Acta Anaesth. Bel., 2022, 73 (1): *5-14*

Review

Management of Acute Respiratory Distress Syndrome in COVID-19 Patients

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Abstract

Acute respiratory distress syndrome (ARDS) is a life-threatening condition characterized by an acute, diffuse inflammation leading to pulmonary edema and hypoxemia. The pathophysiology of the lung failure in COVID-19 ARDS is a combination of the viral infection and the immune response of the host. ARDS due to COVID-19 appears to be similar to the non-COVID-19 ARDS, with exception of hypercoagulability. The mortality due to ARDS remains high and the treatment focuses on supportive measures, such as lung-protective ventilation strategy with small tidal volumes, low driving pressures and PEEP-titration, early consideration of prone positioning and a restrictive fluid management. Oxygen should be titrated, and permissive hypercapnia might be necessary to achieve lung-protective ventilation. The use of extracorporeal membrane oxygenation (ECMO) in COVID-19 ARDS is restricted as a rescue therapy in patients who remain hypoxemic. ECMO should be reserved to experienced ECMO centers. Prophylactic anticoagulant therapy is indicated to reduce the formation of thrombi in the microcirculation of organs, especially in the pulmonary microvasculature. Steroids may reduce the host's immune response and improve mortality in patients requiring oxygen supplementation or invasive ventilation.

Keywords: **Acute Respiratory Distress Syndrome, COVID-19, Pulmonary Ventilation, Antiviral Agents, Dexamethasone.**

Definition of acute respiratory distress syndrome

Acute respiratory distress syndrome (ARDS) is a life-threatening condition, caused by acute and diffuse inflammation of the lung tissues.

ARDS is characterized by an acute onset (1 week or less) of hypoxemia with a PaO_2/FiO_2 ratio of less than 300 mmHg (partial pressure of arterial oxygen divided by the fraction of inspired oxygen) with a minimum of 5 cm H_2O positive end-expiratory pressure (PEEP) (490 Pa). Chest X-ray is characterized by bilateral infiltrates, consistent with pulmonary edema that cannot be explained by cardiac failure or fluid overload[1]. Injury to the alveoli increases the endothelial permeability, often resulting in pulmonary edema and impairment of the alveolar-to-arterial gas exchange (Figure 1). This leads to secondary pulmonary shunting and hypoxemia. The initial exudative phase is often followed by a proliferation of fibroblasts, and eventually, lung fibrosis.

Etiologies of ARDS include direct and indirect lung injuries, such as pneumonia, aspiration, contusion, inhalation injuries, sepsis, pancreatitis, trauma and transfusion. More recently, the viral pneumonia in COVID-19 has been associated with severe ARDS, with mortality rate between 25-55%[2]. Non-COVID-19 ARDS has a reported mortality rate of approximately 40%[3]. Treatment focuses on supportive management as there are no specific treatments of documented outcome benefit. ARDS management remains challenging because it is often associated with multiple organ failure, such as acute kidney injury and cor pulmonale (seen in 25% of patients with ARDS)[4,5].

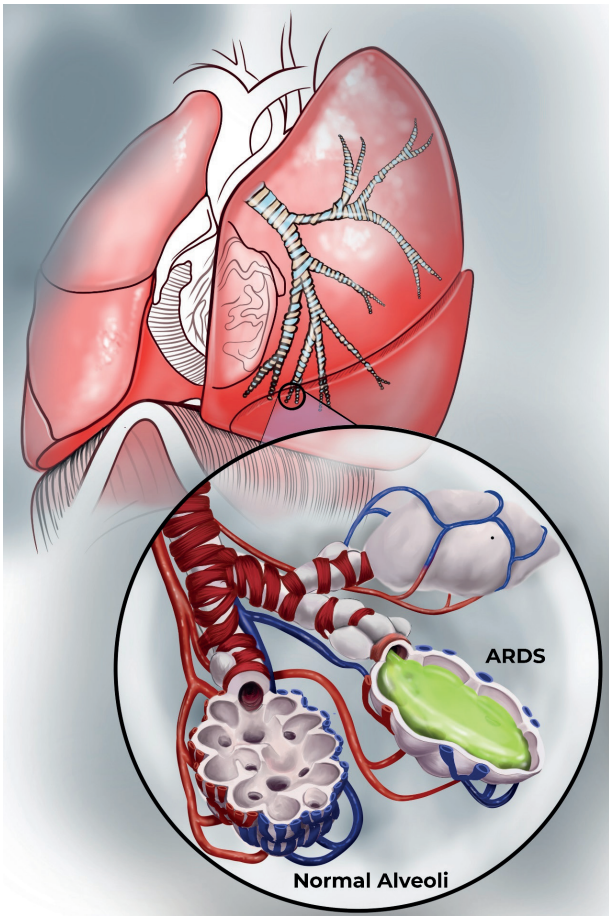

Fig. 1 — Graphic representation of normal lung alveoli versus lung alveoli affected by ARDS. Used with permission from www.NYSORA.com.

Specificities of ARDS associated with COVID-19

During the early experience with COVID-19 pandemic, clinicians recognized that ARDS in COVID-19 patients causes severe hypoxemia often accompanied by a near normal respiratory compliance. This led to the classification of distinction of low versus high elastance subtypes[6,7]. 'Subtype L' with low lung elastance is present in most patients in the early stage, which could deteriorate in some patients to a phenotype 'type H' with high elastance (low compliance). This distinction in subtypes could result in different ventilatory management strategies of ARDS[8]. However, non-COVID-19 ARDS is also characterized by a high heterogeneity[9], and more research showed similarities in the pathophysiological features of COVID-19 and non-COVID-19 ARDS[10]. The mortality rate of COVID-19 ARDS appears to be similar to the mortality due to severe non-COVID-19-related ARDS (around 40%), although the figures substantially vary among different countries and institutions[2,11].

With our increasing experience and understanding of COVID-19 during the pandemic, clinical evidence could not support a substantially different treatment strategy in COVID-19 ARDS versus non-COVID-19 ARDS. The ventilatory management in COVID-19 ARDS is focused on correct timing of intubation and mechanical ventilation, a lung-protective ventilation strategy, permissive hypercapnia, and PEEP titration[12].

Despite similarity in pathophysiological processes, critically ill COVID-19 patients are uniquely prone to developing hypercoagulability. Microvascular thrombosis within the lung vasculature additionally leads to ventilation-perfusion mismatch and right ventricular stress (Figure 2)[13]. This is not observed in non-COVID-19-associated ARDS. The dysregulated inflammation and the direct injury to endothelial cells by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) contribute to the formation of immunopathological microthrombi by activating

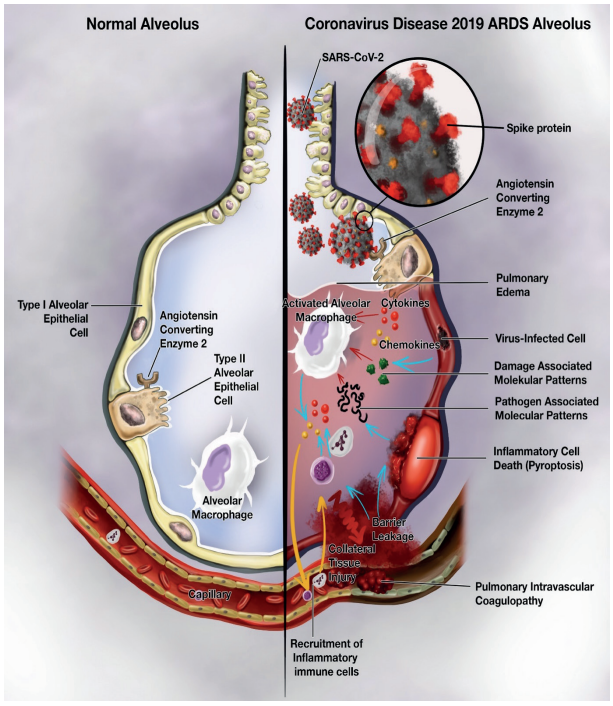

Fig. 2 — Pathophysiology of ARDS in COVID-19 patients. Spike proteins from the SARS-CoV-2 bind to angiotensin-converting enzyme-2 on type 2 alveolar epithelial cells. This viral infection causes cells to release chemokines and cytokines. Furthermore, epithelial cells might die via pyroptosis from the infection, resulting in the release of inflammatory damage- and pathogen-associated molecular patterns. Recognition of these molecular patterns and cytokines activates alveolar macrophages, while chemokines recruit inflammatory immune cells to the affected lung. The resultant release of antimicrobial effectors (i.e., metallomatrix proteases, elastases, and reactive oxygen species) induce collateral tissue injury, leading to loss of epithelial and endothelial barrier integrity, and infiltration of proteinaceous fluid into the alveolar airspace. Moreover, endothelial cells play a role in initiating inflammation and the development of pulmonary intravascular coagulopathy, commonly observed in COVID-19 patients. Components of the figure were modified from Williams et al., Acute respiratory distress syndrome: contemporary management and novel approaches during COVID-19, Anesthesiology 2021.5 Used with permission from www.NYSORA.com.

the coagulation cascade and circulating platelets. The endothelial cell damage further impairs hypoxic pulmonary vasoconstriction, which occurs in response to hypoxia and restricts blood flow to poorly ventilated lung areas. Disruption in this physiologic adaptation in COVID-19 patients results in a sustained supply of blood to the injured parts of the lungs, which leads to shunting of oxygen-poor blood.

Clinical Treatment Concepts

The role of non-invasive ventilation and high-flow nasal cannula (HFNC) in the treatment of COVID-19 related ARDS

Like in non-COVID-19 ARDS, the primary problem in COVID-19 ARDS is hypoxemic respiratory failure. With both, a non-invasive approach is preferred as an initial treatment strategy[14]. While bilevel positive airway pressure (BIPAP) i.e. non-invasive positive pressure ventilation (NIPPV) may be effective in patients with hypoxemic respiratory failure due to cardiogenic pulmonary edema, this approach has a high failure rate in respiratory failure of other etiologies[15]. In COVID-19 ARDS, there is growing evidence that BIPAP may lead to patient self-induced lung injury (P-SILI) by overinflation of the lung parenchyma[16,17]. The use of high-flow nasal cannula (HFNC) on the other hand decreases the need for intubation 18 and has other advantages[19]. Avoiding the use of sedatives allows more effective expectoration of secretions, oral nutrition, and self-pronation, for improvement in oxygenation. Initial concerns for a high viral transmission to health care personnel with HFNC have proven unnecessary[20,21]. However, if oxygen administration and non-invasive support are not sufficient, vigorous inspiratory effort may worsen tissue damage and can cause patient self-induced lung injury (P-SILI)[16,17]. The possible downside of using HFNC may therefore be the risk of postponing intubation, and higher mortality[15,22,23]. The ROX index ($[SpO_2/FiO_2]$/ breathing frequency) is proven successful in the identification of patients at risk for HFNC failure and progression to intubation[24,25]. An alternative to the delivery of oxygen with HFNC is a helmet non-invasive ventilation. The administration of continuous positive airway pressure (CPAP) leads to less atelectatic regions and a more homogenous distention of lung parenchyma. The HENIVOT trial comparing HFNC and helmet non-invasive ventilation showed no significant difference for the days free of respiratory support within 28 days[26].

Mechanical ventilation strategies in COVID-19 related ARDS

The goal of invasive ventilation in ARDS patients with COVID-19 infection is to improve both oxygenation and ventilation. Ideally, this would be achieved while minimizing the risk of ventilator induced lung injury (VILI). ARDS causes atelectasis, interfering with effective oxygenation and ventilation. The 'open lung concept' is a theoretical solution that relies on recruitment maneuvers to keep the lung open with PEEP while using low tidal volumes (Vt) to avoid barotrauma[27]. A common recommendation is ventilation with 6 mL/ kg-1 of the predicted body weight with a maximum plateau pressure (Pplat) of 30 cmH2O and a driving pressure of <15 cmH_2O (figure 3)[28,29]. Ventilation exceeding these thresholds may increase the risk of mortality[30,31]. The respiratory rate is adjusted for an acceptable partial pressure of $PaCO_2$. Permissive hypercapnia might be necessary to achieve lung-protective ventilation and reduction of the risk of lung injury[32]. Maintaining the pH >7.25 with a $PaCO_2$ of 60 mmHg is considered to be acceptable in patients with COVID-19 ARDS[33,34]. Failure to achieve these goals requires rescue strategies, such as prone ventilation, or extracorporeal mechanical oxygenation.

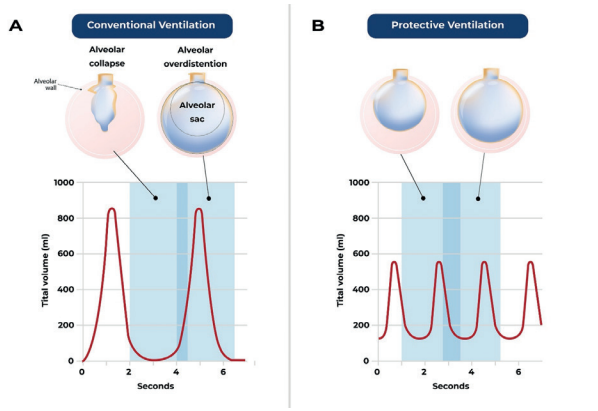

Fig. 3 — Conventional ventilation (A) versus protective ventilation using small tidal volumes (B). Conventional ventilation leads to alveolar overdistension (at peak inflation) and collapse (at the end of exhalation). Protective ventilation administers small tidal volumes and ensures an adequate positive end-expiratory pressure, thereby limiting overinflation and end-expiratory collapse. Modified from Malhotra A., Low-tidal-volume ventilation in the acute respiratory distress syndrome, N Engl J Med 2007.89 Used with permission from www.NYSORA.com.

The role of PEEP in the management of ARDS

PEEP reduces atelectasis trauma (repetitive opening and closing of alveoli) by recruiting collapsed alveoli and therefore reduces ventilation perfusion mismatch (Figure 4). Higher PEEP values improve survival among the subgroup of patients with ARDS

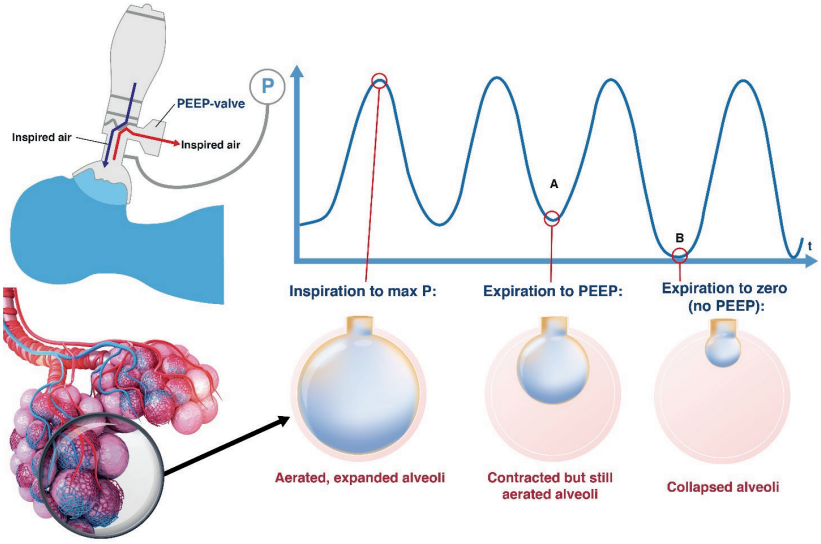

Fig. 4 — Optimal PEEP (A) versus no PEEP (B). Using an optimal PEEP allows the alveoli to remain open during expiration, which facilitates oxygen diffusion and reduces the required amount of pressure to expand the lung upon inhalation. Modified from MedicTests, Positive end-expiratory pressure. Used with permission from www.NYSORA.com.

who show improved oxygenation in response to increased PEEP[35]. The ARDSNet has developed pragmatic tables to optimize the FiO_2 and PEEP based on oxygenation[36]. However, not all patients respond well to PEEP. A personalized PEEP is achieved by finding the PEEP value at which the lung has the best compliance (tidal volume divided by the driving pressure). In practice, an incremental PEEP trial can be used, while checking for the highest compliance. The downside of recruitment maneuvers are overdistention of the healthy alveoli and the risk of damage[37,38]. The maneuver must be carried out with caution and not too often (twice a day)[39]. Although the use of high PEEP increases the arterial oxygen tension, it can paradoxically decrease the tissue oxygen delivery by reducing the cardiac output[40]. Other parameters such as central venous pressure, mean arterial pressure and cardiac output with oxygen delivery (DO_2) can be measured to devise a personalized optimal PEEP.

The role of prone positioning on the outcome

The prone ventilation ("proning") more evenly distributes the dorsal lung space's gravitational force, and decreases alveolar distention 41 (Figure 5), as opposed to the supine position, where the collapse of the dependent lung areas and distention of non-dependent regions is more likely to occur. Importantly, proning decreases alveolar collapse and overdistention with less mediastinal pressure on the lungs, improving the homogenization of alveolar ventilation[42–44].

In ARDS, the distribution of perfusion is less dependent on gravity. This effect is probably due to a degree of hypoxic pulmonary vasoconstriction in the dependent/atelectatic regions and extrinsic vessel compression[45]. Proning improves ventilation in dorsal segments which leads to a reduction in ventilation perfusion mismatch. This in turn allows for reduction in the driving pressure, respiratory rate and/or PEEP, all consistent with lung-protective ventilation[46]. Langer et al. applied proning in 61% of the COVID-19 patients with ARDS, resulting in improvement of the PaO_2/FiO_2 ratio in the majority of patients (≥20 mmHg)[47]. In the PROSEVA trial, proning was helpful in patients with severe ARDS (PaO2:FiO2 ratio of <150 mmHg with an FiO_2 of at least 0.6 and a PEEP of ≥5 cmH2O)[44]. Based on the available data and current clinical experience, proning should be used early in the course of ARDS and applied for 12-16 hours at a time[46].

The role of conservative oxygenation in ARDS patients

The ARDS Clinical Trials Network recommends that the target partial pressure of arterial oxygen (PaO_2) in ARDS is 55 to 80mmHg[36]. Too liberal administration of oxygen can result in hyperoxia associated with peripheral vasoconstriction, decreased cardiac output, absorption atelectasis and increased inflammatory response. In the $LOCO_2$ trial, Barrot et al. hypothesized that targeting the lower limit of this range would improve outcomes in patients with ARDS[48]. However, the trial was terminated early due to increased 28-day mortality and mesenteric ischemia episodes in the conservative oxygen group (target PaO_2: 55-70 mmHg; target oxygen

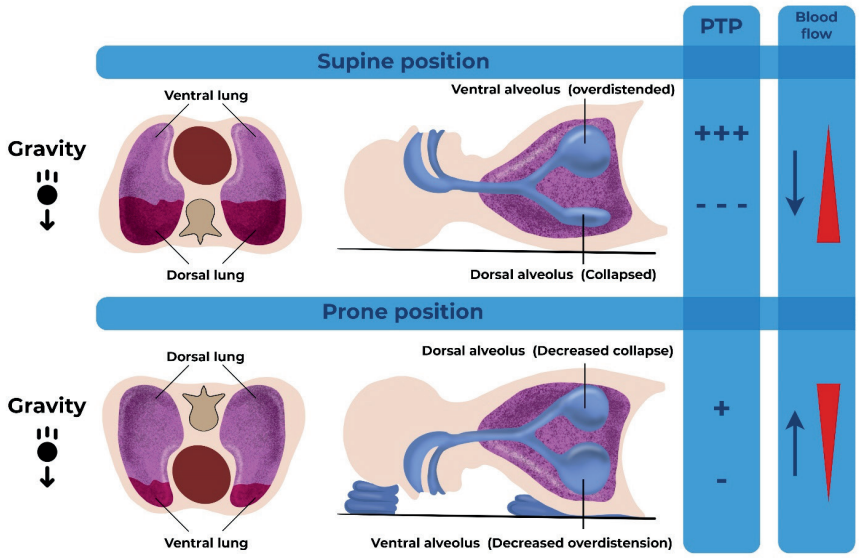

Fig. 5 — Supine versus prone positioning during mechanical ventilation. In the supine position, the ventral transpulmonary pressure (PTP) exceeds the dorsal PTP, resulting in greater expansion of the ventral alveoli than the dorsal alveoli. ARDS exaggerates this effect. The ventral alveoli become overdistended and dorsal alveoli atelectatic (dark purple). Prone positioning reduces the difference between the dorsal and ventral PTP, making ventilation more homogeneous. This ultimately decreases the alveolar collapse and overdistension. Modified from Malhotra A. et al., Prone ventilation for adult patients with acute respiratory distress syndrome, UpToDate 2020.43 Used with permission from www.NYSORA.com.

saturation (SpO_2): 88-92%) compared to the liberal oxygen group (target PaO_2: 90-105 mmHg; target SpO_2: ≥96%). Most recent evidence suggests that a target PaO2 of 60-90mmHg may be the optimal compromise[49].

Fluid balance in ARDS

Management of the fluid balance in ARDS can be challenging. A too liberal fluid administration may worsen pulmonary edema, hypoxemia and prolong mechanical ventilation, ICU stay, hospitalization, and increase the risk of mortality[50]. In FACTT trial, a restrictive fluid management improved lung function and shortened duration of mechanical ventilation, although a survival benefit remains unanswered[51]. However, a too restrictive fluid management can jeopardize extrapulmonary-organ perfusion. As an example, a follow-up study of the cognitive function in survivors of the FACTT trial demonstrated an association of a low central venous pressure with cognitive impairment[52]. In summary, fluid management in ARDS with COVID-19 is challenging, and it requires synthesis of several clinical, laboratory, and radiographic parameters for clinical decision making.

Extracorporeal membrane oxygenation in COVID-19 ARDS patients

Extracorporeal membrane oxygenation (ECMO) is used as rescue therapy in ARDS patients who fail to improve on mechanical ventilation management. The 2009 Conventional Ventilatory Support versus Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure (CESAR) trial group reported a significant survival benefit in adult patients with severe but potentially reversible respiratory failure who met certain criteria (Murray score or pH)[53]. For this benefit to realize, the group recommended transferring these patients to centers experienced with ECMO. In contrast, the 2018 ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) trial demonstrated no statistically significant differences in mortality between the ECMO group and the control group[54]. However, 28% of patients in the control group crossed over to the ECMO group as a rescue therapy, which reduced the mortality in the ECMO group by 11%. These results established an advantage for the early use of ECMO compared to conventional care with late rescue ECMO in ARDS. Survival decreases with prolonged exposure to mechanical ventilation (MV) before ECMO, especially after seven days of MV[55,56]. In patients with COVID-19, high mortality in the initial published experience with ECMO led some clinicians and investigators to recommend withholding ECMO support in the management of COVID-19 ARDS. More recent data from highly experienced ECMO centers however show a similar survival rate in ECMO for COVID-19 ARDS compared with ECMO for non-COVID-19 ARDS[57]. Therefore, ECMO is

best restricted as a rescue therapy in COVID-19 patients with respiratory failure unresponsive to optimized conventional care[58]. ECMO is typically initiated for a COVID-19 patient when duration of mechanical ventilation has been less than seven to ten days, although there are no data to support a clear cutoff[59,60]. The additional impact of prolonged exposure to high-flow nasal cannula or non-invasive positive-pressure ventilation before mechanical ventilation is currently unknown.

Analgesia, sedation, and the use of muscle relaxants

Recent guidelines recommend the use of light sedation in ventilated patients[61]. Oversedation leads to a loss of muscle mass of the diaphragm and accessory respiratory muscles, with associated risk of weaning difficulties and respiratory infections. In patients with severe COVID-19 related ARDS (PaO_2/FiO_2 ratio $\leq$ 150 mmHg) however, lung protective ventilation is the most important goal, which may not be achieved by using ASB (assisted spontaneous breathing)[62].For these patients a deeper level of sedation is often required to reduce the patient's breathing efforts and facilitate mechanical ventilation. The pharmacologic approach to this goal has not been standardized and can be accomplished with a combination of agents, such as midazolam, ketamine, dexmedetomidine, propofol, remifentanil, piritramide (Figure 6). Care should be taken when using a propofol infusion because of the risk of hypertriglyceridemia[63]. If lung-protective ventilation cannot be achieved, the use of a continuous infusion with a neuromuscular blocking agent (NMBA) can be necessary. For COVID-19 patients, cisatracurium is often the muscle relaxant of choice (NMBA), because its elimination is independent of renal- and hepatic function, and it has a possible intrinsic anti-inflammatory effect[64]. Early administration of a NMBA in patients with severe ARDS improved survival in the ACURASYS trial[65], however, this effect was not proven in the ROSE trial[66]. The most recent guidelines do not support the early routine use of a NMBA infusion but state that an infusion for up to 48h is a reasonable option to facilitate lung protective ventilation[67,68].

The role of antiviral therapy in COVID-19 patients

Antiviral therapies target specific viral components necessary for SARS-CoV-2 replication and pathogenicity.

Remdesivir, an inhibitor of viral RNA-dependent RNA polymerase, is currently the most investigated antiviral drug. The Adaptive COVID-19 Treatment Trial (ACTT-1) by Beigel et al. demonstrated a statistically significant reduction in recovery time in hospitalized COVID-19 patients receiving remdesivir but not in the critically ill.69 There was no significant reduction in mortality. At the time of the writing of the current review article, the WHO guidelines on COVID-19 treatment do not recommend the use of remdesivir in COVID-19 patients.

Recently, three anti-SARS-CoV-2 monoclonal antibody products have received urgent FDA clearance for the treatment of mild to moderate COVID-19 in nonhospitalized patients at high risk for progressing to severe disease or hospitalization.70 The products are Casirivimab plus Imdevimab, Bamlanivimab plus Etesevimab and Sotrovimab. The distribution of Bamlanivimab plus Etesevimab is currently paused because of

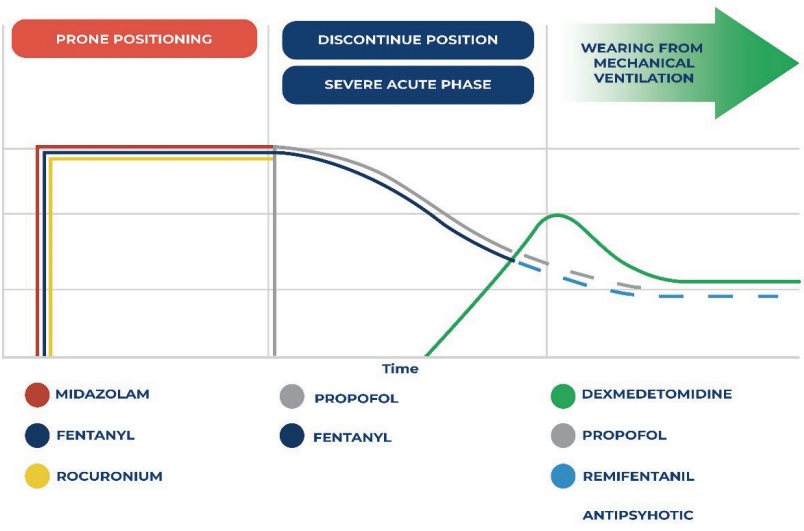

Fig. 6 — Management of analgesia, sedation, and the use of muscle relaxants.
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a reduced susceptibility to the Gamma and Beta COVID variants of concern. Risk factors for disease progression include age ≥ 65 years, obesity, diabetes, and chronic lung disease.

Tocilizumab is a monoclonal antibody against the interleukin-6 (IL-6) receptor, blocking IL-6 signalling and reducing inflammation. The RECOVERY trial 71 and the REMAP-CAP trial[72], the two largest randomized controlled tocilizumab trials, have both reported a mortality benefit of tocilizumab in patients recently hospitalized (i.e. 3 days or less) with rapid respiratory decompensation requiring high-flow oxygen, non-invasive ventilation or invasive ventilation and have increased markers of inflammation. Based on these trials, the NIH (National Institutes of Health) recommends the use of Tocilizumab in addition to dexamethasone in these patients[73].

Several other antiviral treatments for COVID-19 patients that have been tested include hydroxychloroquine[74,75], an antimalarial drug, and lopinavir-ritonavir[76], a protease inhibitor cocktail used in treating the human immunodeficiency virus. Both showed efficiency in vitro but not in patients.

The use of anticoagulants and thrombolytics in COVID-19-associated ARDS

Thrombotic coagulopathy is uniquely common in COVID-19 patients. Several studies reported a higher prevalence of thrombotic complications in COVID-19 ARDS in comparison with non-COVID-19 ARDS. Anticoagulants, such as heparin and low molecular weight heparin (LMWH), can reduce thrombi in the microcirculation, especially in the pulmonary vasculature. Studies have shown a reduced mortality with the use of anticoagulation therapy in patients with COVID-19 related ARDS[77,78]. These studies led to the recommendation of thrombosis prophylaxis in all patients with COVID-19 admitted to the ICU[79,80]. However, the appropriate dose of anticoagulants is yet to be determined[81]. Recent data published in the New England Journal of Medicine suggest a positive effect of therapeutic-dose anticoagulation with heparin in noncritically ill patients with COVID-19 admitted to the hospital. The positive effect was seen on survival to hospital discharge with reduced use of cardiovascular or respiratory organ support[82]. In critically ill patients, however, the use of therapeutic-dose anticoagulation with heparin did not show positive effects in comparison with usual-care pharmacologic thromboprophylaxis[83]. The therapeutic use of direct oral anticoagulants should also be avoided in the absence of evidence-based indications, as it does not improve clinical outcomes and increases the risk of hemorrhagic complications[84].

Treatment with thrombolytics has also been proposed in COVID-19-associated ARDS. Case series of COVID-19 ARDS patients showed some level of improvement in oxygenation and/or hemodynamics after treatment with tissue plasminogen activator in all patients, but ultimately most patients deceased[85,86].

The role of dexamethasone in COVID-19 ARDS

ARDS in COVID-19 patients is characterized by diffuse lung damage, caused by a combination of the viral infection and the host's immune response, leading to organ failure. As corticosteroids suppress the host immune system, it was empirically used to decrease organ damage[87]. Recent data from the United Kingdom Randomized Evaluation of COVid-19 thERapY (RECOVERY) trial in hospitalized COVID-19 patients showed that the administration of dexamethasone does improve mortality[88]. Mechanically ventilated patients randomized to receive 6 mg daily for up to 10 days (with a median treatment duration of 7 days) had a reduction in 28-day mortality by one-third compared to patients undergoing standard care. Interestingly, this mortality benefit was only observed in patients requiring oxygen or invasive mechanical ventilation, but not in patients receiving no respiratory support. In response to these findings, current COVID-19 treatment guidelines from the National Institutes of Health recommend dexamethasone's use in mechanically ventilated patients or patients requiring oxygen supplementation.

Other investigational therapeutic approaches

Trials investigating β2-adrenergics, ketoconazole, lisofylline, vitamin C and D, omega fatty acids, and statins did not show decreased mortality in ARDS patients. However, recent advancements in understanding ARDS pathophysiology indicate the importance of injury subtypes that may help to predict beneficial responses to particular therapies. Appropriate identification and selection of patients with specific ARDS sub-phenotypes may lead to more efficient clinical trials and targeted treatments.

Funding: *No funding, grants or other support was received for this work.*
Conflicts of interest: *The authors have no conflicts of interest to declare that are relevant to the content of this article.*

Ethics approval: *This is a narrative review. No ethical approval is required.*

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doi.org/10.56126/73.1.02