cytokine release syndrome. We administer methyl prednisone 2 mg/kg/day for 5 days as mandated by the national guidelines.<sup>[48]</sup>

#### Thromboprophylaxis

Routine thromboprophylaxis is warranted in all patients receiving mechanical ventilation, in the absence of any contraindications.<sup>[49]</sup> This recommendation is valid for COVID patients as well. Anecdotal evidence and local guidelines at various hospitals across the world suggests that physicians consider COVID patients to be at a higher risk of venous thromboembolism (VTE).<sup>[50]</sup> This is reflected in the adoption of an intermediate intensity (i.e., administering the usual daily LMWH dose twice daily) or even a therapeutic intensity dosing strategy.

We prefer to administer the standard prophylactic once daily dosing of LMWH and instituting therapeutic LMWH dosing if there is evidence of any venous thrombosis, or signs of cytokine storm syndrome. Care should be taken to consider the patient's renal function while selecting the agent and the dose, and to individualize anticoagulation. If the patient is on warfarin at admission (mechanical heart valves, atrial fibrillation, etc.), it should be continued. In case of any contraindications to pharmacological prophylaxis, mechanical thromboprophylaxis should be used.

#### **Renal replacement therapies**

The incidence of acute kidney injury (AKI) in all COVID positive patients is about 5%<sup>[51]</sup> and in critically ill COVID patients it is 25–29%.<sup>[8,11]</sup> Thus the need for renal replacement is ever present in the COVID ICU.

Personnel operating the equipment must don full PPE with well fitted N95 masks, gowns, gloves, and shoe covers. Where possible, dialysis should be performed in the ICU itself, preferably in an isolation room. Continuous renal replacement therapy (CRRT) is our preferred mode of dialysis, even in hemodynamically stable patients. Extended tubing can be used to place the machine outside the isolation room to physically distance the patient from the healthcare personnel staffing the machine while taking care to avoid inadvertent disconnections. In case there is a scarcity of replacement fluid, resources are available on the internet to formulate an in-house solution.<sup>[52,53]</sup> Extracorporeal hemoperfusion devices for cytokine removal (Cytosorb) have no proven role in COVID patients, and as such are not used at our institution.

#### Nebulization

Due to an increased risk of aerosol generation, use of nebulizers is not recommended for drug delivery. In case bronchodilators are required, in-line metered dose inhalers (MDI) can be used. If nebulizer use is unavoidable, it should be done in an AIIR with minimum personnel present inside.

# Specific Treatment Modalities for COVID-19

At the time of writing this review, no proven therapy for COVID-19 exists. Many existing therapies have been re-purposed for use in this pandemic, and their use remains investigational.

## Hydroxychloroquine/Chloroquine

Both hydroxychloroquine (HCQ) and chloroquine inhibit SARS-CoV2 *in vitro*, but there is limited, good quality clinical data which shows a clear benefit. The US FDA has issued an emergency use authorization while most clinical societies discourage their use outside of a clinical trial.

The most concerning side effect of HCQ is QT prolongation. Therefore, the drug should be avoided in patients with prolongd QTc at baseline, and those on other drugs causing conduction abnormalities.

We administer hydroxychloroquine 400 mg q 12h on the first day, followed by 400 mg daily for 5 days.

A recent observational study has allayed fears to some extent about the side effects of hydroxychloroquine usage in COVID patients.<sup>[54]</sup> But in the absence of robust data, its use is not recommended in all COVID patients.

Azithromycin, a macrolide antibiotic, is known to have immunomodulatory properties.<sup>[55]</sup> When combined with HCQ, it is thought to have a synergistic action on viral activity. However, caution should be exercised when combining these drugs as azithromycin also causes QT prolongation.

## **IL-6** antagonists

Drugs such as tocilizumab, sarilumab, and siltuximab are IL-6 antagonists. Tocilizumab has been approved as a therapy for Cytokine Release Syndrome (CRS) related to CAR-T cell therapy. Since CRS is a common feature of severe COVID-19 infections (presence of persistent fever, elevated IL-6 and other cytokines, and elevated ferritin, D-dimer, and other inflammatory markers), it follows that tocilizumab and other IL-6 antagonists have a role to play. Indeed, case reports and observational studies have described the use of tocilizumab in severe COVID-19 patients. The US FDA has recently approved a phase III trial for tocilizumab usage in COVID-19 and multiple RCTs are ongoing to answer questions about its efficacy.

### Remdesivir

Remdesivir is a nucleotide analogue which has *in vitro* activity against SARS-CoV2.<sup>[56]</sup> The US FDA granted emergency use authorization for remdesivir for children and adults with severe COVID-19, but is not available in India yet. There are ongoing trials to ascertain its efficacy in treating COVID-19 with the current evidence inconclusive. Preliminary results demonstrate a probable efficacy in treating COVID infections, but the target patient subset is unclear.

Remdesivir is not recommended in patients with alanine aminotransferase (ALT) level more than 5 times the upper limit of normal. The drug should be discontinued if this ALT level is breached. The drug should not be given in patients with an eGFR <30 ml/min per  $1.73 \text{ m}^2$ .

### Lopinavir-ritonavir

A fixed dose combination of lopinavir-ritonavir, a protease inhibitor and primarily used for HIV, has *in vitro* activity against SARS-CoV.<sup>[57]</sup> It appears to have minimal activity against SARS-CoV2. Cao *et al.* reported no significant difference in time to clinical improvement, reduction in viral load, or 28-day mortality with lopinavir-ritonavir compared with standard care in patients with severe COVID-19.<sup>[57]</sup> The use of Lopinavir-Ritonavir outside the context of a clinical trial is not recommended.

## **Convalescent plasma**

Convalescent plasma is plasma prepared from a patient who has recovered from an illness. It is essentially a way to transfer passive immunity to a sick patient. A systematic review to assess the effectiveness of this therapy in severe acute respiratory illness of viral aetiology concluded that convalescent plasma was effective in reducing mortality.<sup>[58]</sup>

Whether a recovered patient can donate plasma is dependent on several factors such as consent, blood type matching, antibody titres and lack of transmissible infections in the donor.

Ideally, convalescent plasma should be administered in the early stages of the disease when the viral inoculum is low. Possibility of adverse effects such as volume overload, transfusion reactions, antibody dependent enhancement of infections (ADE), etc. should also be considered.

## Other therapies

There are several other therapies under investigations for their role in the management of COVID-19 infections such as favipiravir, intravenous immunoglobulins, recombinant interferons, and plasmapheresis.<sup>[59]</sup> Their use is purely investigational and is not recommended routinely.

## **Infection Control**

The WHO-China Joint mission report mentions that 2055 healthcare workers were infected in China, accounting for 3.7% of total cases.<sup>[60]</sup> Infections in healthcare workers not only degrades morale, it also strains an overstretched system where every worker is precious. Thus, it is imperative that infection control is taken seriously inside the ICU, where the environmental viral load is the highest.

Basic ICU practices such as hand hygiene and changing gloves between patients should be continued. Personal items (mobile phones, wrist watches, jewellery, etc.) of healthcare workers are potent fomites for infection spread and should not be taken inside the critical care unit.

In our dedicated COVID ICU, all personnel wear level 3 PPE at all times. Level 3 PPEs entails either an impermeable coverall or gown, PAPR (Powered Air Purifying Respirator) or fit tested N95 facemask, goggles, cap, gloves, and shoe covers. The specifications for individual items can be found on the CDC website.<sup>[61]</sup> Due to an anticipated paucity of PPEs in the future, we have a rationing policy for PPEs. Physicians, nursing staff, technicians, and other ancillary staff work in 6-h shifts. They are required to don at the start of their shift and doff at the end without taking a break during the shift, to avoid wastage of PPEs. Our entire team is on a dedicated "COVID roster" to segregate personnel working in COVID areas from those working in non-COVID areas.

It is critical to remember that just wearing PPEs is not enough. Donning and doffing correctly is paramount.<sup>[61]</sup> Prescribed donning and doffing instructions must be followed. In our ICU, doffing is carried out in a dedicated area supervised by an infection control nurse who instructs the healthcare personnel at every step.

We have already discussed the aerosol-generating procedures such as intubation, tracheostomy, and nebulization. Open suctioning should also be avoided and replaced where possible with closed suctioning. Non intubated patients should be encouraged to wear surgical three-ply masks. Patients on HFNC should be made to wear a surgical mask over the HFNC.

Viable SARS-CoV2 persists on inanimate objects such as plastics and stainless steel for up to 72 h.<sup>[62]</sup> Regular surface decontamination following local institutional protocols is a must.

Family visits in the ICU should be curtailed or stopped. Alternate arrangements such as video conferencing should be provided for the family to communicate with the patient inside the ICU. A person, preferably a physician should be tasked with communicating with the family daily about the patient's progress.

# Intensive Care Unit Infrastructure and Staffing

India has 30,000 critical care beds (2.3 beds/100,000 population).<sup>[63]</sup> With the expected surge coming, we are grossly under-equipped. There is an urgent need for adding more critical care beds to our system.

Under ideal circumstances, an ICU handling COVID patients (or any infectious disease spread by droplets or airborne transmission) should have a separate AIIR. Very few ICUs in India, and in fact Asia, have such facilities. We have installed industrial exhaust fans, venting to an empty lot, in our ICU to create a negative pressure. Since ours is a dedicated COVID hospital, the HVAC (heating, venting air conditioning) unit is of the recirculating type. In places where COVID and non-COVID areas are in the same hospital, COVID area HVAC would need to be converted to a non-recirculating type. This can be achieved by closing off the return air vents and providing for external air intake for the AHU (air handling unit). In case the HVAC unit cannot be isolated in a mixed hospital, the next best option would be to switch off the HVAC and install multiple split air-conditioning units.

Our beds are spaced 10 feet apart from each other and an attempt is made to cohort patients on ventilators together to make nursing more efficient. For critically ill patients, we try to maintain a 1:1 patient nurse ratio and for stable patients, the ratio can be 1:2 or more. Of course, this ratio can change according to patient load and workforce availability.

Record keeping remains an important aspect of critical care. It is complicated by the possibility of clinical files and papers becoming fomites for the transmission of infection. We record daily progress notes and requisition consultations from other departments using our computer-based hospital information system and where feasible, transcription services can be used. Use of paper should be discouraged as much as possible.

Communication between personnel working in the ICUs while wearing PPEs is an issue. Names and roles should be clearly mentioned on the front and back of all personnel. Words coming out of multiple layers formed by N95 masks and face shield and mingling in the myriad sounds of a busy ICU are often garbled, or completely missed. This can be disastrous leading to errors. We practice the "Hear back, read *back*" policy used widely in aviation. This essentially means confirming an instruction before carrying it out and should be followed.

To conserve PPEs and prevent unwanted exposure, telemedicine has important implications. In the western world, *e-ICUs* which allow remote monitoring of patients by nurses and physicians, are widely used. It is difficult to create such a facility at short notice, especially in a low resource setting; but a modification such as a "two tablet approach" can be adopted to reduce direct patient contact.<sup>[64]</sup> This can also be extended to facilitating "family visits."

Taking consent is also affected by social distancing norms and quarantine requirements for family members of confirmed COVID positive patients. To circumvent this, many hospitals including ours, allows obtaining consent over the phone. Ideally, the conversation should be heard by two witnesses and should be recorded and kept for future reference. The structure of the conversation should be like a conventional face-to-face talk about the need for a procedure, risks involved and concerns/questions from the family member(s). This process can be tailored according to prevailing local norms.

New staff members are constantly being recruited to work in critical care units to handle the surge of patients. Many of these personnel are not used to working in critical care. This makes training even more important and challenging. They are many online teaching programs to achieve this. The mental health of healthcare workers should also be considered, and efforts made to keep their morale up. This can entail giving scheduled breaks in the duty roster or having them de-rostered from the ICU.

## Research

War strategists talk about the "fog of war" which describes the uncertainty regarding one's own capability, the adversary's capability, and intent during an engagement.<sup>[65]</sup> The medical community at large seems to be in the midst of such a 'fog of war'. The medical literature has been flooded with more than 8,500 publications about COVID-19 since the beginning of this pandemic. Many of these are methodologically unsound, single centre, underpowered and non-peer reviewed. The immense increase in pre-prints has also contributed to this confusion.

The pace of the pandemic far outpaces the meandering speed of traditional RCTs. To counter this, collaboration between countries and open sharing of data and results is imperative. There are multiple platforms available which facilitate such cooperation.

There is a huge scope for answering epidemiological and clinical questions related to this current pandemic, especially in resource scarce settings like India. Various therapies are being re-purposed for treatment of COVID-19 around the world and their efficacy is a question to be answered. Role of corticosteroids has to be elucidated. Ideal ventilatory management in various severity grades of COVID-19 is uncertain. The coagulation picture and consequent thromboprophylaxis strategy has to be ascertained.

## Conclusion

Our review outlines the most common issues which one is expected to come across in a COVID ICU. It is by no means exhaustive but is a starting point and essentially a primer.

As the inevitable surge comes, countries are scrambling to ramp up their healthcare capacities. While buying ventilators, beds, and monitors; it must be remembered that ICUs are not made up material alone. The human component is paramount, and scarce. Training and protection of healthcare workers, both physical and mental; should be given special consideration.

Research collaboration and transparency will go a long way in enhancing our understanding of this novel disease and helping administrators and policy makers make informed decisions.

#### **Financial support and sponsorship** Nil.

#### **Conflicts of interest**

There are no conflicts of interest.

## References

- Coronavirus Update (Live): 3,758,094 Cases and 259,505 Deaths from COVID-19 Virus Pandemic - Worldometer [Internet]. Available from: https://www.worldometers.info/coronavirus/. [Last cited on 2020 May 06].
- Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a report of 72 314 cases from the chinese center for disease control and prevention. JAMA 2020;323:1239-42.
- Mortality Analyses [Internet]. Johns Hopkins Coronavirus Resource Center. Available from: https://coronavirus.jhu.edu/ data/mortality. [Last cited on 2020 May 07].
- 4. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, *et al.* Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the

New York City area. JAMA 2020;323:2052-9.

- Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, *et al.* Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region, Italy. JAMA 2020;323:1574-81.
- Xie J, Tong Z, Guan X, Du B, Qiu H. Clinical characteristics of patients who died of coronavirus disease 2019 in China. JAMA Netw Open 2020;3:e205619-e205619.
- Simonnet A, Chetboun M, Poissy J, Raverdy V, Noulette J, Duhamel A, *et al*. High prevalence of obesity in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) requiring invasive mechanical ventilation. Obes Silver Spring Md 2020. doi: 10.1002/oby.22831.
- Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, *et al*. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. Lancet 2020;395:507-13.
- 9. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, *et al*. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet Lond Engl 2020;395:497-506.
- Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, *et al.* Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382:1708-20.
- 11. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, *et al*. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: A single-centered, retrospective, observational study. Lancet Respir Med 2020;8:475-81.
- Couzin-Frankel J. The mystery of the pandemic's 'happy hypoxia.' Science 2020;368:455-6.
- Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, *et al.* Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. JAMA 2020;323:1061-9.
- Wilson MP, Jack AS. Coronavirus disease (COVID-19) in neurology and neurosurgery: A scoping review of the early literature. Clin Neurol Neurosurg 2020;193;105866.
- Mahajan S, Decker CE, Yang Z, Veis D, Mellins ED, Faccio R. Plcγ2/Tmem178 dependent pathway in myeloid cells modulates the pathogenesis of cytokine storm syndrome. J Autoimmun 2019;100:62-74.
- 16. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: Consider cytokine storm syndromes and immunosuppression. Lancet 2020;395:1033-4.
- Ramos-Casals M, Brito-Zerón P, López-Guillermo A, Khamashta MA, Bosch X. Adult haemophagocytic syndrome. Lancet 2014;383:1503-16.
- Seguin A, Galicier L, Boutboul D, Lemiale V, Azoulay E. Pulmonary involvement in patients with hemophagocytic lymphohistiocytosis. Chest 2016;149:1294-301.
- Jamilloux Y, Henry T, Belot A, Viel S, Fauter M, El Jammal T, *et al.* Should we stimulate or suppress immune responses in COVID-19? Cytokine and anti-cytokine interventions. Autoimmun Rev [Internet] 2020;19:102567.
- Salehi S, Abedi A, Balakrishnan S, Gholamrezanezhad A. Coronavirus disease 2019 (COVID-19): A systematic review of imaging findings in 919 patients. Am J Roentgenol 2020;1-7. doi: 10.2214/AJR.20.23034.
- Convissar D, Gibson LE, Berra L, Bittner EA, Chang MG. Application of Lung Ultrasound During the Coronavirus Disease 2019 Pandemic: A Narrative Review. Anesth Analg 2020. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7202122/. [Last cited on 2020 May 10].

- 22. World Health Organization. Global surveillance for COVID-19 caused by human infection with COVID-19 virus: Interim guidance, 20 March 2020. 2020; Available from: https://apps.who.int/iris/ handle/10665/331506. [Last cited on 2020 May 07].
- 23. Guérin C, Reignier J, Richard J-C, Beuret P, Gacouin A, Boulain T, *et al.* Prone positioning in severe acute respiratory distress syndrome. N Engl J Med 2013;368:2159-68.
- Caputo ND, Strayer RJ, Levitan R. Early self-proning in awake, non-intubated patients in the emergency department: A single ED's experience during the COVID-19 pandemic. Acad Emerg Med 2020;27:375-8.
- 25. Rochwerg B, Brochard L, Elliott MW, Hess D, Hill NS, Nava S, *et al.* Official ERS/ATS clinical practice guidelines: Noninvasive ventilation for acute respiratory failure. Eur Respir J 2017;50:1602426.
- Cabrini L, Landoni G, Zangrillo A. Minimise nosocomial spread of 2019-nCoV when treating acute respiratory failure. Lancet 2020;395:685.
- Winck JC, Ambrosino N. COVID-19 pandemic and non invasive respiratory management: Every Goliath needs a David. An evidence based evaluation of problems. Pulmonology 2020. doi: 10.1016/j. pulmoe.2020.04.013.
- Lucchini A, Giani M, Isgrò S, Rona R, Foti G. The "helmet bundle" in COVID-19 patients undergoing non invasive ventilation. Intensive Crit Care Nurs 2020;58:102859.
- 29. Ding L, Wang L, Ma W, He H. Efficacy and safety of early prone positioning combined with HFNC or NIV in moderate to severe ARDS: A multi-center prospective cohort study. Crit Care Lond Engl 2020;24:28.
- Tran K, Cimon K, Severn M, Pessoa-Silva CL, Conly J. Aerosol generating procedures and risk of transmission of acute respiratory infections to healthcare workers: A systematic review. PloS One 2012;7:e35797.
- 31. Orser BA. Recommendations for endotracheal intubation of COVID-19 patients. Anesth Analg 2020;130:1109-10.
- Canelli R, Connor CW, Gonzalez M, Nozari A, Ortega R. Barrier enclosure during endotracheal intubation. N Engl J Med 2020;382:1957-8.
- 33. Acute Respiratory Distress Syndrome Network, Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, *et al.* Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000;342:1301-8.
- Phua J, Weng L, Ling L, Egi M, Lim C-M, Divatia JV, et al. Intensive care management of coronavirus disease 2019 (COVID-19): Challenges and recommendations. Lancet Respir Med 2020;8:506-17.
- Hong X, Xiong J, Feng Z, Shi Y. Extracorporeal membrane oxygenation (ECMO): Does it have a role in the treatment of severe COVID-19? Int J Infect Dis IJID Off Publ Int Soc Infect Dis 2020;94:78-80.
- Marini JJ, Gattinoni L. Management of COVID-19 respiratory distress. JAMA 2020. doi: 10.1001/jama.2020.6825. Available from: https://jamanetwork.com/journals/jama/fullarticle/2765302. [Last cited on 2020 May 06].
- Raimondi N, Vial MR, Calleja J, Quintero A, Cortés A, Celis E, *et al.* Evidence-based guidelines for the use of tracheostomy in critically ill patients. J Crit Care 2017;38:304-18.
- Takhar A, Walker A, Tricklebank S, Wyncoll D, Hart N, Jacob T, *et al.* Recommendation of a practical guideline for safe tracheostomy during the COVID-19 pandemic. Eur Arch Otorhinolaryngol 2020. doi: 10.1007/s00405-020-05993-x.
- 39. Sommer DD, Engels PT, Weitzel EK, Khalili S, Corsten M,

Tewfik MA, *et al*. Recommendations from the CSO-HNS taskforce on performance of tracheotomy during the COVID-19 pandemic. J Otolaryngol 2020;49:23.

- 40. Michetti CP, Burlew CC, Bulger EM, Davis KA, Spain DA, Critical Care and Acute Care Surgery Committees of the American Association for the Surgery of Trauma. Performing tracheostomy during the Covid-19 pandemic: Guidance and recommendations from the Critical Care and Acute Care Surgery Committees of the American Association for the Surgery of Trauma. Trauma Surg Acute Care Open 2020;5:e000482.
- Alhazzani W, Møller MH, Arabi YM, Loeb M, Gong MN, Fan E, et al. Surviving Sepsis Campaign: Guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). Intensive Care Med 2020;46:854-87.
- 42. Clinical management of severe acute respiratory infection when COVID-19 is suspected [Internet]. Available from: https:// www.who.int/publications-detail/clinical- managementof-severe-acute-respiratory-infection-when-novel- coronavirus-(ncov)-infection-is-suspected. [Last cited on 2020 May 08].
- 43. Rodrigo C, Leonardi-Bee J, Nguyen-Van-Tam JS, Lim WS. Effect of corticosteroid therapy on influenza-related mortality: A systematic review and meta-analysis. J Infect Dis 2015;212:183-94.
- 44. Corman VM, Albarrak AM, Omrani AS, Albarrak MM, Farah ME, Almasri M, *et al.* Viral shedding and antibody response in 37 patients with middle east respiratory syndrome coronavirus infection. Clin Infect Dis Off Publ Infect Dis Soc Am 2016;62:477-83.
- 45. Arabi YM, Mandourah Y, Al-Hameed F, Sindi AA, Almekhlafi GA, Hussein MA, *et al*. Corticosteroid therapy for critically Ill patients with middle east respiratory syndrome. Am J Respir Crit Care Med 2018;197:757-67.
- 46. Zumla A, Hui DS, Perlman S. Middle east respiratory syndrome. Lancet Lond Engl 2015;386:995-1007.
- 47. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19 [Internet]. Available from: https://www.idsociety.org/practice-guideline/covid-19guideline-treatment-and-management/. [Last cited on 2020 May 08].
- Revised National Clinical ManagementGuidelinefor COVID1931032020.pdf [Internet]. Available from: https://www. mohfw.gov.in/pdf/Revised National Clinical Management Guideline for COVID1931032020.pdf. [Last cited on 2020 May 10].
- Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, *et al.* Surviving sepsis campaign: International guidelines for management of sepsis and septic shock: 2016. Crit Care Med 2017;45:486-552.
- COVID-19 and VTE-Anticoagulation-Hematology.org [Internet]. Available from: https://www.hematology.org: 443/covid-19/ covid-19-and-vte-anticoagulation. [Last cited on 2020 May 08].
- Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L, *et al*. Kidney disease is associated with in-hospital death of patients with COVID-19. Kidney Int 2020;97:829-38.
- 52. Burgner A, Ikizler TA, Dwyer JP. COVID-19 and the inpatient dialysis unit: Managing resources during contingency planning pre-crisis. Clin J Am Soc Nephrol 2020;15:720-22.
- 53. An In-House Solution to Address a National Shortage of Dialysate (Video) [Internet]. Consult QD. 2020. Available from: https://

consultqd.clevelandclinic.org/an-in-house-solution-to-addressa-national-shortage-of-dialysate-video/. [Last cited on 2020 May 08].

- 54. Geleris J, Sun Y, Platt J, Zucker J, Baldwin M, Hripcsak G, et al. Observational study of hydroxychloroquine in hospitalized patients with Covid-19. N Engl J Med 2020:NEJMoa2012410. doi: 10.1056/NEJMoa2012410.
- 55. Amsden GW. Anti-inflammatory effects of macrolides--an underappreciated benefit in the treatment of community-acquired respiratory tract infections and chronic inflammatory pulmonary conditions? J Antimicrob Chemother 2005;55:10-21.
- 56. Sheahan TP, Sims AC, Graham RL, Menachery VD, Gralinski LE, Case JB, *et al.* Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. Sci Transl Med 2017 28;9:eaal3653.
- Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, *et al.* A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. N Engl J Med 2020;382:1787-99.
- 58. Mair-Jenkins J, Saavedra-Campos M, Baillie JK, Cleary P, Khaw F-M, Lim WS, *et al.* The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: A systematic review and exploratory meta-analysis. J Infect Dis 2015;211:80-90.
- 59. Keith P, Day M, Perkins L, Moyer L, Hewitt K, Wells A. A novel treatment approach to the novel coronavirus: An argument for the use of therapeutic plasma exchange for fulminant COVID-19. Crit Care 2020;24:128.
- Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19) [Internet]. Available from: https://www.who. int/publications-detail/report-of-the-who-china-joint-mission-oncoronavirus-disease-2019-(covid-19). [Last cited on 2020 May 08].
- Guidance on Personal Protective Equipment (PPE) | Personal Protective Equipment (PPE) | Public Health Planners | Ebola (Ebola Virus Disease) | CDC [Internet]. 2019. Available from: https:// www.cdc.gov/vhf/ebola/healthcare-us/ppe/guidance.html. [Last cited on 2020 May 09].
- 62. van Doremalen N, Bushmaker T, Morris DH, Holbrook MG, Gamble A, Williamson BN, *et al.* Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1. N Engl J Med 2020;382:1564-7.
- 63. Phua J, Faruq MO, Kulkarni AP, Redjeki IS, Detleuxay K, Mendsaikhan N, *et al.* Critical care bed capacity in Asian countries and regions. Crit Care Med 2020;48:654-62.
- 64. Hollander JE, Carr BG. Virtually perfect? Telemedicine for Covid-19. N Engl J Med 2020;382:1679-81.
- 65. Fog of war. In: Wikipedia [Internet]. Available from: https://en.wikipedia.org/w/index.php?title=Fog\_of\_ war&oldid=940295811. 2020 [Last cited on 2020 May 12].