

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://ardnet.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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Submitted for publication June 10, 2020. Accepted for publication August 21, 2020. From the Department of Anesthesiology, University of Texas Health Science Center at Houston, McGovern Medical School, Houston, Texas.

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