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Adjunctive Therapies in ARDS

The Disconnect Between Clinical Trials and Clinical Practice

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Nearly 20 years have passed since the advent of low tidal volume ventilation,¹ yet the mortality for patients with ARDS remains high. Revisiting the treatment modalities used to manage this syndrome has become increasingly important in light of the COVID-19 pandemic. Although ventilator management comprises a large component of ARDS care, adjunctive, nonventilator therapies also make up an important part of a clinician's toolkit. Over the years, a number of studies on adjunctive therapies for ARDS² have been conducted, but their implementation and impact as a whole on patient outcomes are unclear. In this issue of *CHEST*, Duggal et al² set out to address an important issue: the use of adjunctive therapies in patients with moderate to severe ARDS, a timely subject in the setting of COVID-19. Their objectives were to evaluate the frequency and patterns of use of adjunctive therapies in this patient population, as well as to understand the factors associated with the use of these therapies. Although the Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (LUNG-SAFE) previously assessed the frequency of adjunctive therapy use all patients with ARDS,³ a closer

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look at patients with a $\text{PaO}_2/\text{FiO}_2$ ratio <150 is needed, as it is primarily this subset of patients in whom adjunctive therapies are recommended. In this cohort assembled in 2014, a small proportion of patients with moderate to severe ARDS (29%) received early adjunctive therapy; the most frequently used modality was neuromuscular blockade (22%). Prone positioning, the adjunctive therapy that has most clearly been shown to have a survival benefit in ARDS,⁴ was only used in 11% of patients.

This study² sheds some light on the patient-, clinician-, and systems-level factors associated with the use of adjunctive therapy, but many questions remain. Although the patient-level characteristics associated with adjunctive therapy use (younger age, more severe hypoxia, and hypercapnia) are unsurprising, other elements associated with adjunctive therapy use are thought-provoking and warrant more in-depth investigation. The finding that differences in geo-economic region and clinician staffing ratios were associated with different rates of adjunctive therapy use suggests that health systems-level issues play a role. Among high-income countries, the fact that decreased adjunctive therapy use was seen in non-European countries compared with European countries was particularly compelling, as this finding suggests that the disparities were not solely related to cost. These relationships must be examined further.

Regarding clinician-level factors, it is worth highlighting that adjunctive therapy was used more frequently in patients who had ARDS recognized on day 1.² The underrecognition of ARDS by clinicians has been previously reported,³ and this phenomenon likely affects treatment decisions. Additional clinician-level factors that might play a role in adjunctive therapy use were not addressed in the current study but may include expertise with specific modalities,⁵ or lack of belief in their utility. Benefits of adjunctive therapies are less well established than benefits of low tidal volume ventilation. Randomized controlled trials, including the Reevaluation Of Systemic Early Neuromuscular Blockade (ROSE)⁶ and Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome (EOLIA),⁷ have failed to show a clear mortality benefit from the routine use of neuromuscular

blockade or extracorporeal membrane oxygenation in patients with ARDS with specific levels of hypoxia. Previous studies have suggested possible harm associated with the use of pulmonary vasodilators.^{8,9} Thus, clinician reservation for the utilization of these therapies may be expected.

Conversely, a lack of evidence cannot be the sole reason for the underutilization of adjunctive therapy. The ROSE study was published after the LUNG-SAFE cohort was collected. Prior to ROSE, Papazian et al¹⁰ reported a potential mortality benefit associated with use of neuromuscular blockade. Although neuromuscular blockade was the most commonly used therapy in the cohort of Duggal et al,² it was still used in less than one-quarter of patients with moderate to severe ARDS. Furthermore, there was a particularly low rate of prone positioning, a modality that has shown mortality benefit in patients with moderate to severe ARDS, yet remains grossly underutilized for reasons that are unclear. A multicenter observational study on prone positioning found that clinician judgment of hypoxemia being insufficiently severe was the most common reason for not using this therapy.¹¹ Although this indicates a clinician-level factor in its underutilization, this study was performed in ICUs that agreed to participate in a study about proning, which likely resulted in a selection bias toward centers whose staff were trained in this technique. The level of clinician training and comfort with prone positioning outside of centers participating in clinical research has not yet been established and potentially plays a substantial role in its underuse. Duggal et al² categorize prone positioning as a “widely available” adjunctive therapy due to the lack of requirement for specialized equipment. Although specific technology is not required for prone positioning, training and expertise of physicians and allied health professionals are crucial and may be lacking in some centers. Prone positioning can also be more labor-intensive for nursing staff, making it less feasible in centers with lower nurse-to-patient ratios. All of these factors may prevent prone positioning from indeed being a widely available therapy in a practical sense.

Ultimately, the study by Duggal et al² highlights the disconnect between evidence-based society guidelines¹² and actual practice patterns in the real world. Whether this disconnect has persisted in the setting of the COVID-19 pandemic has yet to be seen. Nevertheless,

barriers to the use of adjunctive therapies outside of the context of interventional trials must be identified and addressed, particularly regarding prone positioning. Although underrecognition of ARDS represents one culprit and a potential target for improvement, the contribution of other clinician-, systems-, and patient-based factors must be examined before a comprehensive approach to implementation strategies for improving ARDS care can be developed. Mortality in ARDS remains high; the failure of advances in ARDS management to reach this vulnerable patient population may be the reason why.

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