Acute Respiratory Distress Syndrome and Corticosteroids: Reconciling Conflicting Evidence

Telila Mesfin Tadesse[1*], Olifan Getachew Wakjira[2]

[1]School of Medicine, Madda Walabu University, Goba, Ethiopia.
[2]College of Health Science and Medicine, Haramaya University, Harar, Ethiopia.

Corresponding Author:
Telila Mesfin Tadesse, MD, MPHE. School of Medicine, Madda Walabu University. P.O. Box 247, Bale Robe, Ethiopia. Email: telilamesfintadesse@gmail.com.

ABSTRACT

Acute respiratory distress syndrome (ARDS) is a life-threatening form of acute inflammatory lung injury in which loss of alveolar-capillary membrane integrity produces protein-rich pulmonary edema, refractory hypoxemia, and reduced lung compliance, typically within 6–72 hours of a precipitating insult. The 2012 Berlin criteria defined ARDS by acute onset within one week of a known insult, bilateral opacities not fully explained by effusion, atelectasis, or cardiac failure, and a PaO_2/FiO_2 ratio of 300 mmHg or less with a minimum PEEP of 5 cmH_2O. The 2023 global definition expands this framework by accepting SpO_2/FiO_2 of 315 or less when SpO_2 is 97% or below, including patients supported with high-flow nasal oxygen at 30 L/min or more, permitting thoracic ultrasonography as an alternative imaging modality, and waiving the PEEP requirement in resource-limited settings. These revisions are particularly relevant to practice in low- and middle-income countries, where arterial blood gas analysis and mechanical ventilation may be unavailable. Management remains anchored in lung-protective ventilation, conservative fluid strategy, and prone positioning. Glucocorticoids remain the most contested pharmacological intervention: evidence from dexamethasone trials in ARDS and in COVID-19 suggests benefit in selected populations, yet questions persist regarding optimal agent, dose, timing relative to symptom onset, duration, the influence of ARDS subphenotypes, and the risk of secondary infection and neuromuscular weakness. This narrative review summarizes the pathophysiology, evolving diagnostic criteria, imaging findings, and current evidence on corticosteroid therapy, and considers how hyperinflammatory and hypoinflammatory subphenotypes may guide future trial design and individualized treatment.

Keywords*: Respiratory distress syndrome, glucocorticoids, dexamethasone, respiration, artificial, prone position, precision medicine.*

INTRODUCTION

A unique form of hypoxemic respiratory failure, marked by sudden abnormalities in both lungs, was first identified in the 1960s. Military doctors in surgical hospitals in Vietnam dubbed it "shock lung," while civilian doctors referred to it as "adult respiratory distress syndrome.[1] Later, it was recognized that individuals of any age could be affected, leading to the current term: acute respiratory distress syndrome (ARDS). It is a medical condition characterized by severe shortness of breath that begins quickly, low levels of oxygen in the blood, and widespread lung changes that lead to respiratory failure.[2] Acute respiratory distress syndrome is a sudden condition that begins within a week of the triggering event, marked by bilateral lung infiltrates and severe, worsening low oxygen levels in the blood without signs of heart-related pulmonary edema. In ARDS, the development of systemic and pulmonary inflammation during the first week of mechanical ventilation plays a crucial role in determining

whether the disease progresses towards resolution or remains unresolved, ultimately affecting the patient's outcome.[3-5] The Berlin definition of ARDS specifies a rapid onset, bilateral lung infiltrates visible on chest X-ray or CT scan not caused by cardiac issues, and a PaO2/FiO2 ratio below 300 mm Hg. This definition differs from the previous American-European Consensus by excluding the term acute lung injury, removing the need for a wedge pressure under 18 mm Hg, and requiring a positive end-expiratory pressure (PEEP) or continuous positive airway pressure (CPAP) of at least 5 cm H2O. Once ARDS sets in, patients often experience varying levels of constriction in the pulmonary arteries, which can lead to pulmonary hypertension. The condition has a high mortality rate, and there are limited effective treatments available to manage it.[6,7] In the United States, the estimated incidence of ARDS is between 64.2 and 78.9 cases per 100,000 person-years. Initially, 25% of ARDS cases are classified as mild, while 75% are classified as moderate or severe. However, one-third of the mild cases progress to moderate or severe levels of disease.[8,9] Around 10 to 15% of patients admitted to intensive care units, and up to 23% of those who are mechanically ventilated, meet the criteria for ARDS. A review of the literature found that the mortality rate decreased by 1.1% per year from 1994 to 2006. However, the overall combined mortality rate across all studies evaluated was 43%.[10,11] Importantly, the classification of ARDS into mild, moderate, and severe categories aligns with mortality rates of 27%, 32%, and 45%, respectively, adding clarity to clinical practice.[12] Additionally, mortality rates vary based on the cause of ARDS. For instance, ARDS resulting from severe sepsis of a pulmonary origin has an overall mortality rate of 40.6%, while ARDS caused by severe trauma (injury severity score > 15) shows a mortality rate of 24.1%.[13] The lung injury prediction score (LIPS) is a well-established prediction model that utilizes clinical data collected when a patient first arrives at the emergency department (ED) to pinpoint those at high risk for ARDS.[6,14,15] A LIPS score of 4 or higher is currently employed to enroll high-risk individuals in clinical trials aimed at preventing ARDS.[16]

RISK FACTORS AND ETIOLOGIES

Acute respiratory distress syndrome has generally been understood as a pattern of lung injury with clinical symptoms that can result from various triggers. However, this assumption has been challenged because studies have shown that ARDS caused by pulmonary events leads to more severe decreases in lung compliance and a lower response to positive end-expiratory pressure (PEEP) compared to ARDS caused by extrapulmonary factors, such as sepsis.[17-20] Over 60 potential causes of ARDS have been recognized, with new causes continually emerging as adverse pulmonary reactions to new treatments are observed. Despite this, a few common causes are responsible for the majority of ARDS cases.[21-23] In a study of 107 patients in a medical intensive care unit, the most common causes were pneumonia (40%), sepsis (32%), and aspiration (9%).[24] Additionally, factors that may predispose someone to develop ARDS without directly causing it have also been identified. Sepsis is the leading cause of ARDS.[22,25-27] Whenever ARDS arises in a patient who is prone to severe infections or shows new symptoms such as fever or low blood pressure, sepsis should be the primary cause to consider. The likelihood of developing ARDS is notably higher in septic patients who have a history of alcoholism. Chronic alcohol consumption increases the risk of developing ARDS by two to three times.[28, 29] The precise mechanism behind this link is not fully understood, but it is suspected that it might involve a decrease in the lung's antioxidant capacity.[29] Furthermore, both acute and chronic alcohol consumption lead to higher systemic levels of adenosine[30,31] and reduce alveolar fluid clearance in a dose-dependent manner by stimulating the adenosine type 1 receptor, exacerbating lung injury3[2,33] A 2014 study on trauma patients showed that the risk of developing ARDS increased proportionally with the blood alcohol content.[34] A history of tobacco exposure, including second-hand smoke, has been linked to a higher risk of ARDS in trauma patients.[35] Additionally, another study identified a dose–response relationship between current cigarette smoking and the later development of ARDS.[36]

Hypoalbuminemia, a known indicator of acute or chronic illness, malnutrition, and poor surgical outcomes, has also been identified as an independent risk factor for ARDS.[37-39] This seems to be due to decreased plasma oncotic pressure and increased pulmonary permeability in critically ill patients, regardless of the underlying cause and fluid status.[40] Obesity is also recognized as an independent risk factor for developing ARDS.[41] While factors like body positioning and compression atelectasis might partially explain this link other mechanisms have been suggested.[42] These include an imbalance between proinflammatory and anti-inflammatory cytokines, which heightens lung inflammation and injury through the tumor necrosis factor-α and interleukin-6 pathways.[43-46]

It appears that diabetes mellitus might be linked to a reduced risk of acute respiratory distress syndrome (ARDS) in cases of septic shock.[47] A meta-analysis encompassing data from 12,794 adult patients indicated that diabetes may offer a protective effect against ARDS.[48] While the precise mechanism remains unclear, one potential reason is that patients with diabetes may experience reduced activation of the inflammatory response in the lungs.[49]

CLINICAL PRESENTATION

Patients with ARDS exhibit symptoms of the syndrome itself, along with signs related to the underlying cause.[25] Nonetheless, these manifestations are so nonspecific that the diagnosis is frequently overlooked until the condition advances. Patients often develop dyspnea and decreased arterial oxygen saturation within 6 to 72 hours (or sometimes up to a week) after an initiating event. During examination, they might exhibit tachypnea, tachycardia, and diffuse crackles. In severe cases, symptoms like acute confusion, respiratory distress, cyanosis, and diaphoresis may also occur. Symptoms such as cough, chest pain, wheezing, hemoptysis, and fever can vary and are largely influenced by the underlying cause.[50]

WORK-UPS

Laboratory tests typically lack specificity. A complete blood count might show various white blood cell counts (normal, elevated, or decreased) and may or may not display a left shift (indicative of a stress response). Routine chemistry tests could indicate organ damage due to severe hypoxemia, shock, or systemic inflammation, such as acute kidney injury (AKI) or transaminitis. Both prothrombin time and activated partial thromboplastin time may be extended, and D-dimer levels maybe elevated. However, lab evidence of disseminated intravascular coagulation (DIC) is generally only observed in patients with concurrent sepsis or malignancy.[50] Imaging results can vary depending on the severity of ARDS. Initial chest X-rays typically show bilateral diffuse alveolar opacities with dependent atelectasis, although these findings can be subtle.[51] Chest computed tomography (CT) scans might reveal widespread patchy and/or coalescent airspace opacities, which are generally more noticeable in the dependent lung zones.[52-54] These opacities can be subtle, such as patchy ground-glass, especially in the early stages of ARDS, but they may become more consolidative as the condition worsens.[51]

A bedside lung ultrasound is still considered investigational. However, early studies suggest it has a sensitivity rate of 83 to 92 percent for diagnosing ARDS when compared to chest CT scans.[55] Ultrasound has greater sensitivity than chest radiographs in detecting bilateral lung infiltrates. This suggests that utilizing ultrasound is more likely to result in the diagnosis of ARDS compared to relying solely on chest radiography.[56] Ultrasound could be especially valuable as an imaging tool in resource-limited settings. However, further research is needed to establish standardized imaging criteria for diagnosing ARDS with ultrasound.[57]

PATHOPHYSIOLOGY

For normal lung function, dry, open alveoli must be situated near well-perfused capillaries.[58] The pulmonary capillary endothelium is normally selectively permeable, allowing fluid to cross the membranes under the influence of hydrostatic and oncotic forces while keeping serum proteins within the blood vessels. The Starling equation explains the forces that regulate fluid movement between the blood vessels and the interstitial

space.[59] The equilibrium between hydrostatic and oncotic forces typically permits small amounts of fluid to enter the interstitium. However, three mechanisms act to prevent alveolar edema. i) The retention of intravascular proteins maintains an oncotic gradient that promotes fluid reabsorption. ii) Interstitial lymphatics are capable of returning substantial amounts of fluid to the circulation. iii) Tight junctions between alveolar epithelial cells prevent fluid from leaking into the air spaces.[59] ARDS results from alveolar injury that leads to widespread alveolar damage.[60] This injury triggers the release of pro-inflammatory cytokines like tumor necrosis factor and interleukins (IL-1, IL-6, and IL-8).[5,61-64] These cytokines attract neutrophils to the lungs, where they become activated and release harmful substances, such as reactive oxygen species and proteases, which damage both the capillary endothelium and the alveolar epithelium.[60,65,66] The alveolar-capillary membrane suffers damage and becomes leaky, leading to pulmonary edema. This results in an increased transfer of both water and proteins from the intravascular space to the interstitial space. In most patients, the protein concentration in the interstitium surpasses 60 percent of the plasma level, in contrast to less than 45 percent in cases of cardiogenic pulmonary edema.[67] The oncotic gradient that typically promotes fluid reabsorption is lost, leading to an influx of fluid into the interstitium, which overwhelms the lymphatic system.[68] The capacity to enhance alveolar fluid clearance may be compromised.[69] The increase in interstitial fluid, along with damage to the alveolar epithelium, results in the air spaces filling with bloody, protein-rich edema fluid and debris from deteriorating cells. Additionally, the loss of functional surfactant leads to alveolar collapse.[69]

STEROID AND ARDS

Translational research has shown that a central pathogenetic mechanism of dysregulated systemic and pulmonary inflammation in ARDS is the inadequate inhibition of the proinflammatory transcription factor nuclear factor-κB (NF-κB) by glucocorticoid receptors (GR). This issue could potentially be addressed with sufficiently dosed and timed prolonged glucocorticoid administration.[3,5,70] The use of glucocorticoids to treat acute respiratory distress syndrome (ARDS) remains a controversial topic, with current evidence presenting conflicting results.[71-73] In this context, the recent analysis by Meduri is particularly valuable.[74] The authors performed a two-part analysis: an individual patient data meta-analysis (IPDMA) from trials involving methylprednisolone and an updated trial-level meta-analysis that included additional randomized controlled trials (RCTs) with hydrocortisone in early ARDS. They reported that steroid treatment accelerated the resolution of ARDS, resulting in decreased ventilatory support, lower hospital mortality, and reduced healthcare utilization.[74]

In a small randomized trial, administering prolonged methylprednisolone at a dosage of 2 mg/kg/day resulted in swift, continuous, and lasting reductions in plasma and bronchoalveolar lavage inflammatory cytokines, chemokines, and procollagen levels, along with corresponding improvements in the lung injury score (LIS) and the multiple organ dysfunction syndrome score (MODS).[4,70,75] The treatment led to notable decreases in both the duration of mechanical ventilation and intensive care unit mortality rates.[71] A systematic review and meta-analysis conducted by Chaudhuri in 2021, which included 18 randomized controlled trials (RCTs) with a total of 2,826 patients, showed that corticosteroids reduced mortality in ARDS of any cause (RR: 0.82, 95% CI: 0.72–0.95, ARR: 8%, 95% CI: 2.2%–12.5%).[76] In 2021, Lin conducted a meta-analysis of 9 randomized controlled trials (RCTs) involving 1,371 participants. The analysis showed that corticosteroid use was linked to a reduction in mortality (RR: 0.83, 95% CI: 0.74–0.93, $P < 0.01$). Additionally, there was no increased risk of new infections or hyperglycemia identified.[77] In 2022, Chang conducted a systematic review and meta-analysis that included 14 randomized controlled trials (RCTs) with a total of 1,607 patients. Their findings indicated that corticosteroids reduced mortality risk in patients with ARDS (RR: 0.78, 95% CI: 0.70–0.87, $P < 0.01$). Notably, no significant adverse events were observed when compared to placebo or standard support

therapy.[78]

However, these findings seem to conflict with those of the ARDS Network LaSRS study,[73] which included 56% of the patients in the IPDMA. The Late Steroid Rescue Study (LaSRS) investigators reported no benefit from the routine use of methylprednisolone in ARDS patients and found that its use was linked to a higher risk of neuromuscular complications. Additionally, starting methylprednisolone treatment more than two weeks after the onset of ARDS increased the risk of death despite early improvements in cardiopulmonary physiology.[73]

In an article published in The Korean Journal of Internal Medicine, Baek presents the findings of a propensity-matched cohort study examining the impact of early-phase corticosteroid administration on ARDS[79]. The study revealed that corticosteroid use did not significantly affect 28-day (OR, 1.031; 95% CI, 0.657 to 1.618; p = 0.895) or 90-day (OR, 1.435; 95% CI, 0.877 to 2.348; p = 0.151) mortality rates after adjusting for propensity scores. However, patients in the corticosteroid-treated group experienced a longer duration of mechanical ventilation (12 days vs. 8 days in the control group, p < 0.001), which may have contributed to a higher incidence of pneumothorax (10.9% vs. 3.7%, p = 0.007) and extended ICU stays (16 days vs. 10 days, p < 0.001). Additionally, the corticosteroid-treated group had a significantly higher rate of bacteremia (41.1% vs. 30.4%, p = 0.019), suggesting adverse effects related to immunosuppression.[79]

In the randomized controlled trial conducted by Tongyoo,[80] the administration of corticosteroids did not show a significant association with 28-day mortality (22.5% vs. 27.3%, relative risk, 0.82; 95% CI, 0.50 to 1.34; p = 0.51), consistent with the findings reported by Baek.[79] On the other hand, a recent randomized controlled trial conducted by Villar[81] demonstrated that corticosteroid treatment was linked to a lower mortality rate at day 60 (21% vs. 36%; between-group difference, −15.3%; 95% CI, −25.9 to −4.9; p = 0.0047). The Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial, which included COVID-19 patients, indicated a potential benefit of corticosteroids on 28-day mortality (age-adjusted rate ratio, 0.83; 95% CI, 0.75 to 0.93; p < 0.001).[82] This suggests that there might be a subgroup of patients who respond positively to the treatment. In 2022, Yoshihiro performed a network meta-analysis to examine the differences in efficacy among various doses and types of steroids. The comparators included high-dose methylprednisolone, low-dose methylprednisolone, hydrocortisone, dexamethasone, and no steroids. The study found no significant differences in mortality between the groups. However, the use of low-dose methylprednisolone was associated with a higher number of ventilator-free days compared to no steroids. The authors concluded that further research is necessary to determine the optimal type and dose of steroid.[83]

The adverse effects of therapeutic steroids extend beyond neuromuscular weakness, immunosuppression, secondary infections, and elevated blood glucose levels.[84] The mineralocorticoid effect of steroids also causes fluid and sodium retention.[85,86] with both positive fluid and sodium balances being linked to poor outcomes in patients with lung injury.[87-89] Future clinical trials should consider prospective data on this potential confounding factor. A recent meta-analysis conducted by Guowei concluded that the existing data do not support regular initiation of steroids in ARDS patients due to conflicting results between RCTs and observational studies.[90]

There should be an effort to adopt a more inclusive definition of ARDS and to conduct clinical trials that evaluate the efficacy of steroids within this broader framework.[91,92] Previous RCTs have used varying definitions due to evolving ARDS classifications, leading to a diverse patient population, which might obscure any clear indications of benefit or harm. Moreover, while mortality is a crucial metric, it is influenced by numerous other factors, making it difficult to replicate results in critically ill patients. Therefore, future trials should also prioritize other endpoints like ventilator-free days or ICU length of stay, instead of focusing solely on mortality.[93]

Following the principle of primum non nocere (first, do no harm), we believe there is currently insufficient evidence

to support the routine use of steroids in patients with ARDS, as potential short-term benefits seem to be countered by later adverse effects. However, if steroids are administered, abrupt discontinuation should be avoided [94]. Given the conflicting results of existing studies, it is crucial to conduct more comprehensive research. This should involve diverse racial groups, various steroids at appropriate doses, and the assessment of different clinical parameters.

CONCLUSION

Acute respiratory distress syndrome is a critical lung condition that causes fluid to seep into the lungs, making breathing challenging and preventing oxygen from entering the body. Septic patients with a history of alcoholism have a significantly increased risk of developing ARDS. Patients frequently experience difficulty breathing and a drop in arterial oxygen levels within 6 to 72 hours, or occasionally up to a week, following a triggering event. Routine chemistry tests can reveal organ damage resulting from severe hypoxemia, shock, or systemic inflammation, including conditions like acute kidney injury or transaminitis. Due to the inconsistent findings of current studies, it is essential to undertake more thorough research. This research should include diverse racial groups, different steroids at appropriate dosages, and an evaluation of various clinical parameters.

CONFLICT OF INTEREST

No conflict of interest

AUTHOR CONTRIBUTION

TMT: wrote the initial draft, edited, and revised. OGW: revised and edited the manuscript.

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