Fellows Corner

Acute Respiratory Distress Syndrome from a Kidney Perspective

By Camilo Cortesi

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The coronavirus 2019 (COVID-19) pandemic has brought the interaction of the lung and kidney to the fore. Nephrologists have worked in tandem with critical care to manage the acute kidney injury (AKI) that has increasingly occurred in patients with acute respiratory distress syndrome (ARDS) as a result of COVID-19.

Nephrologists and renal fellows are often asked to evaluate patients with acute respiratory distress syndrome (ARDS) for acute kidney injury (AKI), electrolyte or acid–base disturbances, or volume overload. ARDS is associated with high mortality rates and is present in ≤10.4% of patients in critical care units (1). Evidence has shown that ARDS is an independent risk factor for AKI, which is prevalent in up to a third of ARDS patients (2).

Decisions about the initiation of renal replacement therapy (RRT) in patients with ARDS require special attention from nephrologists because there are considerations beyond traditional indications. Determining whether or not ARDS patients meet the criteria for RRT is a common challenge, which is quite difficult to decipher in patients with preserved kidney function. This article provides a concise review of the lung–kidney crosstalk and highlights key points for treating patients with AKI and ARDS.

ARDS is a life-threatening condition and is frequently encountered in the intensive care unit. It is characterized by an alveolo-capillary barrier insult from an ARDS trigger. This insult causes acute pulmonary inflammation and increased vascular permeability, leading to noncardiogenic pulmonary edema, often followed by respiratory failure. Many ARDS triggers should be taken into consideration when evaluating a patient, most commonly but not limited to sepsis, pneumonia, pancreatitis, trauma, extensive burns, pulmonary inhalation injury, aspiration of gastric contents, thoracic surgery, transfusion, and administration of chemotherapy. Treating the underlying cause is the most crucial first step in the management of this condition. ARDS-like conditions such as acute cardiogenic pulmonary edema, vasculitis, and bilateral pneumonia, among others, should also be considered during the evaluation.

ARDS should be suspected in the presence of a known ARDS trigger and the development of acute-onset (<7 days) respiratory symptoms, increased oxygen requirement, and radiologic evidence of bilateral lung infiltrates not solely attributed to acute heart failure or volume overload. The Berlin definition provides a severity stratification for prognosis and therapy guidelines based on PaO_2/FiO_2 levels in patients using ventilatory support with settings delivering ≥5 cm H_2O of peak end-expiratory pressures in moderate and severe forms or delivering ≥5 cm H_2O of continuous positive airway pressure in mild forms of ARDS. Mild ARDS is defined as PaO_2/FiO_2 >200 mm Hg and ≤300 mm Hg, moderate ARDS as PaO_2/FiO_2 >100 mm Hg and ≤200 mm Hg, and severe ARDS as PaO_2/FiO_2 ≤100 mm Hg (3).

Healthcare providers, especially nephrologists and critical care practitioners, should be aware of the lung and kidney crosstalk in ARDS and its implications when evaluating a patient afflicted by this process (Figures 1 and 2). Five factors are crucial for the nephrologist to consider when evaluating ARDS patients; they include: 1) volume overload, 2) mechanical ventilation, 3) hypoxemia, 4) hypercarbia, and 5) acidosis.

Volume overload

Volume overload can increase right-sided heart pressures, worsen venous congestion, and aggravate pulmonary hypertension. Subsequently, this can lead to right ventricular dysfunction and renal interstitial edema from worsening venous congestion. Elevated interstitial and intratubular pressures decrease kidney perfusion pressures and oxygen delivery, which may result in AKI.

At the level of the pulmonary microvasculature, increased hydrostatic pressure from volume overload disproportionately affects the lungs as compared with other organs because of the increased vascular permeability of pulmonary capillaries, which in turn promotes pulmonary interstitial edema and worsens respiratory failure. Increasing ventilator requirements increase the risk of biotrauma and barotrauma and worsen respiratory status, leading to a vicious cycle. A fluid conservative therapy approach has been shown to be associated with improvement in lung function, an increase in ventilator-free days, and a decreased stay in the intensive care unit (4). Positive fluid balance in ARDS is known to be associated with adverse outcomes (5); when management with diuretics is ineffective, RRT should be considered to manage volume overload to offset or prevent its detrimental effects in ARDS.

Mechanical ventilation

Kidney function is impaired in patients with ARDS receiving mechanical ventilation as a result of hemodynamic and neurohormonal changes with a subsequent inflammatory response. Mechanical ventilation reduces preload, which can lead to decreased cardiac output and neurohormonal activation, both of which can affect renal blood flow and thus decrease estimated GFR (eGFR). This seems to be especially exacerbated when the peak end-expiratory pressure is >10 cm H_2O. Moreover, mechanical ventilation can increase intrathoracic pressure and pulmonary vascular resistance, which can worsen pulmonary hypertension, right ventricular dysfunction, and venous congestion, and, as a result, worsen kidney function by way of the mechanism explained in the above paragraph.

Barotrauma and biotrauma from mechanical ventilation result in the release of proinflammatory cytokines, leading to a systemic inflammatory state that can itself trigger AKI or in general exert noxious effects on distal organs. The mechanism by which inflammatory mediators induce injury in distal organs is not completely understood. Elevated levels of plasminogen activator inhibitor-1, interleukin-6, and tumor necrosis factor receptor I and II have been associated with the development of AKI in ARDS patients (6). This observation can elucidate why a lung-protective ventilation strategy with a low tidal volume of 4 to 6 mL/kg of ideal body weight and plateau pressure ≤30 cm H_2O is associated with reduced mortality and improved outcomes (7). In summary, lung protective ventilation strategies decrease serum cytokine levels, i.e., systemic inflammation, thereby decreasing multiorgan failure, which in turn reduces mortality.

Hypoxemia, hypercarbia, and acidemia

Hypoxemia, hypercarbia, and acidemia from ARDS inflict deleterious effects on kidney parenchyma. Severe hypoxemia impairs the nitric oxide, angiotensin II, endothelin, and bradykinin pathways in the kidneys and activates the sympathetic system, with a subsequent reduction in kidney blood flow and eGFR. In addition, severe hypoxia produces pulmonary arterial vasoconstriction, pulmonary hypertension, and venous congestion, which can contribute to kidney dysfunction (8). Hypercarbia, like severe hypoxemia, causes pulmonary vasoconstriction; in the kidneys, it produces renal arterial vasoconstriction, sympathetic activation, and activation of the renin-angiotensin-aldosterone system, which causes a reduction in kidney blood flow and eGFR (9). Severe hypoxemia and hypercarbia have a synergistic effect on kidney blood flow reduction and can also lead to apoptosis of renal tubular cells, as opposed to permissive hypercapnia without hypoxemia, which seems to have an anti-inflammatory effect and reduces apoptosis in both kidneys and lungs (10, 11). Finally, moderate levels of acidemia can result in renal vasodilation, whereas severe acidemia can cause renal vasoconstriction.

In addition to lung-protective ventilation and conservative fluid therapy, supportive therapies that have been shown to improve outcomes in ARDS include prone ventilation, neuromuscular blockade, and extracorporeal membrane oxygenation (12–14). The evidence for early initiation of RRT in ARDS patients remains controversial. The known indications for RRT in ARDS include 1) prevention of volume overload, 2) diuretic-resistant volume, 3) AKI, and 4) electrolyte and acid-base derangements refractory to medical management. A recent post hoc analysis of the AKIKI randomized clinical trial showed no significant difference in 60-day mortality nor

in the time to successful extubation based on the initiation time of RRT in ARDS patients. In fact, recovery of kidney function occurred earlier in the delayed RRT group (15).

In conclusion, it is essential to understand the lung–kidney crosstalk because it elucidates the importance of promptly addressing hypoxia, hypercarbia, acidemia, and volume overload in the evaluation of ARDS patients. Larger clinical trials to evaluate this specific population are needed to determine the most appropriate strategy and indications for RRT. On the other hand, research efforts are ongoing to evaluate the therapeutic implications of biomarkers in ARDS and AKI, aiming to ultimately improve decision-making and, in turn, patient care and outcomes. ■

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Figure 1. The lung kidney axis: interaction of various deleterious effects as a result of AKI and ARDS

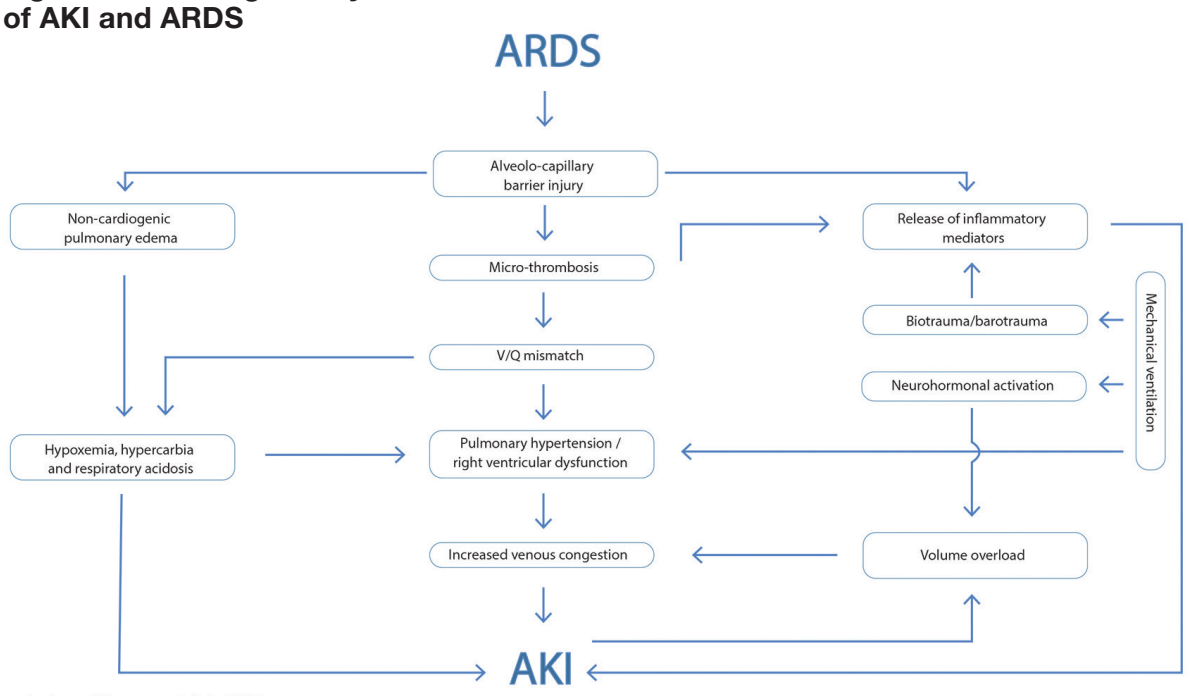
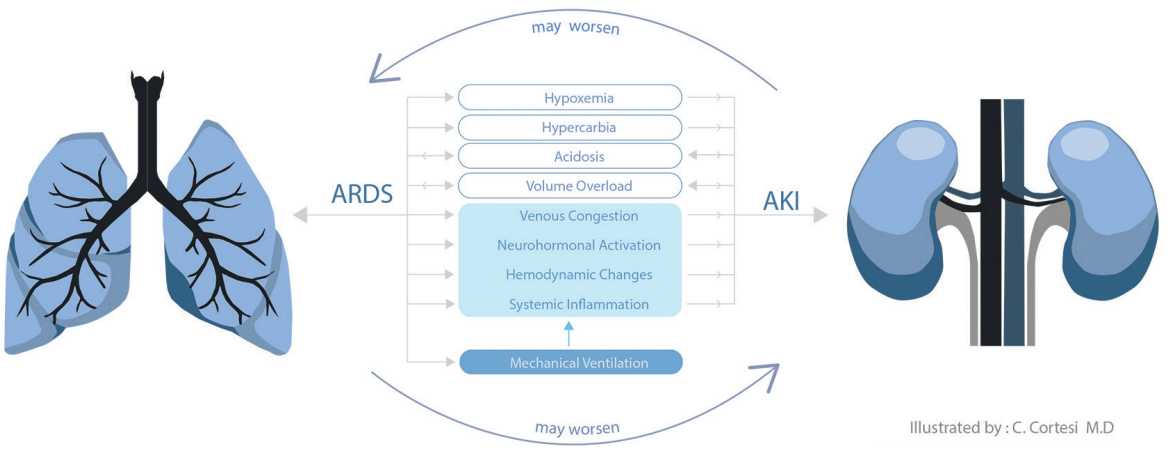


Figure 2. The vicious cycle of ARDS and AKI: conditions created by dysfunction of one system lead to worsening of the other.



Allopurinol Does Not Reduce CKD Progression

Urate-lowering therapy does not reduce the risk of progression in patients with chronic kidney disease (CKD), reports *The New England Journal of Medicine*.

The "Controlled Trial of Slowing of Kidney Disease Progression from the Inhibition of Xanthine Oxidase" (CKD-FIX) enrolled adults with stage 3 or 4 CKD (urinary albumin:creatinine ratio of 265 or higher or estimated glomerular filtration rate [eGFR] at least 3.0 mL/min/1.73 m^2) and no history of gout. Patients were assigned to allopurinol, 100 to 300 mg/d, or placebo. The main outcome of interest was change in eGFR from baseline to 104 weeks.

Planned sample size was 620, but enrollment was stopped after 369 patients due to slow recruitment. On analysis of 363 patients, mean change in eGFR was –3.33 mL/min/1.73 m^2/y in the allopurinol group and –3.23 mL/min/1.73 m^2/y in the placebo group. Rates of serious adverse events were 46% and 44%, respectively.

Secondary outcomes were also similar, including a composite of 40% decrease in eGFR, end stage kidney disease, or death from any cause. After dose escalation, mean serum rate level was 5.3 mg/dL in the allopurinol group and 8.2 mg/dL in the placebo group.

High serum urate levels are a risk factor for progression of chronic kidney disease (CKD), but it is unclear whether there is any causal association. Evidence on the use of urate-lowering medications to slow the progression of CKD is limited.

The CKD-FIX results find no benefit of allopurinol

in slowing CKD progression in high-risk patients. The lack of effect is despite a sustained 35% reduction of serum urate levels with allopurinol, compared to placebo [Badver SV, et al. Effects of allopurinol on the progression of chronic kidney disease. *N Engl J Med* 2020; 382:2504–2513]. ■