Revisiting Old Friends: Adjunctive Therapies in Acute Respiratory Distress Syndrome

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Acute respiratory distress syndrome (ARDS) is an important clinical syndrome that requires a multifaceted therapeutic approach. In the largest multinational epidemiological study to date, the incidence of ARDS in ICU admissions was 10.4% with an estimated mortality of 34.9–46.1% depending on disease severity (1). Despite decades of research, the benefit of many bedside interventions, from specific ventilator settings to pharmacotherapies, remains unclear. Here, we review three recent clinical trials that reevaluate previously studied adjunctive therapies in ARDS management looking at corticosteroids, neuromuscular blockade (NMB), and esophageal balloons. ■

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Villar J, *et al.*; Dexamethasone in ARDS Network. Dexamethasone Treatment for the Acute Respiratory Distress Syndrome: A Multicentre, Randomised Controlled Trial. *Lancet Respir Med* (2)

Reviewed by Catherine A. Gao

Although corticosteroids have been shown to be beneficial in septic shock (3), data on whether their administration improves outcomes for patients with ARDS have been inconclusive (4–7). Interest in corticosteroids has increased after RECOVERY (Randomized Evaluation of COVID-19 Therapy) (8), REMAP-CAP (Randomised, Embedded, Multi-factorial, Adaptive Platform Trial for Community-acquired Pneumonia) (9), and others (10) demonstrating improved outcomes in patients with coronavirus disease (COVID-19) with steroids. Villar and colleagues conducted the DEXA-ARDS randomized controlled trial (2) in 17 ICUs across Spain. Patients were eligible if they met criteria for ARDS and had a $Pa_{O_2}/F_{I_{O_2}} \leq 200$ mm Hg 24 hours after ARDS onset on positive end-expiratory pressure (PEEP) ≥ 10 cm H_2O and $F_{I_{O_2}} \geq 0.5$. Exclusion criteria included those who had already received corticosteroids or were immunosuppressed. The primary outcome was the number of ventilator-free days at 28 days after randomization. The intervention group received dexamethasone 20 mg intravenously daily from Days 1 to 5, then 10 mg intravenously daily from Days 6 to 10, with therapy stopped if patients were extubated. Patients in the control arm received standard critical care.

A total of 1,006 patients were evaluated and 277 were enrolled. Notably, of the 630 ineligible patients, 250 were excluded because they had already received corticosteroids. The trial was terminated early (at 88% of the planned sample size) by an independent data safety monitoring board because of low enrollment. Pneumonia was the most common cause of ARDS (53.0%). NMB was the most frequently administered adjunctive therapy (58.8%), whereas the use of proning was infrequent (25.3%).

Patients in the intervention arm had more ventilator-free days at 28 days than patients in the control arm (12.3 vs. 7.5 days; difference, 4.8 days; 95% confidence interval [CI], 2.6–7.0; $P < 0.001$) and lower 60-day mortality (20.9% vs. 36.2%; difference, −15.3%; 95% CI, −25.9 to −4.9; $P = 0.0047$). Administration of dexamethasone was associated with a higher incidence of extubation failure requiring reintubation within 28 days of randomization (8.6% vs. 5.1%). There was no increased rate of infectious complications in the intervention group.

This trial suggests that dexamethasone, an inexpensive and accessible medication, may improve ventilator-free days and 60-day mortality in moderate to severe ARDS, without increasing adverse events. Strengths of the trial include its inclusion of only patients on standardized ventilator settings (contrary to previous heterogeneous trial participants) with severe hypoxemia (thus enriching the study cohort for those at highest risk of death), a well-articulated rationale for dexamethasone dosing strategy, use of a patient-centered objective primary outcome, and robust follow-up for long-term outcomes. However, several limitations deserve mention. First, the trial was stopped early for low enrollment, reducing confidence in the

(Received in original form October 5, 2020; accepted in final form June 29, 2021)

Supported by Northwestern University's Lung Sciences Training Program (5T32HL076139-14).

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Am J Respir Crit Care Med Vol 204, Iss 4, pp 473–475, Aug 15, 2021

Originally Published in Press as DOI: 10.1164/rccm.202009-3722RR on June 30, 2021
Internet address: www.atsjournals.org

intervention's true effect size and increasing the chance of a type I error. Second, the unblinded nature of the intervention may have biased how patients were treated, although the authors provide compelling evidence to counter this concern. Finally, the prognostic enrichment strategy used precludes generalization of the study's findings to patients with less severe disease.

The choice of dexamethasone to investigate is logical, as it has more antiinflammatory effects and less mineralocorticoid effects compared with other steroids (11). DEXA-ARDS adds to the growing body of literature that steroids may improve outcomes in ARDS (12). However, more work is needed to guide which specific steroid, dose, duration, and population are optimal. ■

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Reviewed by Ruben J. Mylvaganam

For patients with ARDS, NMB may reduce work of breathing, prevent patient–ventilator dyssynchrony, and improve oxygenation (14). In the ACURASYS (Neuromuscular Blockade in Early Acute Respiratory Distress Syndrome) trial, the administration of cisatracurium for 48 hours was associated with a significant reduction in *adjusted* 90-day mortality (15). However, concerns regarding the use of deep sedation in the study's control arm, limited data on the long-term sequelae of NMB administration, and inconsistent adoption of NMB in real-world practice drove calls for additional trials (1, 16).

In the multicenter ROSE (Reevaluation of Systemic Early Neuromuscular Blockade) trial, investigators randomized 1,006 patients in an unblinded study to receive early cisatracurium for 48 hours together with deep sedation or to usual care with lighter sedation (Richmond Agitation-Sedation Scale 0 or −1) (13). Mechanically ventilated patients were eligible if they had a Pa_{O_2}/FI_{O_2} <150 mm Hg with a PEEP of ⩾8 cm H_2O. Notably, 3,840 of the 4,848 eligible patients were excluded, including 655 patients who had already received NMB. The primary outcome was *unadjusted* all-cause 90-day mortality.

ROSE was stopped early for futility by the data and safety monitoring board in the absence of prespecified stopping rules for futility. There was no significant difference in 90-day mortality between patients randomized to cisatracurium and those in the control arm (42.5% vs. 42.8%; between-group difference, −0.03%; 95% CI, −6.4 to 5.9; $P = 0.9$). Patients randomized to NMB experienced more impairment in physical activity while hospitalized and suffered more adverse cardiovascular events. However, rates of ICU-acquired weakness were similar between the two groups (13).

Strengths of the ROSE trial include its large sample size, the exclusion of patients whose Pa_{O_2}/FI_{O_2} improved to >200 mm Hg before randomization, an unadjusted primary outcome, protocolized cointerventions with high protocol adherence, and relevant longer-term follow-up. The use of higher PEEP and lighter sedation targets than the ACURASYS trial may more closely replicate consensus on best practice and improve the trial's external validity (17). The trial has several limitations. First, the intervention was unblinded. Second, the liberal Pa_{O_2}/FI_{O_2} cutoff used for study entry and the exclusion of patients already receiving NMB may have biased the trial toward the null. Third, 79% of patients screened for eligibility were excluded. Finally, compared with ACURASYS, ROSE enrolled patients earlier after the diagnosis of ARDS and less frequently used prone positioning. The trial can therefore not exclude a benefit to NMB if used after additional ventilator optimization, sedation titration, and prone positioning.

The ROSE trial suggests that the routine use of NMB for patients with early moderate to severe ARDS does not improve mortality and may be associated with important adverse events. NMB remains an important consideration when ventilator optimization and judicious sedation fail to achieve lung-protective ventilation (18). ■

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Reviewed by Taylor A. Poor

PEEP is a key ventilator variable in patients with ARDS. Although capable of improving Pa_{O_2} (20, 21), PEEP may contribute to ventilator-induced lung injury by overdistending ventilated alveoli (22, 23). The optimal method to titrate PEEP in patients with ARDS remains debated (24). The use of esophageal manometry (Pes) to approximate pleural pressure and estimate transpulmonary pressure (P_L) may facilitate more physiologic PEEP titration (25).

EPVENT-2 was a multicenter, prospective, randomized, unblinded, phase 2 trial comparing Pes-guided PEEP titration to an empiric high PEEP-F_{IO_2} table in adult patients with moderate to severe ARDS for $<$36 hours (19). Notable exclusions included the prior use of rescue therapies and active air leak from the lung. In the intervention arm, P_L was measured daily, with PEEP titrated to an end-expiratory P_L of 0–6 cm H_2O, an end-inspiratory P_L of $\leqslant$20 cm H_2O, and a P_L-F_{IO_2} table. PEEP in the control arm was guided by the high PEEP-F_{IO_2} table (26). Decisions regarding resuscitation, sedation, and neuromuscular blockade were left to the discretion of the treatment team. The primary analysis included 102 patients in the intervention arm and 98 in the control arm.

There was no difference between groups in the primary outcome, a ranked composite measure of death and days free of the ventilator reported as a probabilistic index (intervention arm, 49.6%; 95% CI, 41.7–57.5%; vs. control, 50.4%; 95% CI, 42.5–58.3%). Safety endpoints were similar between groups. Although the average PEEP between groups was similar, 12 patients in the intervention arm had at least 1 day during which they received a PEEP $>$24 cm H_2O compared with zero patients in the control arm. Patients in the intervention arm also required fewer rescue therapies (4 vs. 12 patients; $P = 0.04$).

Strengths of the trial include its multicenter design, high protocol adherence, and balanced use of cointerventions. Limitations include infrequent use of prone positioning, an aggressive PEEP strategy in the control arm (e.g., a PEEP of 20 cm H_2O beginning at F_{IO_2} 0.5) that may not reflect practice at many centers, and an enrollment size that leaves it underpowered to detect smaller treatment effects. In addition, the inclusion of a heterogeneous group of patients with ARDS rather than a cohort enriched for those likely to have increased chest wall elastance (e.g., patients with significant obesity or ascites) may have biased the trial toward a negative result.

The results of EPVENT-2 suggest that the routine use of Pes-guided PEEP titration does not improve patient-centered outcomes compared with the empiric application of a high PEEP table in moderate to severe ARDS. Whether the use of Pes-guided PEEP titration might be uniquely beneficial in patients with elevated pleural pressure remains an open question. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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