Acute Respiratory Distress Syndrome

Contemporary Management and Novel Approaches during COVID-19

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Acute respiratory distress syndrome (ARDS) is defined as hypoxemia secondary to a rapid onset of noncardiogenic pulmonary edema.[1] Etiologic risk factors for ARDS encompass both direct and indirect lung injuries including but not limited to pneumonia, sepsis, noncardiogenic shock, aspiration, trauma, contusion, transfusion, and inhalation injuries. Although clinical recognition and management of ARDS have improved significantly over the past 25 yr, it is still a leading cause of death in critically ill patients, with mortality rates consistently reported around 30 to 40%.[2] An important factor in the high mortality rate in ARDS is that treatment is mainly focused on clinical management and no targeted therapies currently exist. Furthermore, ARDS management is often challenging as it commonly occurs in a clinical setting of multiple organ failure and can also lead to the development of nonpulmonary organ injury, such as acute kidney injury.[3] Recently, the pandemic caused by coronavirus disease 2019 (COVID-19), which results from infection by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has led to a dramatic incidence in COVID-19–related ARDS. Thirty to forty percent of COVID-19 hospitalized patients develop ARDS, and it is associated with 70% of fatal cases.[4,5] At the time of this writing (July 31, 2020), there are more than 4.5 million COVID-19 cases and 152,000 related deaths in the United States.[6] Here, we describe select management strategies that have become foundations of ARDS clinical management and provide an update of emerging approaches for the treatment of ARDS related to COVID-19.

Clinical Treatment Concepts

Nationally Organized Research Consortia to Study ARDS

To improve outcomes and develop treatment protocols for ARDS, the National Heart, Lung, and Blood Institute of the National Institutes of Health (Bethesda, Maryland) funded a series of multicenter clinical trials, which formed a research collaboration called the ARDS Network (http://ardsnet.org, accessed July 22, 2020).[7] Beginning in 1994, the network studies enrolled more than 5,500 patients, included 10 clinical trials and one observational study, led to the development of new clinical parameters such as ventilator-free days,[8] and resulted in seminal advances that have helped to shape current ARDS management. National Heart, Lung, and Blood Institute–funded clinical trials continue currently under the Prevention and Early Treatment of Acute Lung Injury (PETAL) Network (http://petalnet.org, accessed July 22, 2020). Figure 1 and table 1 briefly summarize the results and implications of the results for ARDS and PETAL Network trials, along with other important trials performed internationally.

Small Tidal Volumes

Among the best-established guidelines in managing ARDS patients is the use of small tidal volumes during mechanical ventilation (fig. 1). In 2000, investigators from the ARDSNet Lower Tidal Volume (ARMA) trial reported significantly decreased rates of mortality (31.0% *vs.* 39.8%) in ARDS patients ventilated with 6 ml/kg of predicted body weight tidal volumes *versus* those with 12 ml/kg of predicted body weight.[9] While small tidal volume ventilation remains a tenet of lung-protective ventilation during ARDS, recent efforts have sought to determine whether small tidal volumes play a lung-protective role more broadly in all critically ill ventilated patients. In 2018, the Protective Ventilation in Patients Without ARDS (PReVENT) trial indicated that ventilation with low tidal volumes may not be more effective than intermediate volumes in non-ARDS intensive care unit patients.[10]

Positive End-expiratory Pressure

In their seminal 1967 report of ARDS cases, Ashbaugh *et al.* reported that improvement of hypoxemia and atelectasis was achieved by the implementation of positive end-expiratory pressure (PEEP).[11] Since then, PEEP continues to be employed in ARDS management and remains the focus of many clinical research efforts. Conceptually, PEEP is administered in order to reduce atelectrauma (repetitive opening and closing of alveoli) by recruiting collapsed alveoli.[12] Much attention has been directed at

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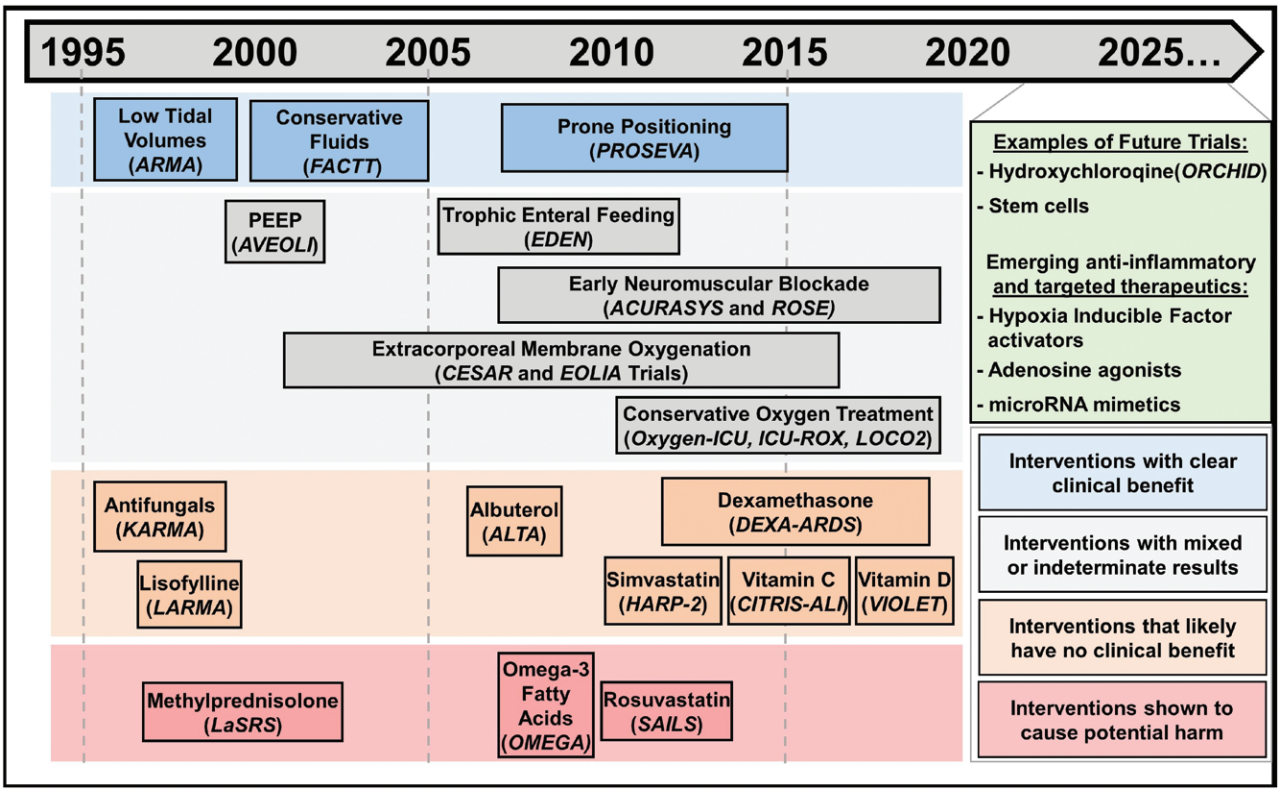

Fig. 1. A summary of 25 yr of acute respiratory distress syndrome (ARDS) intervention trials. Interventions are chronologically displayed with corresponding clinical trials italicized underneath and color-coded to denote clinical efficacy. Interventions that have clear clinical efficacy, in *blue boxes*, include the use of small tidal volumes,[9] prone positioning,[20] and restrictive fluid administration,[37] which have demonstrated clear mortality or ventilator-free days benefits. Interventions in *gray boxes* include those that have mixed results from different trials, as is the case for conservative oxygen treatment[32,33,75] and early neuromuscular blockade.[38,39] This category (*gray boxes*) also includes interventions with indeterminate results, such as the case for positive end-expiratory pressure (PEEP)[15]—itself is a component of lung-protective ventilation, but the appropriate amount to use is still contended—or those that have value in ARDS patients aside from improving ARDS outcomes, such as early trophic enteral nutrition to prevent gastric intolerance[40] and extracorporeal membrane oxygenation as a rescue therapy.[35,36] In *orange boxes* are interventions that failed to demonstrate improvements in ARDS outcomes, such as antifungals, lisofylline, albuterol, simvastatin, vitamin C, and vitamin D.[41–47,76,77] Dexamethasone is also listed in this category given that the DEXA-ARDS trial was conducted in an unblinded fashion[28] and previous randomized trials showed no clinical efficacy for steroid administration in ARDS. Methylprednisolone,[27] rosuvastatin,[49] and omega-3 fatty acids,[48] listed in *red boxes*, have been shown to cause potential harm in randomized controlled trials. Current, ongoing, or planned trials and emerging therapeutic targets are displayed in *green*.

the levels at which PEEP is applied, with clinical evidence yielding mixed results (fig. 1). Several trials that report protective benefits from higher *versus* lower targets of PEEP employed higher tidal volumes in their control (lower PEEP) groups, which perhaps introduced bias in their conclusions.[13,14] Trials that have controlled for low tidal volumes (6 ml/kg), including the 2004 ARDS Network Higher vs Lower PEEP (ALVEOLI) trial, have failed to establish a survival benefit for higher PEEP.[15,16] Subgroup analysis does, however, suggest that higher PEEP is associated with improved survival among the subgroup of patients with ARDS who objectively respond to increased PEEP (patients who show improved oxygenation in response to increased PEEP).[17] Still, it has yet to be demonstrated whether survival in selected patients improves with increased PEEP in large randomized trials.

Prone Positioning

Beneficial effects of prone positioning during mechanical ventilation of ARDS patients are considered in order to establish a more even distribution of gravitational force in pleural pressure, allowing for improved ventilation of the dorsal lung space[18] and limiting overdistention of alveoli.[19] In 2013, Guérin *et al.* reported the results of the Proning Severe ARDS Patients (PROSEVA) trial in which severe ARDS patients (Pao_2/fractional inspired oxygen tension [Fio_2] less than 150 on Fio_2 of at least 0.6) were randomized to prone positioning for a minimum of 16 h/day.

Table 1. Summarized Results of Select Large-scale Intervention Trials Aimed at Improving Outcomes in Patients with Acute Respiratory Distress Syndrome

Clinical Intervention	Trial Name	Study Groups	Outcomes
Small tidal volumes	The 2000 Acute Respiratory Distress Syndrome Network trial (ARMA)[9]	Low tidal volume (6 ml/kg of predicted body weight) or Traditional tidal volume (12 ml/kg of predicted body weight)	Reduction in 180-day mortality 31.0% *vs.* 39.8% ($P = 0.007$)
PEEP	Higher *vs.* Lower PEEP (ALVEOLI)[15]	Low PEEP or High PEEP (inspiratory plateau pressure of 28–30)	No change in death before discharge 24.9% *vs.* 27.5% ($P = 0.48$)
Prone positioning	Proning Severe ARDS Patients (PROSEVA) trial[20]	Supine position or Prone position (at least 16 h/day)	Reduction in 28-day mortality 16.0% *vs.* 32.8% ($P < 0.001$)
Steroids	Late Steroid Rescue Study (LaSRS)[27]	In patients 7–28 days after onset of ARDS: Placebo or Methylprednisolone	No change in 60-day mortality 28.6% *vs.* 29.2% and Increased mortality in patients receiving methylprednisolone at least 14 days after ARDS diagnosis
	Dexamethasone Treatment for the Acute Respiratory Distress Syndrome (DEXA-ARDS)[28]	Standard of care or Dexamethasone	Increase in ventilator-free days 12.3 *vs.* 7.5 days ($P < 0.0001$) and Reduction in all-cause mortality at day 60 21% *vs.* 36%
Conservative oxygenation	Normal Oxygenation Versus Hyperoxia in the Intensive Care Unit (ICU) (OXYGEN-ICU) trial[32]	Conventional oxygen: Pa_{O_2} up to 150 mmHg or Sa_{O_2} up to 97 to 100% or Conservative oxygen: Pa_{O_2} 70 to 100 mmHg or Sa_{O_2} of 94 to 98%	Reduction in ICU mortality 11.6% *vs.* 20.2% ($P = 0.01$)
	Intensive Care Unit Randomized Trial Comparing Two Approaches to Oxygen Therapy (ICU-ROX)[75]	Usual oxygen therapy: no upper limit to Fi_{O_2} or Sa_{O_2} or Conservative oxygen therapy: Sa_{O_2} between 90 and 97%	No change in ventilator-free days 21.3 *vs.* 22.1 days and No change in 180-day mortality 35.7% *vs.* 34.5%
	Liberal or Conservative Oxygen Therapy for ARDS (LOCO2)[33]	Liberal oxygenation: target Pa_{O_2} 90–105 mmHg; $Sa_{O_2} > 96\%$ or Conservative oxygenation: target Pa_{O_2} 55-70 mmHg; Sa_{O_2} 88–92%	Increased mortality in conservative oxygen group 34.3% *vs.* 26.5%
Extracorporeal membrane oxygenation	Conventional Ventilatory Support *vs.* ECMO for Severe Adult Respiratory Failure (CESAR)[35]	Conventional management or Extracorporeal membrane oxygenation	Increased survival without severe disability at 6 months 63% *vs.* 47%
	Rescue Lung Injury in Severe ARDS (EOLIA)[36]	Early extracorporeal membrane oxygenation or Conventional mechanical ventilation with extracorporeal membrane oxygenation as a rescue therapy	Non–statistically significant reduction in mortality 35% *vs.* 46% ($P = 0.09$)
Fluid restriction	Fluids and Catheters Treatment Trial (FACTT)[37]	Liberal fluids (CVP 10–14) or Conservative fluids (CVP < 4)	No change in all-cause mortality at 60 days 25.5% *vs.* 28.4% ($P = 0.30$)
Early neuromuscular blockade	ARDS et Curarisation Systematique (ACURASYS)[38]	Patients first sedated to a Ramsay sedation score of 6, then given: Placebo or Cisatracurium	Adjusted hazard ratio for death at 90 days of 0.68 in NM blockade group ($P = 0.04$)
	Reevaluation of Systemic Early Neuromuscular Blockade (ROSE)[39]	Usual care: lightly sedated or Early neuromuscular blockade: deep sedation and cisatracurium	No change in 90-day mortality 42.5% *vs.* 42.8%

(*Continued*)

Table 1. (Continued)

Clinical Intervention	Trial Name	Study Groups	Outcomes
Statin treatment	Simvastatin in the Acute Respiratory Distress Syndrome (HARP-2)[47]	Placebo or Simvastatin for maximum 28 days	No significant change in ventilator-free days 12.6 *vs.* 11.5 days or 28-day mortality 22% *vs.* 26.8%
	Statins for Acutely Injured Lungs from Sepsis (SAILS)[49]	Placebo or Rosuvastatin for maximum 28 days	No change in 60-day mortality 28.5% *vs.* 24.9% and Fewer days free of renal or hepatic failure
Vitamins, nutrition, and supplements	Early *vs.* Delayed Enteral Nutrition (EDEN)[40]	Trophic enteral feeding: 10–20 kcal/h or Full enteral feeding: 25–30 kcal/kg per day of nonprotein calories and 1.2 to 1.6 g/kg per day of protein	No change in ventilator-free days 14.9 *vs.* 15 days and No change in 60-day mortality 23.2% *vs.* 22.2%
	Omega Nutrition Supplement Trial (Omega)[48]	Enteral supplementation of omega-3 fatty acids, γ-linolenic acid, and antioxidants or An isocaloric control	Reduction in ventilator-free days 14.0 *vs.* 17.2 days and Non-statistically significant increase in mortality 26.6% *vs.* 16.3% ($P = 0.054$)
	Vitamin C Infusion for Treatment in Sepsis Induced Acute Lung Injury (CITRIS-ALI)[76]	Matched placebo (5% dextrose in water) or Vitamin C 50 mg/kg total body weight every 6 h for 96 h	No change in Sequential Organ Failure Assessment (SOFA) score 3 *vs.* 3.5
	Vitamin D to Improve Outcomes by Leveraging Early Treatment (VIOLET)[77]	Placebo or Vitamin D3	No difference in 90-day mortality 23.5% *vs.* 20.6% ($P = 0.26$)
β_2-Agonist	Albuterol for the Treatment of ALI (ALTA)[41]	Aerosolized albuterol (5 mg) or Placebo (aerosolized saline)	No difference in ventilator-free days 14.4 *vs.* 16.6 and No difference in mortality before hospital discharge 23% *vs.* 17.7%
Antifungals	Ketoconazole for ALI/ARDS (KARMA)[46]	Ketoconazole, 400 mg/day or Placebo	No difference in in-hospital mortality 34.1% *vs.* 35.2%
Lisofylline	Lisofylline for ALI/ARDS (LARMA)[45]	Lisofylline (3 mg/kg with a maximum dose of 300 mg) or Placebo	No difference in mortality 31.9% *vs.* 24.7% ($P = 0.215$)

ARDS, acute respiratory distress syndrome; CVP, central venous pressure; F_{IO_2}, fractional inspired oxygen tension; ICU, intensive care unit; PEEP, positive end-expiratory pressure; S_{aO_2}, arterial oxygen saturation.

Patients randomized to prone positioning had a 50% reduction in mortality (16% *vs.* 32.8%) at 28 days (fig. 1).[20] A recent meta-analysis corroborates these results and supports the survival benefits of prolonged prone positioning (greater than 12 h) in patients with severe ARDS.[21] Despite these encouraging results in reducing mortality with the use of prone positioning, data from a large, multinational prospective observational study indicate that the maneuver was employed in only 16.3% of severe ARDS patients.[2] Possible reasons for this low implementation could be attributed to the relative complexity and logistic considerations of prone positioning (*e.g.*, multiple persons required for the maneuver, increased workloads, management of secretions, and nutrition) or to the inherent risks of the procedure such as endotracheal tube and vascular line displacement. Nonetheless, the use of prone positioning for more than 12 h/day remains a strong recommendation for patients with severe ARDS.[22]

Although the efficacy of prone positioning is almost exclusively suggested in patients with P_{aO_2}/F_{IO_2} ratios of 150 or less, trials that failed to show efficacy in mild and moderate ARDS are largely underpowered and failed to administer prone positioning for recommended lengths of time.[23] As such, randomized trials implementing early prone positioning in mild to moderate cases of ARDS are necessary to determine any survival benefits and to make recommendations for clinical implementation.

Steroids in Non–COVID-19 ARDS

In the report of ARDS patients by Ashbaugh *et al.* in 1967, it was suggested that corticosteroids appeared to have

clinical value in cases associated with fat emboli and viral pneumonia.[11] Randomized control trials conducted in the 1980s have since demonstrated that early administration of methylprednisolone did not result in improved ARDS survival.[24,25] However, in 1998 a prospective trial by Meduri *et al.* showed an improved outcome in ARDS patients treated with prolonged methylprednisolone.[26] The results of the study were subject to scrutiny due to the small sample size (n = 8) of the control group, significant crossover into the methylprednisolone group (all of whom died), and a relatively large mortality rate of 60%. Subsequently, in 2006 the ARDS Network addressed the role of corticosteroid administration late in ARDS with the Late Steroid Rescue Study (LaSRS) in which 180 patients were randomized to methylprednisolone administration 7 to 28 days after diagnosis of ARDS. Administration of methylprednisolone was not linked with significant reduction in mortality (fig. 1).[27] Furthermore, patients who started steroid treatment after 14 days of diagnosis experienced increased mortality.

Based on the postulate that, compared to other corticosteroids, dexamethasone has an improved potency, lengthened duration of action, and weak mineralocorticoid effect, Villar *et al.* performed a prospective trial randomizing ARDS patients to receive either dexamethasone or placebo.[28] Compared to patients in the control group, the dexamethasone treatment group showed a reduced time on mechanical ventilation and 60-day mortality; however, drug allocation and data analysis were performed in an unblinded fashion, potentially leading to bias. Furthermore, 250 patients were excluded for already receiving steroids before randomization, indicating that participating physicians already favored the use of corticosteroids, which might have influenced clinical decisions to modify mechanical ventilation duration. In summary, guidelines supporting routine glucocorticoid administration in ARDS based on rigorously performed randomized controlled trials are currently not supporting their use. However, as discussed later in this review in the section of "Steroids in COVID-19 ARDS", dexamethasone treatment has been the first therapy to show mortality improvement in mechanically ventilated COVID-19 patients.[29]

Conservative Oxygenation

Among the most common therapies implemented in critically ill patients and nearly all ARDS patients is the supplemental provision of oxygen. Oxygen is frequently delivered generously in order to increase Pao_2, and oftentimes patients become hyperoxic while attempting to reverse tissue hypoxia. However, evidence indicates that liberal oxygen use is associated with vasoconstriction, decreased cardiac output, absorption atelectasis, increased proinflammatory responses, and increased mortality.[30,31] As such, establishing a protocol of oxygen treatment that balances essential delivery to organs while preventing excessive harmful effects of hyperoxia has been an important subject of recent investigations (fig. 1). In a single-center randomized trial published in 2016, critically ill intensive care unit patients with a length of stay of 3 days or longer who were assigned to receive conservative oxygen therapy (Pao_2 between 70 and 100 mmHg) had lower mortality than those who received more conventional care (Pao_2 up to 150 mmHg).[32] A more recent study, the 2020 Liberal Oxygenation *versus* Conservative Oxygenation in Acute Respiratory Distress Syndrome ($LOCO_2$) trial, Barrot *et al.* recruited ARDS patients to conservative (oxygen saturation measured by pulse oximetry [Spo_2] between 88 and 92%) or liberal (Spo_2 greater than 96%) oxygen treatment arms. The trial was terminated early due to an associated increase in mortality at 28 days and five episodes of mesenteric ischemia in the conservative oxygen treatment group.[33] Worse outcomes in conservative oxygenation may be attributed to the deteriorated gas exchange in ARDS patients, making them more prone to hypoxemia in the conservative oxygen treatment arm. Going forward, trials will need to carefully assess how to determine target oxygenation levels (*e.g.*, Spo_2 and Pao_2 targets, measurements from mixed venous blood, different targets for different organ injuries) to better answer how oxygen concentrations are selected.

Extracorporeal Membrane Oxygenation

Extracorporeal membrane oxygenation is a rescue therapy that has been employed in ARDS patients who fail to improve on mechanical ventilation management and as a means to avoid potential injurious aspects of ventilator-associated lung injury. Advances in extracorporeal membrane oxygenation delivery have been associated with an increase in the number of centers and cases using it, particularly since the 2009 influenza A virus subtype (H1N1) influenza pandemic.[34] Investigators from the 2009 Conventional Ventilatory Support *versus* Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure (CESAR) trial group sought to answer whether the use of extracorporeal membrane oxygenation during severe ARDS would provide a survival benefit when compared to conventional support by mechanical ventilation (fig. 1).[35] The results of the trial indicated that there was a survival benefit in favor of patients being randomized to extracorporeal membrane oxygenation treatment, but this difference was not statistically significant. Furthermore, the study was impaired by the use of heterogeneous mechanical ventilation strategies in the control group (including the use of large tidal volumes). Additionally, a large percentage of patients in the extracorporeal membrane oxygenation group who were transferred to extracorporeal membrane oxygenation–capable hospitals never received extracorporeal membrane oxygenation, allowing for the potential confounding effects attributed to the fact that extracorporeal membrane oxygenation–capable hospitals may attain enhanced ARDS survival regardless of whether patients actually received extracorporeal membrane oxygenation. A

subsequent international multicenter study was conducted to specifically address weaknesses of previous trials implementing extracorporeal membrane oxygenation in early severe ARDS, the 2018 ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) trial.[36] Despite achieving a high quality of control for ventilation strategies in both groups and nearly universal implementation of extracorporeal membrane oxygenation in patients randomized to receive it, the results demonstrated that there was no significant difference in mortality between the extracorporeal membrane oxygenation group and the control group. Given the lack of strong evidence supporting the use of extracorporeal membrane oxygenation as a routine early treatment for ARDS, it is recommended that extracorporeal membrane oxygenation is reserved as rescue therapy in patients who remain hypoxemic despite conventional evidence-based approaches.

Other Investigated Therapeutic Approaches

A large number of pharmacologic approaches have been tested in large, randomized controlled trials in order to improve clinical outcomes in patients with ARDS. These trials have included approaches such as the use of β_2-adrenergics, ketoconazole, lisofylline, vitamin C and D, omega fatty acids, restrictive fluid administration, and statins (fig. 1 and table 1).[37–49] Although none of these trials have demonstrated a mortality benefit in ARDS patients, it should be highlighted that recent advancements in our understanding of ARDS pathophysiology indicate that there are likely important subtypes of injury that predict beneficial response to particular therapies.[50] Appropriate identification and selection of patients with specific subphenotypes of ARDS may allow for a targeted approach to effective treatments and more efficient clinical trials.

ARDS in COVID-19

ARDS in COVID-19 patients (fig. 2) presents with several unique characteristics that are not regularly described in non–COVID-19–associated ARDS. Among these characteristics is the significant development of microvascular thrombosis within the lung vasculature that contributes to ventilation-perfusion mismatch and right ventricular stress.[5,51,52] Although the cause for widespread activation of the coagulation cascade is not yet fully understood, dysregulated inflammation and direct injury to endothelial cells by SARS-CoV-2 contribute to the development of microthrombotic immunopathology.[51–53] Additionally, endothelial cell damage in SARS-CoV-2 infection impairs pulmonary vasoconstriction that normally occurs in response to hypoxia to restrict blood flow to poorly ventilated areas of the lung. Disruption in this physiologic adaptation in COVID-19 patients results in shunting of blood. To this end, treatment for COVID-19–related ARDS has been focused on mitigation of these drivers of disease pathophysiology through the use of antivirals, steroids, anticoagulants, and prone positioning.

Antiviral Therapy

The use of antiviral therapeutics in COVID-19–related ARDS is an approach that has gained tremendous effort and attention. Their mechanisms of action are directed at specific viral components that are necessary for SARS-CoV-2 replication and pathogenicity. In this way, antivirals are unique in that they target the inciting virus instead of host-related factors, such as tissue inflammation and immune cell functions, to prevent lung injury and subsequent excessive inflammation. Remdesivir, an inhibitor of viral RNA-dependent RNA polymerase, is perhaps the most noted antiviral currently under investigation.[54] In mere months after the emergence of SARS-CoV-2, Beigel *et al.* published the preliminary results of the Adaptive COVID-19 Treatment Trial (ACTT-1), a large randomized, placebo-controlled trial for the antiviral drug remdesivir.[55] The results demonstrate a statistically significant reduction in time to recovery in severe COVID-19 patients who received remdesivir. The shortened time to recovery effect was strongest in the early severe disease group (patients requiring oxygen, but not yet intubated), which likely indicates that the timing of administration will be critical for future use. Unfortunately, the trial did not demonstrate efficacy for remdesivir in patients who began treatment after already requiring mechanical ventilation. Indeed, the follow-up time may have been too short to evaluate these patients, and the results for the complete cohort are still pending.

Additional antiviral treatments that have been proposed for the treatment of hospitalized COVID-19 patients include hydroxychloroquine, an antimalarial drug, and lopinavir-ritonavir, a protease inhibitor cocktail used for treating human immunodeficiency virus. Indeed, both drugs have demonstratable efficacy in reducing SARS-CoV-2 infection *in vitro*, but both have failed to translate into therapeutic results in COVID-19 patients.[56–58] On June 29, 2020, the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial terminated its lopinavir-ritonavir arm due to lack of clinical benefit (http://www.recoverytrial.net/results/lopinavar-results, accessed July 5, 2020). Similarly, on June 20, 2020, the National Institutes of Health PETAL Network halted its trial investigating hydroxychloroquine use (http://www.nih.gov/news-events/news-releases/nih-halts-clinical-trial-hydroxychloroquine, accessed July 5, 2020).

Anticoagulation and Thrombolytics

Given that a key pathologic finding in COVID-19 is the prevalence of thrombotic coagulopathy within lung vasculature, a great deal of attention has been directed at whether anticoagulation or thrombolytic therapy may provide therapeutic efficacy in COVID-19 ARDS. Indeed, a French multicenter prospective study identified a statistically significant increase in thromboses in COVID-19–related ARDS when compared with a historic cohort in

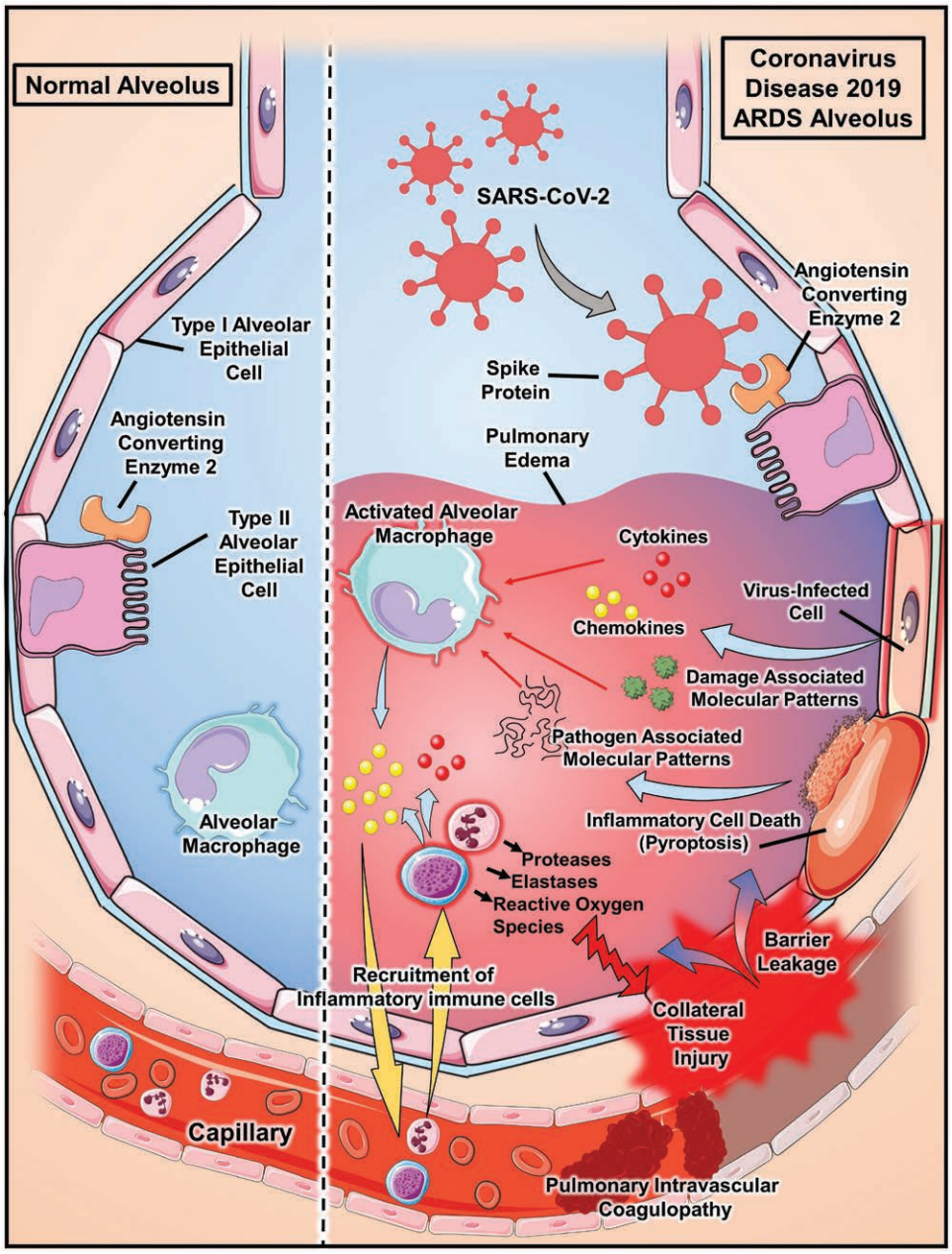

Fig. 2. Pathophysiology of acute respiratory distress syndrome (ARDS) in coronavirus disease 2019 (COVID-19). Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) infection is mediated by virus spike binding to angiotensin converting enzyme–2 on type 2 alveolar epithelial cells.[78,79] Viral infection prompts cells to react by releasing chemokines and cytokines.[80] Infection can also overwhelm epithelial cells and cause them to die *via* pyroptosis, which results in the release of inflammatory damage and pathogen–associated molecular patterns. Recognition of damage and pathogen–associated molecular patterns and cytokines activates alveolar macrophages and chemokines act to recruit inflammatory immune cells to the lung. Excessive immune cell release of antimicrobial effectors, such as metallomatrix proteases, elastases, and reactive oxygen species, induce collateral tissue injury that results in loss of epithelial and endothelial barrier integrity and infiltration of proteinaceous fluid into the alveolar airspace.[80] Furthermore, increasing evidence supports the important role of endothelial cells in the initiation of inflammation and the development of extensive pulmonary intravascular coagulopathy that is common in COVID-19 patients.[51–53] In severe cases, patients with COVID-19 have developed disseminated intravascular coagulopathy.[81] Components of the figure were modified from SMART Servier Medical Art Library.

non–COVID-19 ARDS.[59] Although there is currently a lack of evidence from randomized control trials that support the use of intermediate or treatment-level doses of prophylactic anticoagulation, some centers have adopted the use of such strategies. In an early Chinese retrospective analysis of severe COVID-19, anticoagulation therapy was associated with reduced 28-day mortality.[60] Furthermore, in another retrospective observational study of 2,773 patients hospitalized for COVID-19 in New York City, patients receiving mechanical ventilation (n = 395) had significantly reduced in-hospital mortality when treated with treatment-dose levels of anticoagulation (29.1% *vs.* 62.7%).[61] In light of these observations and the current recognition for the pathophysiologic role for coagulopathy in SARS-CoV-2 infection, several clinical trials aimed at ascertaining the role of empiric therapeutic dosing with anticoagulation in COVID-19 ARDS have been initiated.

In addition to anticoagulation, thrombolytic treatment in COVID-19 ARDS patients has been proposed as a salvage therapy. Current evidence for the use of thrombolytic treatment in ARDS is limited to a 2001 phase I trial in which 20 patients with severe ARDS were treated with urokinase, which demonstrated improved oxygenation and no risk of bleeding.[62] Indeed, some groups have published case series for patients with COVID-19 ARDS who were treated with salvage antithrombolytic agents.[63–65] All patients had some level of improvement in oxygenation and/or hemodynamics after the administration of tissue plasminogen activator, but in most cases, patients ultimately died. Nonetheless, the scientific rationale for using fibrinolytic therapy in COVID-19 ARDS—namely, the consistent findings of pulmonary microvascular thrombosis—has resulted in the initiation of urgently needed clinical trials studying the role of antithrombotic agents in COVID-19 ARDS.[66]

Prone Positioning in COVID-19 ARDS

Based on the significant prevalence for ventilation-perfusion mismatch as a result of microvascular thromboses in COVID-19 patients, prone positioning in mechanically ventilated patients is recommended in order to improve lung recruitability and oxygenation.[67–70] In a detailed characterization of mechanically ventilated COVID-19 patients in two hospitals in Boston, Massachusetts, patients who underwent prone positioning had increased median Pao_2/Fio_2 ratios from 150 to 232, an improvement that persisted 72 h later when Pao_2/Fio_2 ratios of 233 were measured while patients were supine.[71] Although there are currently not enough data to conclude that prone positioning improves long-term outcomes and mortality in mechanically ventilated patients, the National Institutes of Health COVID-19 treatment guidelines currently suggest its use.[72]

Steroids in COVID-19 ARDS

Recent data from the United Kingdom Randomised Evaluation of COVid-19 thERapY (RECOVERY) trial investigating the use of dexamethasone in hospitalized COVID-19 patients have demonstrated that dexamethasone is the first drug to improve mortality.[29] Mechanically ventilated patients who were randomized to receive 6 mg once per day for 10 days were found to have a reduction of mortality by one third when compared to patients who underwent usual care. Interestingly, this mortality benefit was not observed in patients who did not require respiratory support. In response to these findings, current COVID-19 treatment guidelines from the National Institutes of Health recommend its use in patients who are mechanically ventilated or require oxygen supplementation.[72] Moreover, similar to ARDS and PETAL Network studies, the RECOVERY trial provides an example of the power of organized multicenter investigations for new treatment approaches in critically ill patients, especially those with ARDS. Moving forward, data from the dexamethasone arm are likely to reinvigorate studies for its use in non–COVID-19 ARDS patients that may support the open-label dexamethasone studies previously mentioned.[28]

Conclusions

The past 25 yr of large, randomized clinical trial efforts have contributed a tremendous amount of insight that has advanced the clinical practice of lung-protective mechanical ventilation. Indeed, implementation of clinically proven management interventions, such as the use of low tidal volumes and prone positioning, has dramatically improved the outcomes for ARDS. However, mortality remains high, and there is a lack of targeted treatment options. Nonetheless, emerging basic science research has resulted in novel therapeutic targets, such as hypoxia, adenosine, and microRNA signaling, that might pave the way for new pharmacologic ARDS treatments. Advancements in our appreciation for pathologic and clinical subtypes of ARDS will likely also play a critical role in designing clinical trials to identify efficacy for treatments in specific cohorts of ARDS patients.[50] Furthermore, the recent COVID-19 pandemic has stimulated the rapid initiation of clinical trials aimed at targeting ARDS. At the time of this writing, there are over 100 registered controlled trials for COVID-19 ARDS listed on ClinicalTrials.gov. Potential interventions that demonstrate clinical efficacy in COVID-19 ARDS could also provide usefulness in treating ARDS patients independent of SARS-CoV-2 infection. It is important to note, however, that insights gained from proven therapies for COVID-19 ARDS could translate to non–COVID-19 ARDS subtypes that share pathophysiologic components with COVID-19 cases. For example, the efficacy reported with dexamethasone could indicate specific use for patients with viral-associated ARDS who are characterized by immune profiles similar to what is seen in COVID-19 and not for patients with other etiologic types of ARDS. Additional clinical studies will be required to carefully address such hypotheses. Last, to establish efficacy for novel ARDS interventions, collaborative efforts, such as the multicenter trials ongoing

in the PETAL Network, will continue to be vital for the successful improvement of ARDS outcomes. In addition to these large-scale studies, a network of smaller clinical trials investigating the efficacy of novel treatment concepts[73,74] may be required to identify new approaches for ARDS therapy. Channeling enthusiasm for new trials targeting COVID-19 ARDS may provide a catalyst and framework for these important collaborations going forward.

Research Support

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Competing Interests

Dr. Williams is a scientific speaker about sugammadex for Merck Pharmaceuticals (Kenilworth, New Jersey). The other authors declare no competing interests.

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