

COVID-19 ARDS: A Multispecialty Assessment of Challenges in Care, Review of Research, and Recommendations

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Abstract

Physicians and care providers are familiar with the management of ARDS, however, when it occurs as a sequelae of COVID-19, it has different features and there remains uncertainty on the consensus of management. To answer this question on how it compares and contrasts with ARDS from other causes, the authors reviewed the published literature and management guidelines as well as their own clinical experience while managing patients with COVID-19 ARDS. For research, a PubMed search was conducted on 01.04.2021 using the systematic review filter to identify articles that were published using MeSH terms COVID-19 and ARDS. Systematic reviews or meta-analyses were selected from a systematic search for literature containing diagnostic, prognostic and management strategies in MEDLINE/PubMed. Those were compared and reviewed to the existing practices by the various treating specialists and recommendations were made. Specifically, the COVID-19 ARDS, its risk factors and pathophysiology, lab diagnosis, radiological findings, rational of recommendation of drugs proposed so far, oxygenation and ventilation strategies and the psychological ramifications of the disease were discussed. Because of the high mortality in mechanically ventilated patients, the above recommendations and findings direct the potential for improvement in the management of patients with COVID-19 ARDS.

Keywords: ARDS, COVID19, ICU

Introduction

The coronavirus disease 2019 (COVID-19) is an acute infectious disease caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The World Health Organization (WHO) has labelled COVID-19 as a global infectious disease pandemic. COVID-19 is the third major outbreak caused by coronavirus in this century, with the earlier ones being severe acute respiratory syndrome (SARS) and Middle

East respiratory syndrome (MERS). Physicians and care providers are familiar with the management of acute respiratory distress syndrome (ARDS), however, when it occurs as a sequela of COVID-19, it has different features and there remains uncertainty on the consensus of management. To answer this question on how it compares and contrasts with ARDS from other causes, we undertook a review of the published literature (Pubmed Search on 01-04-2021, using MeSH terms “covid-19”, “pneumonia”, “ARDS”, “pathogenesis”, “epidemiology”,

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“survival”, “therapeutics”, and “complications”) and also based on our own clinical experience of managing patients with COVID-19 ARDS in DR Congo and India. This information will provide an insight to the pattern of patient response and challenges faced by the ICU teams and give a comprehensive multispeciality recommendation for circumnavigating these difficulties.

History

The World Health Organization on 31 December 2019 formally notified about a cluster of cases of pneumonia in Wuhan City, central China. By 05 January 2020, 59 cases were known and none had been fatal.^[1] Ten days later, there were 282 confirmed cases, of which four were in Japan, South Korea, and Thailand.^[2] By then, there had been six deaths in Wuhan, 51 people were severely ill, and 12 were critical. The responsible pathogen was isolated on 7 January and its genome was shared on 12 January.^[3] The causative organism of the SARS, now named as COVID-19, was a novel coronavirus, SARS-CoV-2. Today, history is continuously being rewritten, and as of 08 July 2020, there are 12M confirmed cases and 548K deaths worldwide. 168,957 new cases of COVID-19 worldwide were being confirmed daily and the death rate was over 4,147 per day.^[4] These numbers are conceivably an underestimate of the actual infected and dead because of restrictions of surveillance and testing.

Clinical Features and Classification

The patients are classified vide, WHO, and CCDC guidelines into mild, moderate, severe and critical illness on the basis of their symptoms.^[5]

The details can be removed as the focus of the article is ARDS. The symptomatology is already discussed in many articles.

Definition of ARDS

The affected patients are classified vide, WHO, and CCDC guidelines with mild, moderate, severe and critical illness on the basis of their symptoms.^[5,6] COVID-19 ARDS (CARDS) is diagnosed when someone with a confirmed COVID-19 infection meets the Berlin 2012 ARDS diagnostic criteria,^[7] which include:

- (i) acute hypoxemic respiratory failure;
- (ii) presentation within 1 week of worsening respiratory symptoms;
- (iii) bilateral airspace disease on chest X-ray, computed tomography (CT), or ultrasound that is not fully explained by effusions, lobar or lung collapse, or nodules; and

(iv) cardiac failure is not the primary cause of acute hypoxemic respiratory failure

Phenotypes of CARDS

CARDS is of two phenotypes and also varies in terms of management:

- a. Type L - characterized by low elastance, high compliance, low lung weight, low lung recruitability, and low ventilation-to perfusion (V/Q) ratio.^[8] This phenotype displays normal breathing but has low oxygen saturations (“silent hypoxemia” or “happy hypoxic”)
- b. Type H - characterized by high elastance, low compliance, high lung weight, high lung recruitability, and high right-to-left shunt. This type of pneumonia has features similar to typical ARDS.

Possible Pathogenesis and Treatment Strategy

Clinical studies on pathogenesis of COVID-19 shows association with coagulopathy. This however differs from sepsis-associated disseminated intravascular coagulation (DIC) by the relatively normal levels of PT, fibrinogen, and platelets, despite markedly elevated d-dimer levels. Although the primary pathogenesis was thought as pulmonary type II pneumocyte injury, viral pneumonia, ARDS or macrophage activating like syndrome complicating ARDS leading to DIC; the pathological evidence from autopsy series show that the major pathogenic mechanism is “Pulmonary Intravascular Coagulopathy (PIC)” as firstly named by McGonagle *et al.* This is a kind of immune thrombosis that is distinct from classical DIC.

SARS-CoV2 binds to Angiotensin Converting Enzyme 2 (ACE2) receptors on type II pneumocytes and possibly on vascular endothelial cells and causes lysis of the cells immediately leading to direct activation of the endothelium causing procoagulant activity and activates accumulation of fibrin deposits in pulmonary microcapillary venous vessels. The fibrin deposits cause a compensatory mechanism of increased plasminogen at the beginning but as the disease progresses fail to break down the fibrin deposits reflected in increased d-dimer levels.

In the lung, SARS-CoV-2 causes acute diffuse alveolar damage, pneumocyte hyperplasia, and interstitial pneumonia.

In the acute stage of ARDS, there is diffuse alveolar damage in the lung along with formation of hyaline membrane in the alveoli which is followed sequentially by interstitial widening edema and later proliferation of fibroblasts in the organizing

Table 1: Protocol for laboratory testing

Patient Category	Specimen	Test
Suspect Case	Upper respiratory tract (URT) specimen (nasopharyngeal and oropharyngeal)	RT-PCR
URT Specimen negative, but clinical suspicion	Lower respiratory tract (LRT) specimen - expectorated sputum. If ventilated patient - endotracheal aspirate/bronchoalveolar lavage	RT-PCR

stage.^[9] COVID-19 ARDS causes the typical ARDS pathological changes of diffuse alveolar damage in the lung.^[10] During the illness, lung fibrosis appears in the long term.

Coagulation dysfunction is common in COVID-19 (detected by raised D-dimer levels). Fatal cases have shown diffuse microvascular thrombosis, suggesting a thrombotic microangiopathy, and evidence of thrombotic DIC.^[11] This explains the atypical manifestations seen in the lung, like dilated pulmonary vessels on the CT Chest, and episodes of pleuritic pain. Vascular enlargement is not seen in typical ARDS, but seen in most cases of COVID-19 ARDS.^[12]

Microscopy: Microscopic picture shows exudative and proliferative phases of diffuse alveolar damage. Electron microscopy reveals that viral particles were predominantly located in the pneumocytes. The predominant pattern of lung lesions in patients with COVID-19 is diffuse alveolar damage, as described in patients infected with SARS and MERS coronaviruses. Hyaline membrane formation and pneumocyte atypical hyperplasia are frequent. The presence of platelet–fibrin thrombi in small arterial vessels is consistent with coagulopathy, which appears to be common in patients with COVID-19 and should be one of the main targets of therapy.^[13]

Biomarkers: Recent studies have suggested that in addition to direct viral damage, uncontrolled inflammation contributes to disease severity in COVID-19. Consistent with this hypothesis, high levels of inflammatory markers, including C-Reactive protein (CRP), ferritin, D-dimer, high neutrophil-to-lymphocyte ratio, increased levels of inflammatory cytokines and chemokines have been observed in patients with severe disease. Pathogenic inflammation, also referred to as cytokine storm, shares similarities with SARS-CoV and MERS-CoV10. Inflammatory cytokines IL-6, IL-8, TNF- α , and IL-1 β could help predict the course and outcome of disease in COVID-19. A high IL-6 predicted a 227% increase in chances of death, and TNF- α reduced the chances of survival by 150%. It has been found that when IL-6 and TNF- α are high at the time of admission, the patient is likely to have severe disease and reduced survival, irrespective of the use of other clinical and laboratory findings.^[14]

Procalcitonin (PCT) has emerged as a crucial biomarker for the severity and prognosis of COVID19 infection. Italian researchers have reported that the risk of severe SARS-CoV-2

infection was nearly five times higher in COVID-19 patients with raised PCT levels. A retrospective, multi-center study of 191 confirmed COVID-19 cases in Wuhan, China, reported that three indicators—higher Sequential Organ Failure Assessment (SOFA) score, a D-dimer $\geq 1 \mu\text{g/L}$, and advanced age—produced significantly higher mortality risk. These markers could help identify patients in the early stages of COVID-19 with a poor prognosis.

Laboratory: The protocol for doing a RT-PCR is as per Table 1. Peripheral white blood cell (WBC) count, neutrophil-to-lymphocyte ratio (NLR), derived NLR ratio [(d-NLR), neutrophil count divided by the result of WBC count minus neutrophil count], platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR) are indicators of the systematic inflammatory response that are widely investigated as useful predictors for the prognosis of viral pneumonia. WBC count, NLR, LMR, PLR, CRP, and d-NLR of severe patients were significantly higher than those of non-severe patients. The optimal threshold at 3.3 for NLR showed a superior prognostic possibility of clinical symptoms to change from mild to severe, which had the highest of sensitivity and specificity. When age ≥ 49.5 years and NLR ≥ 3.3 , 46.1% of the COVID-19 patients with mild disease became severe in a mean time of 6.3 days. Therefore, these patients must be closely attended to by clinicians. By contrast, when age < 49.5 years and NLR < 3.3 , COVID-19 patients with mild disease were cured and discharged in approximately 13.5 days.^[15]

The Systemic Inflammation Index (SII = neutrophil \times platelet-to-lymphocyte ratio), the aggregate index of systemic inflammation (AISI = neutrophil \times platelet \times monocyte-to-lymphocyte ratio), and systemic inflammation response index (SIRI = neutrophil \times monocyte-to-lymphocyte ratio), are all used as markers to predict mortality in COVID-19 patients admitted to hospital. However, SII emerged as the sole reliable COVID-19 prognostic hematological parameter in the retrospective evaluation of COVID-19 patients.

Determinants of Adverse Outcomes

COVID-19 ARDS appears to have significantly worse outcomes compared to ARDS from other causes, as per Table 2.

Table 2: Mortality and Outcomes

Patient Category	ICU Mortality	Hospital Mortality
Typical ARDS	33.3-37.2%	38.1-42.1%
CARDS ^[16]	26-61.5%	
Mechanically ventilated patients of CARDS ^[17]	65.7-94%	

Risk factors for poor outcomes include advanced age; presence of comorbidities such as hypertension, cardiovascular disease, and diabetes mellitus; lower lymphocyte counts; kidney injury; and raised D-dimer levels.^[18] Patients with pulmonary arterial hypertension (PAH) often fare worse compared to patients with other conditions.

Radiodiagnosis and Imaging in COVID19 ARDS

Imaging assists in establishing diagnosis; triage; and providing management guiding actionable results.^[19] The radiological armamentarium available for COVID includes routine chest radiograph (CXR), CT, and point-of-care thoracic ultrasonography (POCUS).^[20]

CXR is sensitive only when patients present late or with advanced symptoms. CXR findings include patchy peripheral consolidation or ground glass opacities (GGO) with predilection for lower and middle lobes. The consolidation is bilateral in 75% of patients and unilateral in 25%.^[21] Occasional nodules, perihilar consolidation, and prominence of perihilar vasculature are also noted.^[22]

Non-contrast high-resolution continuous helical CT scan of the thorax is the preferred protocol for evaluating COVID-19 patients. However, contrast may be administered in select cases to exclude other complications like pulmonary thromboembolism.^[23] GGO with peripheral and lower lobe predilection are the most common findings. In addition, crazy paving (GGO with thickened interlobular and intralobular septa), vascular distension in region of GGO may be seen early in the disease.^[19,23] Later, the imaging appearance progresses to architectural distortion, subpleural bands, fibrosis, and traction bronchiectasis [Figure 1]. Consolidation may superimpose on the GGO later in the disease and in older and high-risk individuals. Pleural effusion, pericardial effusion, lymphadenopathy, and pneumothorax are also uncommonly seen.^[19,23]

COVID-19 can initially present as a subpleural disease. Therefore, the accuracy of POCUS as screening tool is limited. It has significant value, however, in monitoring the progress of critically COVID patients in ICU. The findings are described with images in Table 3.





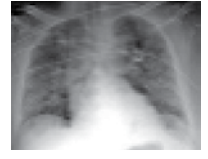

Patient Details	Chest Radiograph	CT image
42 yr/M with breathlessness and SpO2 of 90%.		
	Subtle patchy consolidation in left lower zone	HRCT of the chest confirms findings on CXR
62 yr/M with fever, breathlessness and SpO2 of 85%.		
	Bilateral peripheral consolidation	Peripheral patchy ground glass opacities with prominence of vessels
65 yr/M diabetic patient, post MVR status, with fever, breathlessness and SpO2 of 85%. Had a rapid downhill course and succumbed to his illness 24 hours after the HRCT scan.		
	Significant lung involvement with consolidation in whole of the lungs	Crazy paving appearance with some sub-pleural sparing and prominence of vessels

Figure 1: Imaging comparison of three patients of COVID-19

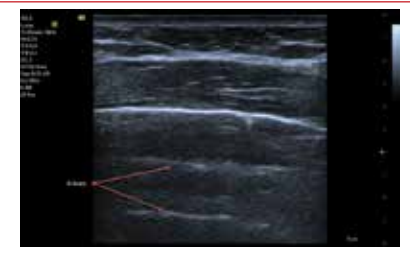

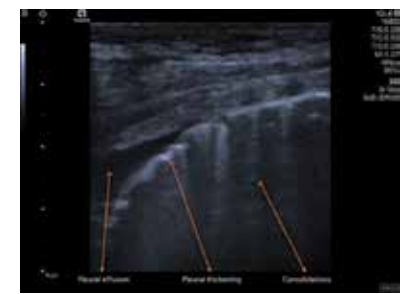
The recommendations of Fleischner Society on the role of chest imaging in COVID patients are mentioned in Figure 2^[19]:

In March 2020, the Dutch Radiological Society developed another score system based on chest CT and patient’s data; the COVID-19 Reporting and Data System (CO-RADS) included data of clinical finding and laboratory test results in addition to CT records. The degree of suspicion ranged from very low to very high (CO-RADS categories 1–5), while category 0 reflects negative infection and category 6 establishes RT-PCR-positive SARS-Cov-2 infection at time of examination [Table 5]. CT score in addition to patient’s clinical parameters empowers the triage options especially during the peak of the pandemic wave.

Echocardiographic Evaluation in Cards

Recent reports suggest that cardiac complications not only are common (≈20–25%) in COVID-19 infection but also are associated with increased mortality. The most frequent abnormality was found to be right ventricular dilation or dysfunction. However, in those reports, cardiac complications were defined according to clinical and laboratory parameters (troponin levels), without any systematic cardiac imaging. Transthoracic echocardiography is indicated only when there is clinical deterioration.

Table 3: POCUS and its interpretation

POCUS appearance	Image	Pathological representation
A line - Horizontal lines occur at multiples of distance between the ultrasound probe and the lung.		Normal lung. Represent reverberation artefacts produced by sound waves and visceral pleural or lung surface. Should be associated with sliding lung. Absence of sliding lung indicates presence of pneumothorax.
B Line Vertical lines <3/field is a normal finding. However, B line with varying thickness or increase in number is abnormal.		Indicates fluid deposition in pulmonary interstitial space or alveoli. Apex- Base gradient is seen in pulmonary edema due to heart failure. No gradient is seen in ARDS. Number of lines correlate with severity
Sonographic air bronchogram is seen. Anechoic or dark pleural effusion is noted		Corresponds to consolidation

Alongside the subclinical ventricular relaxation impairment (given the advanced age and comorbidities like systemic hypertension), the conglomeration of factors specific to COVID-19 such as systemic inflammatory milieu, endothelial dysfunction, microvascular thrombosis, arrhythmias, disturbed ventricular cross-talk (owing to the concomitant right ventricular dysfunction resulting from pulmonary hypertension), and myocardial oxygen supply--demand perturbations, can contribute significantly to the LVDD with a subsequent accentuated potential to culminate as heart failure with preserved ejection--fraction (HFpEF).

At the same time, the use of high positive end-expiratory pressure (PEEP), quite commonly employed while ventilating hypoxemic COVID-19 patients can also result in an attenuated cardiac output in the face of an already impaired ventricular filling in HFpEF.

Among patients developing clinical deterioration during follow-up (20% of hospitalized patients), repeat echocardiogram shows further deterioration of the right ventricular parameters, probably related to increased pulmonary resistance.

The underlying cardiopulmonary interactions present unique challenges in weaning the mechanically ventilated patients with co-existent LVDD.

Medical Management of SARS CoV-2 Infection

In view of the lack of availability of approved specific drug therapy for SARS Cov-2 treatment is essentially supportive and symptomatic. The initial step involves triage of patients of SARS CoV-2 into mild, moderate, severe, and critical categories depending upon the severity of clinical presentation vide WHO and CCDC guidelines.^[24]

Patients with worsening hypoxia require management in hospital with supplemental oxygen by either high flow nasal cannula (HFNC) or non-invasive ventilation. Intubation and mechanical ventilation are indicated in patients having severe illness. They may also require concomitant intensive care management of multiorgan dysfunction by a multidisciplinary team of treating specialists. The treatment of severe COVID-19 illness includes aggressive treatment of complications, prophylaxis for secondary infection, thrombotic events, and organ function support based on treatment of underlying disease.^[25] ICU practices that prevent ARDS or aid in early recognition and effective treatment of the events leading to ARDS, like lung-protective ventilation and conservative fluid management, remain essential elements to achieve desired improved outcomes.

As there is no approved specific pharmacotherapy for COVID-19, various drugs have been tried by treating doctors across the world with variable results. Currently, research trials are underway to find a definite cure, but there is no consensus on a specific drug being effective in curing SARS CoV-2 infection. Experimental and repurposed therapies that stand unsupported by strong evidence are to be strongly discouraged.

Treatments Evaluated for COVID-19

- (a) Hydroxychloroquine: Based on experience with earlier viral illnesses, HCQ was proposed to be likely effective therapy for COVID-19 besides prophylaxis. In an observational study by Joshua *et al.*^[26] involving 1,376 patients with COVID-19 admitted to the hospital, HCQ administration was not associated with either a greatly lowered or an increased risk of the composite end point of intubation or death.^[26] It has now been stopped because of lack of efficacy. WHO guidelines recommend against prescribing HCQ for prophylaxis (both post and pre-exposure) in individuals with confirmed or suspected exposure to SARS-CoV-2.
- (b) Hydroxychloroquine plus Azithromycin: Combination therapy was initially attempted to treat COVID-19, however, subsequently discontinued because of cardiac arrhythmias secondary to increased QT interval resulting in fatality in a few.
- (c) Lopinavir-Ritonavir: These anti-retroviral drugs, initially considered promising in SARS-CoV-2 infection failed in expected outcomes. WHO accepted the recommendation from Solidarity Trial's International Steering Committee vide press release dated 04 July 2020 to discontinue lopinavir-ritonavir arm of the trial because of evidence of little or no reduction in mortality of hospitalized COVID-19 patients when compared to standard of care.
- (d) Favipiravir: This selective RNA polymerase inhibitor, under study in various trials around the world, inhibits viral replication. Two clinical trials (Japan, USA) and a phase-3 clinical trial in India using favipiravir combined with another antiviral agent, Umifenovir are ongoing.^[27] Results are awaited.
- (e) Remdesivir: A nucleotide analogue prodrug that is intracellularly metabolized to an analogue of adenosine triphosphate that inhibits viral RNA polymerases has shown *in vitro* activity against SARS-CoV-2. The first published report with a group of patients receiving remdesivir in a compassionate-use programme, described clinical improvement in 36 of 53 hospitalized patients (68%) with severe COVID-19.^[27] US FDA issued an EUA of remdesivir to allow its emergency use for severe

Table 4: Summary of drugs evaluated for COVID-19

Drugs	Indications	Doses	Special Considerations
Hydroxychloroquine	COVID-19 (moderate/severe/critical)	400 mg BD on day 1, then 200 mg BD x next 4 days	Due to its propensity to develop QT prolongation and cardiac arrhythmias now it is not recommended. Also has risk of fetal ocular toxicity.
HCQS plus Azithromycin	COVID-19 (moderate/severe/critical)	HCQS dose as above. Azithromycin 500 mg OD on D1, then 250 mg OD x 4 days	Obtain baseline EKG preferably not during sinus tachycardia (if QTc >500 msec then avoid giving this drug combination due to risk of cardiac arrhythmias). Currently not recommended for use due to poor risk-benefit ratio.
Lopinavir-Ritonavir	Severe to critical COVID-19 illness	Lopinavir 400 mg + Ritonavir 100 mg BD upto 10 days	In hospitalized patients no benefit observed beyond standard care. Cause QT prolongation and ALT elevation
Favipiravir	COVID-19 (mild to moderate illness)	Loading dose of 1800 mg BID on day 1, followed by a maintenance dose of 800 mg BID from day 2 to maximum of day 14.	Recommended in COVID-19 management protocols for use in some countries. Early trends of various trials have shown better viral clearance among patients started early on treatment with it, however, more trials needed to assess its clinical efficacy in COVID-19. Contraindicated in pregnancy (due to teratogenic effects), hepatic impairment, renal impairment, hypersensitivity.
Remdesivir	Severe to critical COVID-19 illness	200 mg IV on day 1, followed by 100 mg IV OD x 9 days	Currently suspended by WHO for routine use for most patients outside clinical trials except for emergency use in pregnant patients and children. Monitor hepatic transaminases.
Tocilizumab	Critical COVID-19 cases on already optimized treatment who meet criteria for cytokine storm	400 mg IV once	To be considered on case to case basis only. Exclusion criteria: Age >70 years, ILD, pancreatitis, AST/ALT >5 x ULN, CHF with EF<30%, Neutrophils <500 cells/cumm, platelet count 50000/cumm, myoglobin >100 ng/mL, sepsis due to other pathogens, poor prognosis (unlikely to survive >48 h)
Dexamethasone	Severe/critical COVID-19	6-8 mg PO/IV daily for upto 10 days or discharge whichever is early	RECOVERY trial showed systemic steroids reduce 28-day mortality & systemic inflammatory response leading to lung injury & MODS in hospitalized patients with COVID-19 patients who required supplemental oxygen with maximum benefit in those requiring mechanical ventilation. No survival benefit seen in those not requiring oxygen supplementation.

COVID-19 (confirmed or suspected) in hospitalized patients.^[28,29] Currently, several phase-3 clinical trials are evaluating it for treatment of moderate and severe COVID-19.

- (f) Dexamethasone: Practise of using dexamethasone varied widely across the world with many treatment guidelines having conflicting reports on use of corticosteroids in COVID-19 illness^[30] but in China they were being used in severe cases.^[31] However, the RECOVERY trial (with over 11,500 patients enrolled from over 175 NHS hospitals in the UK) provided clear evidence that dexamethasone 6 mg per day for up to 10 days reduces 28-day mortality in COVID-19 patients receiving invasive mechanical ventilation by one-third, and by one-fifth in patients receiving oxygen without invasive mechanical ventilation. No benefit was demonstrated in hospitalized COVID-19 patients who were not receiving respiratory support and results were consistent with possible harm in this group.^[32]
- (g) Convalescent Plasma: Convalescent plasma, collected from donors having recovered from recent COVID-19 infection, contains anti-SARS-CoV-2 virus antibodies that can be used to treat other COVID-19 patients. Data from a study in USA involving 20,000 patients transfused with COVID-19 convalescent plasma demonstrate that its use is safe and carries no excess risk of complications and supports the premise that administration of the same early during illness is likely to reduce mortality.^[33] Another study by Liu *et al.* showed that convalescent plasma transfusion improved survival in non-intubated patients but not in intubated patients.^[34] The FDA states that it is important to determine its safety and efficacy via clinical trials before routinely administering convalescent plasma to patients with COVID-19.
- (h) Interleukin-6 (IL-6) inhibitors: Interleukin-6 is a pleiotropic pro-inflammatory cytokine produced by various cell types including lymphocytes, monocytes, and fibroblasts. SARS CoV-2 virus induces IL-6 production from bronchial epithelial cells causing inflammation. Various IL-6 inhibitors (like sarilumab, tocilizumab) are under evaluation for their efficacy in management of COVID-19. However, presently there is inconclusive data to recommend for or against the use of IL-6 inhibitors.^[35]
- (j) Nitric Oxide: Potential role of inhaled nitric oxide (iNO) in preventing progression of disease in those with severe ARDS is under evaluation.^[36] Routine use of iNO in patients with COVID-19 pneumonia is not recommended and the trial is recommended only in mechanically ventilated patients with severe ARDS and hypoxemia despite other rescue strategies.^[37] Studies are

ongoing to evaluate for the efficacy and safety of iNO in SARS-CoV-2 patients requiring supplemental oxygen before the disease progresses to necessitating mechanical ventilatory support.

- (k) Anticoagulants: To break fibrin deposits in pulmonary microvasculature, the treatment strategy is focussed at blockage of hypercoagulation with low-molecular weight heparin (LMWH) for blocking thrombin and dampen the inflammatory response. LMWH at prophylactic doses should be administered to all symptomatic patients with microbiologically or radiologically documented COVID-19 diagnosis and escalated to therapeutic doses in case of respiratory distress. In case LMWH is insufficient of preventing further activation of PIC and the thromboses extend to pulmonary veins, the process will proceed to secondary pulmonary hypertension and cardiac insufficiency. Increased intravascular pressure in lungs will result in extensive alveolar exudation, resulting causing marked hypoxia. As a consequence of decreased pulmonary venous flow, the left ventricular stroke volume will decrease leading to systemic hypotension. The treatment option at this step should be Tissue Plasminogen Activator (TPA) or defibrotide. These two fibrinolytic modalities can prevent intubation and progression to DIC.
- (l) COVID-19 Vaccine: As of 18 February 2021, at least seven different vaccines across three platforms have been rolled out in countries. Vulnerable populations in all countries are the highest priority for vaccination. The vaccines must be proven safe and effective in large (phase III) clinical trials. Some COVID-19 vaccine candidates have completed their phase III trials, and many other potential vaccines are being developed. An external panel of experts convened by WHO, called the Strategic Advisory Group of Experts on Immunization (SAGE), analyses the results from clinical trials, along with evidence on the disease, age groups affected, risk factors for disease, programmatic use, and other information. SAGE then recommends whether and how the vaccines should be used.

The vaccines available for use in the USA, and India are displayed in Tables 6 and 7.

In India, on April 12, 2021, Russian Sputnik V COVID-19 vaccine was approved for use.

Status of COVID-19 Vaccines within WHO EUL/PQ evaluation process as on June 03rd is attached as Appendix 1.^[38]

While a COVID-19 vaccine will protect you from serious illness and death, we still don't know the extent to which

Table 5: Overview of CO-RADS categories and the corresponding level of suspicion for pulmonary involvement in COVID-19

CO-RADS	Level of suspicion for pulmonary involvement of COVID-19	Summary
CO-RADS 0	Not interpretable	Scan technically insufficient for assigning a score
CO-RADS 1	Very low	Normal or non-infectious
CO-RADS 2	Low	Typical for other infection but not COVID-19
CO-RADS 3	Equivocal/unsure	Features compatible with COVID-19, but also other diseases
CO-RADS 4	High	Suspicious for COVID-19
CO-RADS 5	Very high	Typical for COVID-19
CO-RADS 6	Proven	RT-PCR positive for SARS-CoV-2

Table 6: Vaccines used in the United States

Vaccine Brand Name	Who Can Get this Vaccine?	How Many Shots You Will Need	When Are You Fully Vaccinated?
Pfizer-BioNTech	People 16 years and older	2 shots Given 3 weeks (21 days) apart	2 weeks after your second shot
Moderna	People 18 years and older	2 shots Given 4 weeks (28 days) apart	2 weeks after your second shot
Johnson & Johnson's Janssen	People 18 years and older	1 shot	2 weeks after your shot

Table 7: Vaccines used in India (till April, 2021)

Vaccine Brand Name	Who Can Get this Vaccine?	How Many Shots You Will Need	When Are You Fully Vaccinated?
Covishield (Oxford-AstraZeneca vaccine being manufactured by the Serum Institute of India)	People 18 years and older	Time interval between two doses of the Covishield vaccine has been extended from four-six weeks to four-eight weeks	2 weeks after your second shot
Covaxin	People 18 years and older	2 shots Given 4-6 weeks apart	2 weeks after your second shot

it keeps you from being infected and passing the virus on to others. To help keep others safe, COVID appropriate behaviour is necessary. Always follow guidance from local authorities based on the situation and risk where you live.

Oxygenation and Ventilation for COVID-19 ARDS Patients

COVID-19 ARDS follows an anticipated time course, with a median time to intubation of 8–10 days after symptom onset.^[39] It is therefore imperative to constantly monitor patients for the development of ARDS as the days of infection progresses. The primary strategy for COVID-19 patients is supportive care, which includes oxygen therapy for hypoxemic patients. Oxygen therapy is instituted if respiratory rate is of 30 breaths/min. or above and/or SpO₂ of 93% on breathing air.

NON-INVASIVE MODES

High-flow oxygen therapy (HFNO) should be started if there is a respiratory failure and mild–moderate ARDS. HFNO is used as first-line treatment, followed by noninvasive ventilation (NIV) in CARDS.^[39] However, NIV is not recommended for patients with failed HFNO. NIV provides benefit via PEEP, to patients with mild–moderate ARDS by reducing

the respiratory load and intubation rate but it can cause significant aerosol generation.

High-flow nasal cannula (HFNC) for HFNO is effective in improving oxygenation, but due to reports of high amount of aerosol dispersion it was not recommended initially. However, further studies in patients with acute hypoxemic respiratory failure, HFNC was proven to avoid intubation compared to conventional oxygen devices, and the scientific evidence of generation and dispersion of bio-aerosols via HFNC showed a similar risk to standard oxygen masks. HFNC prong with a surgical mask on the patient's face is thus a reasonable modality to benefit hypoxemic COVID-19 patients and avoid intubation.^[40]

INTUBATION AND INVASIVE MECHANICAL VENTILATION OF COVID-19 ARDS PATIENTS

Mechanical ventilation of COVID-19 patients with ARDS is really a challenging task as these patients usually have non-homogenous lung pathology. This requires a targeted lung-protective ventilation strategy to improve the outcome.

The indications for mechanical ventilation for COVID-19 ARDS^[41,42] are as follows:

1. Acute hypoxic respiratory failure with severe respiratory distress.
2. Worsening hypoxia associated with increased labored breathing.
3. Increased work of breathing associated with use of accessory muscles of respiration.
4. Failure to maintain $SpO_2 > 90\%$ with > 50 L/min of HFNO or with maximal supplemental oxygen.
5. Hypoxia with altered mental status and failure to maintain airway patency.
6. Patient with multiorgan failure, persistent hemodynamic instability requiring vasopressor support, or those with multiple comorbidities like (DM, Cardiovascular disease, hypertension, advanced age, frailty, cancer, or chronic respiratory disease).
7. Arterial pH < 7.3 with $PaCO_2 > 50$ mm Hg.
8. $PaO_2/FiO_2 < 200$.^[43]
9. High respiratory rate with persistent thoraco-abdominal asynchrony or paradoxical respiration.
10. Low ROX index^[44] (< 4.88) with patient on HFNC.
8. Use both hands to hold the mask to ensure a tight seal using the V-E technique rather than the C-E technique with one hand.
9. Video laryngoscope is preferred for intubation.
10. Airway management should be safe, accurate, and should be accomplished within 15–20 s.
11. After tracheal intubation, clamp the endotracheal tube (ETT) and inflate the cuff before instituting ventilation. A COVID aerosol barrier has been used extensively for intubation.^[48]
12. Viral and HME filter to be applied between endotracheal tube and circuit.
13. Proper tube placement can be identified by $EtCO_2$ monitoring and visible bilateral chest rise. Avoid auscultation to confirm tube placement.
14. Supraglottic airway devices (SGAD) to be used in CICO (Can't intubate and can't oxygenate) situations only and bedside tracheostomy to be performed as early as possible.

The indications for intubation and mechanical ventilation in COVID-19 patients are not limited to the above-mentioned conditions and is at the discretion of the treating physician.^[45]

Precautions and Procedures while intubating COVID-19 patients

Airway management and intubation in COVID-19 patients is an aerosol-generating procedure and is associated with increased risk of viral transmission to the healthcare providers. Hence, a high level of attentiveness and alertness is necessary to prevent infection when intubation is performed. The following points are to be ensured for safety of patients and healthcare providers^[46]–

1. Standard level 3 protection should be donned while performing intubation.
2. Standard monitoring, IV access, instruments, drugs, ventilator, and suction should be pre-checked.
3. Tracheal intubation should be performed by the most experienced anesthesiologist in an airborne infection isolation room to ensure patient safety as well as of healthcare worker (HCW)
4. Limit the number of healthcare providers in the room/cubicle prior to intubation.
5. Use 3–5 min. pre-oxygenation with 100% oxygen as these critical patients have poor oxygen reserve.
6. Spontaneous ventilation should be preserved and assisted bag mask ventilation during preoxygenation should be avoided.
7. RSI (rapid sequence intubation) technique should be used to avoid manual ventilation of the patient's lungs and the potential aerosolization of the virus from the airways.^[47]

Ventilatory strategy for COVID-19 ARDS

The most appropriate time to intubate COVID-19 patients is still not clear. However, early and timely institution of mechanical ventilation can be considered if the COVID-19 patient develops moderate to severe ARDS ($PaO_2/FiO_2 < 200$) to prevent Patient self-induced lung injury (P-SILI).^[43] Non-intubated spontaneously breathing ARDS patients are at increased risk of P-SILI because of high intake of inhaled tidal volume. Therefore, esophageal pressure measurement by manometer can be considered in spontaneously breathing, non-intubated patients to decide the time for intubation.^[49] The esophageal pressure between 05 and 10 cm H_2O is usually well tolerated. However, if pressure progresses beyond 15 cm H_2O , then the risk of P-SILI increases and intubation shouldn't be delayed. If esophageal manometry is not available, then change in CVP (central venous pressure) with respiration or clinical assessment of excessive inspiratory effort for increased work of breathing can be considered [Figure 3].^[50]

Mortality is very high for COVID-19 ARDS patients on mechanical ventilation. Inappropriate ventilatory strategy in ARDS patients can lead to Ventilator induced lung injury (VILI), which includes barotrauma (high airway pressure), volutrauma, atelectrauma, biotrauma, myotrauma (diaphragmatic injury), and oxytrauma (oxygen free radicals).

Strategies to promote lung protection in ARDS: -

- a. Lung protective ventilation^[51].
This approach of ventilation in patients with ARDS is based upon several randomized trials and meta-analyses that have reported survival benefit from lung-protective

ventilation. Initial ventilatory settings for these patients are recommended as below:

b. Role of PEEP in COVID-19 ARDS

There is an ambiguity with respect to the usage of adequate PEEP for COVID-19 ARDS patients. Using higher PEEP (any PEEP >10 cm H₂O) was not recommended based on the heterogeneity of lung involvement in COVID-19 patients with simultaneous existence of severely affected areas with non-affected areas in the lung.^[52] However, surviving sepsis campaign guidelines on management of critically ill adults from COVID-19, European Intensive and Critical Care Guidelines, recommend PEEP >10 cm H₂O for management of ARDS because of SARS-CoV-2.

c. Compliance

In COVID-19 patients, lung compliance needs to be constantly assessed. If compliance is high or normal with the existence of hypoxemia, it is recommended to use a PEEP of less than 10 cm H₂O to avoid over-distention of normal healthy alveoli. However, if compliance is low as seen in ARDS, then it's advised to use adequate PEEP of just above the lower inflection point on the pressure volume loop on the ventilator to recruit collapsed alveoli, to prevent atelectasis, and thereby improve oxygenation. Once the initial setting on the ventilator is entered, monitoring of the following parameters is done to ascertain patient progress:

1. Plateau pressure – P_{plat} should be below 30 cm H₂O.
2. Driving pressure is kept below 15 cm H₂O. This can be achieved by either decreasing tidal volume (at the risk of development of hypercapnia) or by increasing PEEP, which can cause over-distention of alveoli. Therefore, careful titrations are required.
3. Compliance – Normally the total compliance of both lungs in an adult is about 200 ml/cm H₂O. Low compliance is usually found in ARDS patients with stiff lung. There are two types of lung compliance:
 - a. Static compliance = Tidal volume/(P_{plat} - PEEP)
Static compliance measures pulmonary compliance when no airflow such as during inspiratory pause and it is slightly higher than dynamic compliance.
 - b. Dynamic compliance = Tidal volume/(PIP - PEEP)
It represents pulmonary compliance during active inspiration and depends upon peak inspiratory pressure (PIP). PIP depends on airway resistance. COVID-19 pneumonia usually has high compliance (>40 ml/cm H₂O). Therefore, management should be instituted with low PEEP and high tidal volume up to 8–9 ml/kg, if hypercapnia presents.

However, COVID-19 ARDS is to be managed like ARDS with lung-protective ventilation by keeping low tidal volume (4–6 ml/kg) and high PEEP.

4. Airway occlusion pressure (PO.1) – The normal value of PO.1 in a spontaneously breathing patient is about 1 cm H₂O. However, in mechanically ventilated patients, values above 3.5 cm H₂O are associated with increased effort. Keep airway occlusion pressure value in COVID-19 ARDS patients less than 3.5 cm H₂O to obtain a ventilatory strategy protective for the lung to prevent it from VILI and diaphragmatic injury (Myotrauma).

d) Target goals of mechanical ventilation

- Target SpO₂ = 90-94%
- PaO₂ >55 mm Hg.
- pH >7.2
- Fio₂ <0.4
- PaO₂/Fio₂ >300 mm Hg.

Subsequent ventilatory setting can be decided by periodic checking of P_{plat} pressure, driving pressure, compliance, and ABG (pH, Oxygenation level). If P_{plat} pressure >30 cm H₂O, then tidal volume can be decreased to 5 ml/kg or if required, further decreases then tidal volume set to 4 ml/kg of predicted body weight.

- (e) Adjunctive therapy: The use of adjunctive treatment is relatively less during initial presentation in patients with ARDS, but gradually increase with ARDS severity.

• Sedation

A combination of multiple agents like (propofol, ketamine, fentanyl, morphine, hydromorphone, dexmedetomidine, and midazolam) may be considered for sedation of COVID-19 patients on mechanical ventilator. Usually, COVID-19 patients require high level sedation to ensure patient comfort, alleviate pain, anxiety, avoid ventilator asynchrony, and self-extubation.^[53]

• NMBA (neuromuscular blocker agents)

Can be used in boluses in patients with refractory hypoxemia or ventilator asynchrony to facilitate protective and improved lung ventilation. It also causes reduction of high pulmonary inflation pressures (e.g., ARDS), raised intracranial pressure, and metabolic rate (e.g., work of breathing, shivering).

• Recruitment maneuvers

WHO interim guidelines recommend the use of intermittent recruitment manoeuvres with high PEEP to improve oxygenation in ARDS. However, there are contradicting reports on the use of the same.

• Steroid administration

WHO recommends steroid administration in COVID-19 ARDS patient on mechanical ventilator if

they develop septic shock and require increasing dose of vasopressor to maintain MAP >65 mm Hg in a dose of Inj. Hydrocortisone - 200 mg/day or Prednisolone 75 mg/day.

- Fluid therapy

Conservative or restricted fluid therapy over liberal fluid is advised, as it may worsen oxygenation in mechanically ventilated ARDS patients.

- Management of septic shock

WHO interim guidelines^[51] recommend the use of crystalloid intravenous balanced fluids like normal saline, Ringer's lactate as fluid bolus (01 litre over 30 min. or faster) for septic shock to check for fluid responsiveness; and avoid using hypotonic fluids, starch-based solution for resuscitation. If no fluid response occurs OR signs of fluid overload appear like crackles on auscultation, then discontinue the fluid and consider using vasopressors. In vasopressors, norepinephrine is the drug of choice, followed by vasopressin and dobutamine to maintain MAP >65 mm Hg and preferably be given through central venous line. These vasopressors to be given as per strictly controlled rate decided as per targeted blood pressure to maintain tissue perfusion. However, peripheral lines can be considered in resource-limited settings keeping a close watch for necrosis of skin or extravasation of vasopressors.

(f) Prone ventilation

If lung-protective ventilation fails to maintain adequate oxygenation and if PaO₂/FiO₂ <150 mm Hg with PEEP >5 and FiO₂ >0.6, then prone ventilation should be considered. Prone ventilation improves oxygenation and decreases V/Q mismatch, particularly when applied early with other lung-protective strategies. In COVID-19 patients, good response to prone positioning may be because of their well-preserved lung compliance compared to patients who develop ARDS from other causes.^[48,54] By optimizing patient selection and treatment protocols, the recently Proning Severe ARDS Patients (PROSEVA) trial demonstrated a significant mortality benefit with prone ventilation.

(g) Role of pulmonary vasodilators

The two most commonly used vasodilators in mechanically ventilated patients are inhaled nitric oxide gas (NO) and Epoprostenol, which are administered by continuous inhalation. They can be considered to improve oxygenation even when PaO₂/FiO₂ <100 mm Hg despite prone ventilation and if severe hypoxemia is associated with acute pulmonary arterial hypertension.^[55] If there is no improvement in the oxygenation after instituting inhaled pulmonary vasodilators, then it should be tapered off without undue delay. The risk of aerosolization and clogging of HME filters is particularly more with

epoprostenol, and this remains a concern in COVID-19 patients. That is why inhaled NO is preferred over epoprostenol. In COVID-19 ARDS patients, there is yet no conclusive evidence on the use of pulmonary vasodilators.^[55]

(h) Role of ECMO

Even after prone ventilation, if oxygenation doesn't improve and hypoxia still persists, then veno-venous extracorporeal membrane oxygenation (VV-ECMO) can be considered. Its use as rescue therapy is considered only in refractory hypoxic respiratory failure.^[56] No RCTs or meta-analyses have been conducted for ECMO in COVID-19 patients with ARDS, however, there are reports from China stating its beneficial use. But the process and outcomes have not been mentioned.^[57]

(i) Ventilator Weaning and Extubation

Special focus needs to be ensured to avoid viral transmission to the healthcare providers during extubation as it is also an aerosol-generating procedure. Since there is a high chance for reintubation in many patients, some physicians like to use cuff leak test criteria along with spontaneous breathing trials (SBT). This is done to assess the readiness for weaning from mechanical ventilation on the assumption that these patients could have developed airway oedema due to prolonged ventilation. Aerosol generation in cuff leak test is similar to extubation, so caution needs to be taken while performing a cuff leak test. SBT without T-piece at lower pressure support (0-3 cm H₂O) and along with prior use of steroid to extubation yielded promising results. The following weaning criteria is recommended before extubation:

1. Patient should be conscious, comfortable, and oriented.
2. PaO₂/FiO₂ >300 mm Hg with PEEP <5 cm H₂O.
3. Hemodynamically stable and maintaining SpO₂ with FiO₂ <0.4.
4. RSBI (Rapid shallow breathing index <105) – calculated by respiratory rate/tidal volume in liters when the intubated patient is breathing spontaneously
5. No signs of increased work of breathing or respiratory distress like use of accessory muscles, paradoxical or asynchronous respiration, nasal flaring, profuse diaphoresis, agitation, tachypnoea, tachycardia and cyanosis.

(j) Prevention of complications

1. The prevention of complications associated with mechanical ventilation in COVID-19 patients is important and should be implemented (Table.....). The following can be incorporated. In a table. Prevention of VAP^[58]

2. Reduce pressure sores and ulcers by frequent change of position every 2 hours.
3. Reduce stress ulcer, gastric bleeding by early enteral feeding, and consider PPI or H2 blocker.
4. Reduce ICU related weakness by early mobilization.
5. Reduce urinary catheter related infection by using sterile aseptic technique while insertion and consider removal when not needed.
6. Reduce the number of days on mechanical ventilation by daily assessment for readiness of extubation through spontaneous breathing trials.
7. Reduce the incidence of venous thromboembolism by use of pharmacological agents or mechanical compression devices.

Neuropsychiatric Symptoms in COVID-19

Long-term outcomes of patients with ARDS are being increasingly recognized as important research targets, as many patients survive ARDS only to have ongoing functional and/or psychological sequelae.

Neuropsychiatric symptoms are atypical presentations of COVID-19. There is a myriad of symptoms ranging from mild headache and myalgia in majority of cases to life threatening seizures and delirium in patients with severe respiratory compromise (ARDS), especially in patients with underlying comorbidities.

Neuropsychiatric symptoms are estimated to appear in around 30% of COVID-19 infected patients.^[59] Moderate to severe infection can impair executive functions, confusion, and agitation.^[60]

The neurological complications can be divided into primary neuroinvasion^[61] by the coronavirus or secondary wave by activated immune and inflammatory mediators. The virus enters the nervous system either directly from the olfactory nerves pathway or is spread via hematogenous route and attaches onto the ACE-2 receptors on the neuronal endothelium.^[62] This acute involvement can cause meningitis/encephalitis leading to altered sensorium, delirium, seizures, and/or even coma.^[63] It is also hypothesized that direct invasion of medullary neurons could be responsible for severe respiratory failure.^[64] Alterations in sensorium and delirium could also be because of hypoxia from respiratory failure, aberrations in coagulation pathways, metabolic imbalances, multiorgan dysfunction, or even iatrogenic (drugs used during mechanical ventilation). Long-term sequelae could be attributed to alterations in immune response and consequent aberrant inflammatory response^[65]

Delirium- The prevalence of delirium in intubated patients is up to 80%^[66] which expectedly upswings in a COVID-19 patient with ARDS.

The risk factors include old age (>65 years), medical comorbidity, drugs (propofol, opioids, and high-dose benzodiazepines, which are routinely used during mechanical ventilation,^[67] and hydroxychloroquine).^[68] There are certain COVID-specific environmental risk factors such as mandatory wearing of personal protective equipment (PPE) which accentuates the anxiety and feeling of vulnerability in an alien environment. The patient is deprived of the reassuring and empathetic look on the doctor's face.^[69] All these risk factors can impair the patient's perception of the reality and cause disorientation and confusion.

Scales for assessment of Delirium:

The time-tested Confusion Assessment Method for the ICU^[70] should be followed routinely. Other useful scales are Intensive Care Delirium Screening Checklist^[71] and the Stanford Proxy Test for Delirium.^[72]

Management

A) Non pharmacologic:

1. Ensuring a comfortable ambient light in sync with the diurnal cycle.
2. Ensuring a pain-free spell of 6--8 h of sleep without significant treatment related disruptions.
3. Regular cognitive stimulation and reorientation of the patient to time, place, and person (utilizing AV aids for virtual communication with family members/other familiar people).
4. Encouraging physical mobilization at the earliest.
5. Providing all kinds of possible aids (glasses, hearing aids, mobiles, etc.) to convey a feeling of self-sufficiency and sense of control over the situation.

B) Pharmacologic

1. Sleep cycle:

Melatonin should be used for regularizing sleep--wake cycle in delirium as it has a short half-life, has additional mild anti-inflammatory properties, and does not cause respiratory depression.^[73] Suvorexant (Orexin antagonist) has also been used especially in conjunction with Melatonin.^[74] Benzodiazepines should be avoided (except in cases of delirium tremens), as cumulative doses run the risk of respiratory depression and may cause paradoxical disinhibition. Zolpidem (2.5--5 mg) is relatively safer in terms of respiratory functioning, but levels are increased in patients taking ritonavir.

2. Acute agitation/Disruptive behavior

Main Recommendations	Additional Recommendations
<ul style="list-style-type: none"> Imaging is not routinely indicated as a screening test for COVID-19 in asymptomatic individuals or patients with mild features of COVID-19 unless they are at risk for disease progression Imaging is indicated for patients with moderate to severe features of COVID-19 regardless of COVID-19 test results Imaging is indicated for patients with COVID-19 and evidence of worsening respiratory status When access to CT is limited, chest radiography may be preferred for patients with COVID-19 unless features of respiratory worsening warrant the use of CT 	<ul style="list-style-type: none"> Daily chest radiographs are not indicated in stable intubated patients with COVID-19 CT is indicated in patients with functional impairment and/or hypoxemia after recovery from COVID-19

Figure 2: Recommendations on chest imaging

Antipsychotic drugs like haloperidol, olanzapine, or quetiapine are found to be beneficial in the management of the agitation. However, monitoring of QTc interval, neurologic side effects (EPS), and sedation are required. The risk of QTc prolongation gets further amplified, given the potential use of COVID-19-specific medications that themselves prolong QTc (hydroxychloroquine, azithromycin), leading to a potentially increased risk of torsades de pointes.^[75]

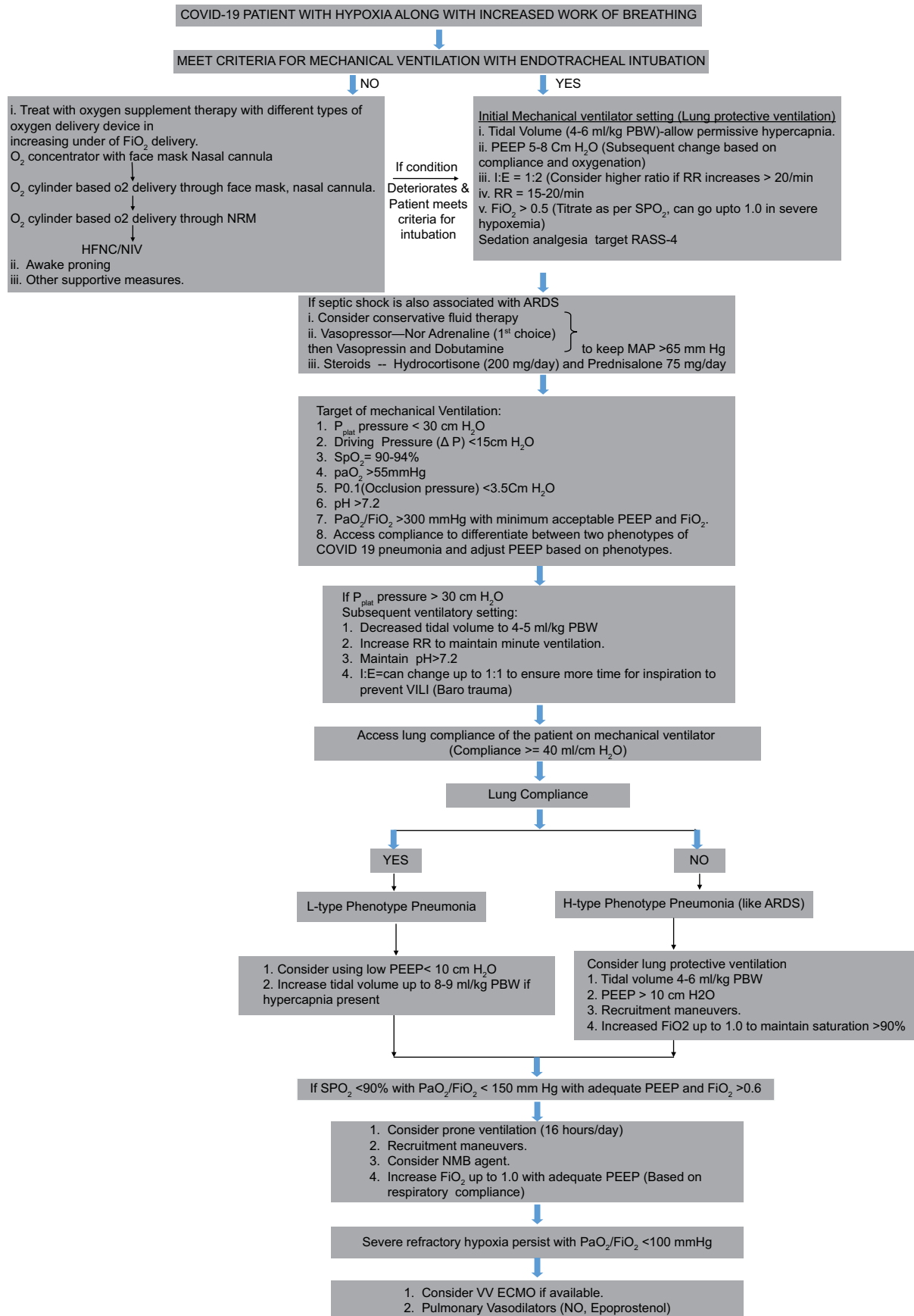
- Haloperidol being a potent dopamine receptor blocker with insignificant anticholinergic and antihistaminic activity (2.5--5 mg) can be used orally or intramuscularly. Intravenous administration should be accompanied by ECG monitoring. Recent research has also shown that haloperidol, due to its effects on sigma receptors, is investigated as a treatment for COVID-19.^[76,77]
- Olanzapine 5--10 mg can also be considered either orally or parenterally. In acutely disturbed patients, intramuscular (IM) is the preferred route of administration compared to intravenous (IV) route and gluteal IM injections may be preferred over deltoid injections to increase the distance between respiratory secretion/droplet. IM olanzapine has minimal effect on QTc interval and lesser risk for EPS compared to haloperidol.
- Quetiapine (25--50 mg) can be given orally.
- Dexmedetomidine is alpha-2 agonist and reduces the release of noradrenaline and helps curtailing restlessness. Clonidine can also be used for the same reason and is more convenient as its available in skin patches form.
- Valproic acid is known for its neuroprotective^[78] potential and can be used to control extreme emotional fluctuations. It also provides prophylaxis against the potentially epileptogenic state by

S NO	Initial ventilator setting	Remarks
1.	Tidal volume 6ml/kg (4-6ml/kg)	Tidal Volume setting should be based on predicted body weight and not on total body weight. Predicted body weight formula :- Male= 50+ 2.3[height in inches-60] Female= 45.5 + 2.3[height in inches-60]
2.	Respiratory rate <35/min, (start with initial setting of 15-20/min)	Adjust respiratory rate to maintain minute ventilation. However, permissive hypercapnia (PH >7.2) allowed to prevent VILI.
3.	I: E (Normal ratio of 1:2 may be changed up to 1:1)	Purpose of increasing ratio is to give more time for inspiration to prevent barotrauma.
4.	FIO2	Start with 0.5 and titrate it based on arterial saturation.
5.	PEEP (start with 5-8 cm H2O)	Adjusted PEEP based on Fio2 requirement and respiratory compliance of the patient

Figure 3: Ventilatory settings

increasing the seizure threshold. However, liver function tests and platelets need to be constantly monitored.

- In extreme cases not responding to the above measures, only short acting low dose oral benzodiazepines (e.g., lorazepam 1--2 mg) may be considered with close monitoring for respiratory distress and respiratory failure.
 - Mechanical restraint: Mechanical restraint should be used as a last resort for minimum possible time.
- Mechanical Ventilation
Weaning off mechanical ventilation at times can be associated with acute and severe anxiety that could result in delay in extubation. A very low dose of antipsychotic- Tab Olanzapine 2.5 mg is advisable for anxiolysis.
Drug treatment of patients with pre-existing psychiatric illness
Most psychiatric illnesses are remitting and relapsing in nature and generally require long-term prophylaxis. In the absence of a confirmed treatment for management of COVID-19, a multitude of pharmacotherapeutic agents have been tried in the recent past and can have significant drug interactions with psychotropics and can precipitate a relapse of the illness. Hence, it is imperative to be mindful of such interactions.
 - Antipsychotics
Haloperidol, quetiapine, ziprasidone, etc., can prolong QTc interval. Hence, chloroquine, hydroxychloroquine, azithromycin, etc., can have a synergistic effect and should be used with caution. Certain protease inhibitors like atazanavir, sequinavir, lopinavir/ritonavir can also cause QTc prolongation. The safer alternatives are lurasidone followed by aripiprazole, olanzapine, and risperidone.
 - Antidepressants



Flow Chart: flow chart of recommendations on initial ventilatory management of Covid – 19 patients

Citalopram, tricyclic antidepressants, and mirtazapine can prolong QTc interval, which might be augmented when combined with hydroxychloroquine, chloroquine. Escitalopram and sertraline are safer in view of lesser drug interactions and side effects.

III. Mood Stabilisers

Non-steroidal anti-inflammatory drugs (NSAIDs) increase lithium levels, which may lead to toxicity. Valproate levels may be reduced with lopinavir/ritonavir.

IV. Sedatives/hypnotics

Longer acting benzodiazepines like diazepam or clonazepam may be avoided. Lorazepam is preferred as it has the least interaction with antiviral drugs and shorter half-life.

Conclusion

COVID-19 ARDS is an anticipated severe complication of COVID-19 that requires prompt recognition and comprehensive multispeciality management [Flowchart 1]. Extensive research and studies are required to address the vital unanswered queries about treatment for COVID-19 ARDS. Because of the high mortality in mechanically ventilated patients of CARDS, the above recommendations and findings direct the potential for improvement in the management of patients with COVID-19 ARDS.

Ethical approval and consent to participate

Not applicable.

Consent for publication

The authors certify that they have obtained all appropriate permissions for publication.

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Conflicts of interest

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APPENDIX 1 : Status of COVID-19 Vaccines within WHO EUL/PQ evaluation process

	Manufacturer / WHO EUL holder	Name of Vaccine	NRA of Record	Platform	EOI accepted	Pre-submission meeting held	Dossier accepted for review*	Status of assessment**	Anticipated decision date***
1.		BNT162b2/COMIRNATY Tozinameran (INN)	EMA	Nucleoside modified mRNA	✓	✓	✓	Finalized	31/12/20
2.		AZD1222	EMA	Recombinant ChAdOx1 adenoviral vector encoding the Spike protein antigen of the SARS-CoV-2.	✓	✓	Accepted core data	Finalized	16 April 2021
Data for Covax sites expected in April 2021 onwards							Finalized: SK-Catalent Wuxi (DS) Chemo Spain	16 April 2021 30 April 2021 04 June 2021	
3.		AZD1222	MFDS KOREA	Recombinant ChAdOx1 adenoviral vector encoding the Spike protein antigen of the SARS-CoV-2.	✓	✓	✓	Finalized	15 Feb 2021
4.		Covishield (ChAdOx1_nCoV-19)	DCGI	Recombinant ChAdOx1 adenoviral vector encoding the Spike protein antigen of the SARS-CoV-2.	✓	✓	✓	Finalized	15 Feb 2021
5.		Ad26.COV.2.S	EMA	Recombinant, replication-incompetent adenovirus type 26 (Ad26) vectored vaccine encoding the (SARS-CoV-2) Spike (S) protein	✓	✓	Core data	Finalized (US +NL sites)	12 March 2021
Additional sites: - Aspen South Africa - Other sites							- Ongoing* - Awaited	- June 2021 - As submitted	
6.		mRNA-1273	EMA	mRNA-based vaccine encapsulated in lipid nanoparticle (LNP)	✓	✓	✓	Finalized	30 April 2021
7.		SARS-CoV-2 Vaccine (Vero Cell), Inactivated (InCoV)	NMPA	Inactivated, produced in Vero cells	✓	✓	✓	Finalized	07 May 2021

	Manufacturer / WHO EUL holder	Name of Vaccine	NRA of Record	Platform	EOI accepted	Pre-submission meeting held	Dossier accepted for review*	Status of assessment**	Anticipated decision date***
8.		SARS-CoV-2 Vaccine (Vero Cell), Inactivated	NMPA	Inactivated, produced in Vero cells	✓	✓	✓	Finalized	01 June 2021
9.		Sputnik V	Russian NRA	Human Adenovirus Vector-based Covid-19 vaccine	Additional information submitted	Several meetings held.	"Rolling" submission of clinical and CMC data has started.	Additional data (Non-CLIN, CLIN, CMC) Required. Inspections in April, May and June 2021	Will be set after all data is submitted and inspections completed.
10.		Ad5-nCoV	NMPA	Recombinant Novel Coronavirus Vaccine (Adenovirus Type 5 Vector)	✓	✓	Rolling data starting June 2021		
11.		NVX-CoV2373/Covovax	EMA	Recombinant nanoparticle prefusion spike protein formulated with Matrix-M™ adjuvant.	✓	✓			
12.		Inactivated SARS-CoV-2 Vaccine (Vero Cell)	NMPA	Inactivated, produced in Vero cells	EOI submitted on 30 April and more on 26 May 2021.	Planned for 14 June 2021			
13.		Zorecimeran (INN) concentrate and solvent for dispersion for injection; Company code: CVnCoV/CV07050101	EMA	mRNA-based vaccine encapsulated in lipid nanoparticle (LNP)	Submitted EOI on 12 April	Planned for 15 July 2021, based on company request			
14.	Bharat Biotech, India	COVAXIN	DCGI	SARS-CoV-2 Vaccine, Inactivated (Vero Cell)	Submitted EOI on 19/04/2021. More information required.	planned in June 2021			
15.	Vector State Research Centre of Virology and Biotechnology	EpiVacCorona	Russian NRA	Peptide antigen	Letter received not EOI. Reply sent on 15/01/2021				
16.	Zhifei Longcom, China	Recombinant Novel Coronavirus Vaccine (CHO Cell)	NMPA	Recombinant protein subunit	Response to 2 nd EOI sent 29 Jan 2021. Additional				

	Manufacturer / WHO EUL holder	Name of Vaccine	NRA of Record	Platform	EOI accepted	Pre-submission meeting held	Dossier accepted for review*	Status of assessment**	Anticipated decision date***
					information requested.				
17.	IMBCAMS, China	SARS-CoV-2 Vaccine, Inactivated (Vero Cell)	NMPA	Inactivated	Not accepted, still under initial development				
18.	Clover Biopharmaceuticals	SCB-2019	EMA	Novel recombinant SARS-CoV-2 Spike (S)-Trimer fusion protein	In discussion on submission strategy and timelines				
19.	BioCubaFarma - Cuba	Soberana 01, Soberana 02 Soberana Plus	CECMED	SARS-CoV-2 spike protein conjugated chemically to meningococcal B or tetanus toxoid or Aluminum	Awaiting information on strategy and timelines for submission.				

1. Beijing Bio-Institute of Biological Products Co Ltd
2. Wuhan Institute of Biological Products Co Ltd

* Dossier Submission dates: more than one date is possible because of the rolling submission approach. Dossier is accepted after screening of received submission.

**Status of assessment: 1. Under screening; 2. Under assessment; 3. Waiting responses from the applicant; 4. Risk-benefit decision 5. Final decision made

*** Anticipated decision date: this is only an estimate because it depends on when all the data is submitted under rolling submission and when all the responses to the assessors' questions are submitted.