Adjuvant Therapies for ARDS: Not Ready for Prime Time?

Yael Aschner and Ellen L. Burnham

Division of Pulmonary Sciences and Critical Care Medicine, Department of Medicine, University of Colorado School of Medicine, Aurora, Colorado

Investigations on nationally representative cohorts of patients for more than a decade have indicated an overall decline in fatality associated with the acute respiratory distress syndrome (ARDS). Nevertheless, an increase in the incidence and prevalence of ARDS, with persistently high morbidity and mortality in certain patient subgroups, has also been reported (1–3).

In 2012, the ARDS Definition Task Force performed a meta-analysis using patient-level data to establish what would become the Berlin definition, in part to better inform clinical care for patients with ARDS (4). Classification of ARDS hinged on the degree of hypoxemia, enabling patient categorization into mild, moderate, or severe ARDS on the basis of their $\text{PaO}_2/\text{FiO}_2$ ratio. Notably, patients with severe ARDS having a $\text{PaO}_2/\text{FiO}_2$ ratio ≤ 100 comprised approximately 28% of all patients with ARDS, demonstrated an associated mortality of 45%, and spent a median of 9 days (interquartile range, 5–17) on mechanical ventilation.

Given the substantially poorer survival and increased morbidity among this subgroup, patients with severe ARDS are often the focus of adjuvant treatment strategies aimed at improving survival, including the use of extracorporeal membrane oxygenation (ECMO), inhaled pulmonary vasodilators, including nitric oxide and epoprostenol, and continuous neuromuscular blockade agents (cNMBA).

To establish the rates of use for adjuvant therapies in acute respiratory failure, including ARDS, in this month's issue of the *AnnalsATS*, Munshi and colleagues (pp. 94–102) performed a longitudinal analysis of administrative

data derived from 500 U.S. hospitals, representing 20% of all hospital discharges occurring during 2009–2013 (5). Data from more than 500,000 patients with *International Classification of Diseases, Ninth Revision*, codes representing acute respiratory failure or ARDS, and in whom mechanical ventilation was required for at least 24 hours, were evaluated.

The major risk factor for ARDS was pneumonia. Although clinical data (e.g., $\text{PaO}_2/\text{FiO}_2$ ratio) to confirm ARDS were not available, patients spent a median of 4 days (interquartile range, 3–9 days) receiving mechanical ventilation, and the majority (73%) required ventilator support within 2 days of admission; more than 50% needed vasopressor support. Hospital mortality was 33%. According to the Berlin working group's observations (4), more than 100,000 patients in the cohort potentially had severe ARDS, and adjuvant therapies may therefore have been reasonable to consider.

Nevertheless, the authors determined that adjuvants were used in fewer than 12,000 patients, despite the publication of seminal investigations regarding adjuvant use during the time the data were collected (6–8). cNMBAs were most commonly used (in 2%), followed by inhaled pulmonary vasodilators (0.4%). ECMO was used in only 0.04% of all patients. Potential reasons for the low adoption of adjuvant therapies in a population of relatively sick patients with ARDS deserve further consideration.

A multisociety statement focused on understanding adoption of clinical research findings into care of critically ill patients noted that providers may be more or

less compelled to consider clinical research in their practice for reasons unrelated to a study's primary outcome (9). One obvious reason is cost. Cost is certainly dynamic, and may be influenced by availability, technology, personnel, or other factors. ECMO costs vary widely across the U.S. centers. Although it may be less expensive when used for pulmonary compared with cardiac indications, ECMO use significantly raises the cost of intensive care unit care (10). Inhaled epoprostenol, although less expensive than inhaled nitric oxide, lacks extensive evaluation in ARDS, and even cNMBA can become costly when used over several days.

Recent investigations related to adoption of early mobility in the intensive care unit characterized four barriers influencing adoption of new therapeutic strategies in critically ill patients (11). Examining those barriers in the context of adjunctive therapies for ARDS can shed light on observations reported by Munshi and colleagues (5).

One barrier is patient-related, including severity of illness and instability. It is easy to envision a severely ill patient with ARDS either too sick to transport within the hospital or to an external facility to receive ECMO. Caregivers may perceive that risks of moving such a fragile patient outweigh ECMO's potential benefits, and not pursue this strategy.

A second barrier is structural, relating to human and technical resources. Only 62 of the 500 facilities included in the data provided ECMO to at least one patient, potentially indicating lack of technology and resources. It is also possible that facilities

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Correspondence and requests for reprints should be addressed to Ellen L. Burnham, M.D., 12700 E. 19th Street, Mailstop C272, Aurora, CO 80045. E-mail: Ellen.burnham@ucdenver.edu

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had resources to provide adjunctive therapies, but lacked protocols to implement them in the ARDS setting.

A third barrier is cultural, including habits, attitudes, and context within intensive care units and institutions. In some centers, physicians and staff may have lacked knowledge regarding the relationship between severe ARDS and outcomes, or the potential benefit of readily available adjunctive therapies such as cNMBA. Alternatively, staff may have been skeptical of certain adjuncts' utility, for valid reasons. Despite the gradual increased use of ECMO over the study period (12), its role in ARDS treatment remains controversial. The 2009 influenza pandemic, in which large numbers of patients with severe ARDS were admitted to intensive care units, may have fostered an abrupt increase in knowledge regarding ECMO, and an acculturation to its use after 2009 (13). Although additional analyses performed by Munshi and coworkers excluding 2009 data do not support an effect of the pandemic on ECMO use, abrupt shifts in knowledge during this time may have had an unmeasured effect on decisions made in subsequent years regarding adjunctive therapies (5).

A final barrier group is process-related. The publication of the Berlin definition occurred toward the end of the data collection period. Having this definition available to formalize processes within health care facilities may have supported earlier identification of severe ARDS patients, and to define roles and responsibilities for providers, including provision of adjunctive therapies for the sickest patients.

Although Munshi and colleagues did not observe a substantial effect of seminal article publication on adjunctive therapy use, a trend for increased ECMO and inhaled epoprostenol use was present during the 2009–2013 period (5). Notably, examination of published literature with reference to ARDS and each adjunctive

Figure 1. Terms including extracorporeal membrane oxygenation (ECMO), inhaled nitric oxide (iNO), epoprostenol, and continuous neuromuscular blocking agents (cNMBA) were searched in conjunction with the term acute respiratory distress syndrome (ARDS) in the PubMed (U.S. National Library of Medicine, National Institutes of Health) search engine, by years from 2008 to 2015, to determine the number of publications for each therapy in the context of ARDS that were available per year. The relative number of ECMO publications has increased since 2008.

therapy reveals a steadily increasing number of ECMO–ARDS publications since 2008, but relatively unchanged publication numbers for others (Figure 1). This may indicate that research interest in ECMO for ARDS is increasing, translating to improved generalizable knowledge to guide practice. For other interventions such as cNMBA, in which research interest appears steadier, ongoing multicenter randomized clinical trials in ARDS (NCT02509078) will help further define these agents' clinical benefit for patients with ARDS.

It has been estimated that 17 years must elapse before evidence-based observations are incorporated into health care practice, and that only 50% will be widely used (14). The failure to effectively employ evidence-based data in clinical use has come into closer scrutiny as research funding has diminished, leading to the advent of implementation science, defined as the study of methods to promote systematic uptake of research and evidence-based practices into routine practice to improve

health services. As such, effectiveness trials that aim to generate more broadly generalizable knowledge have emerged.

Unlike efficacy trials, effectiveness trials use populations selected for a condition of interest that may be otherwise heterogeneous. Outcomes examined are typically smaller in number and are more circumscribed, and analyses are performed to compensate for heterogeneity. Administrative data are often employed in clinical effectiveness research to quantitatively measure baseline and rate of change in clinical practices, such as was performed by Munshi and colleagues (5).

Given the relative paucity of evidence-based therapies to improve ARDS survival, both researchers and practitioners responsible for these patients' care will need to understand and implement practices that have the potential for significant benefit in a manner that is cost-effective, informed, and timely. ■

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