Editorial

Pharmacotherapy in acute respiratory distress syndrome—the long and winding road

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Ashbaugh's original case series of patients with acute respiratory distress syndrome (ARDS) had a mortality of 58% (1). Significant gains have been made in the treatment of ARDS with contemporary mortality ranging between 25% and 45% depending upon disease severity (2). In part, improvements are due to general advancements in critical care. Since 1967, new antibiotics have become available for treating pneumonia, continuous renal replacement therapies allow for improved volume management in patients with ARDS and acute renal failure, and sepsis resuscitation is more aggressive and protocolized. Changes in mechanical lung ventilation practices have also improved outcomes. The most salient of these is the widespread adoption of low tidal volume, "protective", mechanical lung ventilation. In a landmark clinical trial, the ARDS network demonstrated a 9% mortality reduction in patients ventilated with a 6 mL per kilogram tidal volume, compared to patients ventilated with a 12 mL per kilogram tidal volume. Subsequently the practice has become widespread (3). Recently, prone positioning was also shown to lower mortality in patients with severe ARDS (4).

Despite these improvements, the role of pharmacotherapy in ARDS remains uncertain. There have been multiple negative studies with pharmacologic agents including rosuvastatin, methylprednisolone, aerosolized surfactant, prostaglandin E1, and ketoconazole (5-10). Recently the lung injury prediction score (LIPS)-A trial published by Kor *et al.* failed to demonstrate a reduced incidence of ARDS in a cohort of nearly 400 patients who received aspirin or placebo adding to the list of negative studies (11).

Platelets have a critical role in the pathophysiology of ARDS and Kor and colleagues hypothesized that aspirin could be a useful therapeutic. ARDS affects the alveolar space, the interstitium, and the pulmonary vasculature. When platelets are activated in the pulmonary circulation, they increase production of thromboxane A2 and expression of P selectin, propagating platelet-neutrophil aggregation and extravasation into the interstitium and alveolar space (12). Animal studies have repeatedly shown that disruption of platelet signaling decreases neutrophil chemotaxis and platelet-neutrophil aggregation (13-15). Unfortunately these findings have not translated into consistent benefits in human studies of aspirin in ARDS. In fact, several recent studies showed no benefit with aspirin use in cardiac surgery patients and other critically ill patients after using propensity scores to adjust for confounding (16,17).

It is important to consider why aspirin may have failed to show a benefit in the LIPS-A trial. The first and most obvious limitation of the LIPS-A trial is that the incidence of ARDS was unexpectedly low in both the control and treatment groups (8.7% and 10.3% respectively) (11). In their sample size calculation, the authors assumed an ARDS incidence of 18% and an absolute risk reduction of 10% with aspirin. The authors used a LIPS ≥4 for entering patients into the study because previous work identified this threshold as the optimal cutoff point for balancing sensitivity and specificity. In a previous cohort study, patients with LIPS of 4 had a 6% rate of ARDS, patients with LIPS of 5 had an 11% rate, and patients with LIPS of 6 had a 15% rate (18). The median LIPS in the LIPS-A trial was 6, but the rate of ARDS was less than 15%. It seems that using a cutoff of 4 for inclusion into the study may have been too liberal and perhaps too many "low risk" patients were included negating any potential benefits for aspirin.

Also, the optimal timing of aspirin administration for preventing lung injury is unknown making the intervention window in the study somewhat arbitrary. Aspirin may have been given either too early or too late to patients. In fact, 20% of patients in the study were already receiving mechanical ventilation at the time of randomization and perhaps these patients were beyond the optimal window for aspirin administration.

Regardless of its negative findings, LIPS-A is an important contribution to the ARDS literature for a number of reasons. First, it shows the difficulty in accurately predicting which patients will develop ARDS in future clinical trials. The LIPS performed differently than it had in prior validation cohorts and ultimately this led to a lower risk cohort than anticipated. LIPS-A also demonstrated that performing a multicenter ARDS prophylaxis trial is feasible, but challenging because the optimal timing for intervention may be uncertain. Finally, the majority of patients in the LIPS-A trial had sepsis, but perhaps aspirin could prevent lung injury in other settings such as transfusion related acute lung injury (TRALI) where animal models have shown that it may be beneficial (19).

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Footnote

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