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Acute Respiratory Distress Syndrome: A Case Report and Review on Diagnosis and Novel Interventions in Management

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ABSTRACT

Acute respiratory distress syndrome is a type of acute diffuse lung injury, frequently brought on by sepsis, trauma, and severe pulmonary infections and continues to be one of the major causes of morbidity and mortality in critically ill patients, despite the constantly involving advancements. The management strategies have constantly evolved with a wide array of ventilation strategies, conservative fluid management, neuromuscular blockade. As we move into the post pandemic Era, the mortality rate due to ARDS continues to remain high hence improving patient outcomes is the primary goal of the various treatment approaches. The two most effective techniques are still prone ventilation and lung protection ventilation. In this report we aim to present the case of a 30-year old female who has undergone left lobectomy in childhood and presents to the clinic with palpitations, fever, shortness of breath and spasmodic cough with phlegm. The workup included chest Xray, CT scan, arterial blood gas with electrolytes, echocardiography and urinalysis. Based on clinical and imaging findings, the diagnosis of acute respiratory distress syndrome was made. Against the background of intensive treatment, the patient's condition improved to some extent, with positive dynamics. Lung protective ventilation, prone ventilation, high frequency oscillatory ventilation among many other novel interventions and futuristic direction of ARDS with mesenchymal stromal cells and Ulinastatin, a urinary glycoprotein and protease inhibitor provides a ray of hope in the management of this acute condition.

Keywords: Acute respiratory distress syndrome; hypoplasia; lung ventilation; prone ventilation; mesenchymal stem cells; ulinastatin

INTRODUCTION

Acute Respiratory Distress Syndrome (ARDS) continues to be one of the major causes of morbidity and mortality in critically ill patients, despite the constantly involving advancements. To avoid subsequent lung injury and enhance patient outcomes, mechanical ventilatory techniques are an essential part of ARDS care. Numerous techniques have been shown to reduce morbidity and mortality, including the use of low tidal volumes, aiming for low plateau pressures to reduce barotrauma, using low FiO2 (fraction of inspired oxygen) to prevent injury related to oxygen free radicals, optimizing positive end expiratory pressure (PEEP) to maintain or improve lung recruitment, and using prone ventilation. [1]

ARDS is a type of acute diffuse lung injury, frequently brought on by sepsis, trauma, and severe pulmonary infections. Dyspnea, severe hypoxemia, reduced lung compliance, and diffuse bilateral infiltrates on chest radiography are its clinical hallmarks.

Three conditions must be met for an ARDS diagnosis:

- Acute onset (within 1 week)
- Chest x-ray with bilateral opacities
- A PaO2/FiO2 (arterial to inspired oxygen) ratio of 300 on a continuous positive airway pressure (CPAP) of 5 cm H2O.[2]

By arterial partial pressure of oxygen (PaO2), the acute respiratory distress syndrome (ARDS) is graded as mild, moderate, or severe according to the Berlin classification to a threshold of 300, 200, and 100 mm Hg for the fraction of inspired oxygen (FIO2), respectively.[1]

The Covid-19 Pandemic has led to a sharp increase in the number of ARDS cases and hence increase in mortality rate due to it. The management strategies have constantly evolved with a wide array of ventilation strategies, conservative fluid management, neuromuscular blockade. As we move into the post pandemic Era, the mortality rate due to ARDS continues to remain high hence improving patient outcomes is the primary goal of the various treatment approaches. The two most effective techniques are still prone ventilation and lung protection ventilation. Additional adjuvants that can be applied to patients in particular clinical conditions include conservative hydration management and neuromuscular blocking. Additional research is required to examine driving pressure, the ideal PEEP, and the function of Extracorporeal membrane oxygenation in the treatment of ARDS.[2]

CASE STUDY

A 30-year-old female was brought to the clinic by 112 brigades with complaints of feeling of suffocation, heart palpitations, fever, chills, shivering, sweating difficulty breathing, shortness of breath along with spasmodic cough with a small amount of phlegm. The symptoms along with joint pain and headache started yesterday evening which was accompanied with an increase in temperature up to 38 degrees Celsius.

Past Medical History

Previous hospitalization: Hypoplasia of left lung for which lobectomy of left lower lobe was performed in 2000, was diagnosed with bronchial asthma in childhood, excision of bulky tumor in 2011, was diagnosed with a thrombus in right atrium and underwent C-section in 2020.

Allergies: Honey, milk, walnut, citrus fruits, dust, plants.

Medications: Symbicort Cardiomagnil
75mg for 1 year.

Physical Examination

Patient in acute distress.

Vitals: RR- 30-32
HR- 120
BP - 130/80 mmHg
Temp – 39.2 C

Skin: Physical appearance, skin and mucus membranes pale

Respiratory: The clinics of respiratory failure are expressed, shortness of breath at rest, bilateral weakened wheezing tachypnea, orthopnea, tachycardia, fever, chills, tremors, sweating, intercostal muscles actively involved in breathing. SnO2-85 percent.

Cardiovascular system: HR 120, sinus tachycardia; Tones: muffled, rhythmic, pulsation preserved on peripheral blood vessels.

Gastrointestinal- Soft on palpation, painless, liver and spleen not palpable.

Urinary System: Diuretic glucose, urine concentrated.

Diagnostic Examinations and work up

Chest X-ray

Focal and infiltrative changes not observed, roots are structural, in the right lower lobe, the image of lung is enhanced, sinuses of lung are free, borders are not enlarged.

CT Scan

Thyroid gland slightly asymmetric, lymph nodes 0.5-0.8cm bilaterally in the axillary fossa, heart is not enlarged, metal clips are

visible in upper part, diameter of main blood vessel4.4cm, descending aorta 1.7cm, aortic arch 1.9cm, lung truck 2.2cm.
In bilateral upper lobes mid fibrotic changes are observed, in left lower lobe, dense fibrous blackheads with small metal density inclusions are visible. There's no fluid in the pleural cavity.

***A*rterial blood gases with electrolytes**
pH – 7.496, pCO2- 33.3, pO2- 67.9, HCO3- 26.9,
K- 3.4, Na- 138, Ca-1.10 WBC- 4.66 X 10^3/microliter, RBC-4.74 X 10/microliter, hemoglobin -13.8 g/dl, HCT-40.8 percent, MCV-86.1 FL, platelets 87X10/ L, CRP- 32.2

Echocardiography
Size of left ventricle is normal, systolic and diastolic function is normal, ejection fraction -55 percent, disruption of regional contractility is not observed. Right ventricle size and systolic function normal, tricuspid valve defect is small (+1/+4). Systolic pressure in pulmonary artery is normal, pericardial activity is normal.

Coagulogram,
PT-16.9, PT percent -71, INR-1.26, aPTT-33.1
D-Dimer- 0.34

Urinanalysis
SG-1.015, pH-5, leukocyte negative, Nitrate negative, ketone negative, bacteria positive, urates positive.
Antibodies against hepatitis C, complete blood analysis with sixfold differentiation of leukocytes.

Differential diagnosis
1. Cardiogenic pulmonary edema
2. Diffuse alveolar hemorrhage
3. Acute interstitial pneumonia
4. Acute eosinophilic pneumonia

The most challenging differential diagnosis for ARDS undoubtedly stands the cardiogenic pulmonary edema especially the acute phase. Upon radiological assessment the acute phase is characterized by septal lines, peribronchovascular haze and cuffing. The characteristic bat wing appearance will be observed in less than 10 percent of cases. On echocardiography systolic, diastolic function and ejection fraction is in normal limits which rules out acute cardiogenic pulmonary edema.
Diffuse alveolar hemorrhage is identified on the chest Xray with diffuse alveolar bilateral infiltrates. Specimens show blood with numerous erythrocytes and siderophages. Along with these findings patients often presents with hemoptysis and drop in hematocrit. Since none of these findings are observed we can rule out Diffuse alveolar hemorrhage.
Acute interstitial pneumonia is generally considered to be a complication of ARDS. It is characterized by abrupt onset of fever, cough and shortness of breath which keeps increasing within a week or two and progresses to respiratory failure. CT shows bilateral patchy symmetric areas of ground glass attenuation and sometimes bilateral areas of airspace consolidation in a predominantly subpleural distribution. Sometimes its accompanied with mild honeycombing as well, these finding are absent in the patient and hence rules it out.
Acute eosinophilic pneumonia is a diagnosis of exclusion and since there's no known causes of eosinophilic pneumonia like toxin, drugs, helminths' infection and non-elevation of eosinophil counts in CBC, thus ruling it out.

Treatment and Management Plan
Oxygen therapy, infusion therapy, crystalloid infusion, Dexamethasone 4mg twice IV antibiotic therapy, inhalation therapy with broncholytic and mucolytic agents, anticoagulation and gastroprotection.
Medical recommendations
Family doctor, pulmonologist, allergist, ambulatory supervision
1.5-2 liters of water per day, Elkozol (proton pump inhibitor) 40 mg in the

morning on empty stomach, 30 mins before meals.

Xarelto (Rivaroxaban) 10 mg once a day for 20 days

Clarithromycin 500 mg twice a day for 2 days.

The first round of treatment with oxygen, infusions and inhalation therapy did not show any signs of clinical improvement and hence the patient was shifted to the ICU and treatment was made intense with addition of corticosteroids, oxygen, crystalloids and since our patient had the history of thrombectomy due to thrombus in the right atrium , D dimer tests were also performed which turned out in normal range. Against the background of intensive treatment, the patient's condition improved to some extent, with positive dynamics. The tolerance to physical exertion increased, external parameters of breathing improved, without oxygenation SaO2- 95 percent, on auscultation scattered dry wheeze can be heard in the background.

Patient's condition was stable and was discharged under outpatient supervision, given strict recommendations. Patient was informed about the continuous combined inhalational therapy that is needed, otherwise there is high risk of the disease and rehospitalization. Thus, as the patient had already undergone lobectomy due to pulmonary hypoplasia, the effective management plan and treatment was the most critical aspect in improving the respiratory and vital parameters and hence increase in chances of survival. Therefore, the next segment will be about the wide array of management strategies for ARDS and a few latest pharmacological agents too which has been approved for its treatment.

DISCUSSION

Novel Interventions in Management of ARDS

1. Lung Protective Ventilation

Protective lung ventilation is the cornerstone of ventilatory care in ARDS patients, as it improves treatment outcomes. Hyperventilation in lungs can disrupt the endothelium and epithelium, leading to inflammation, atelectasis, hypoxemia, and release of inflammatory mediators. It is recommended that patients have low tidal volumes (4 to 8 ml/kg estimated body weight)

The implementation of ventilation methods has led to a significant decrease in hospital mortality rates and the requirement for mechanical ventilation. Earlier, conventional ventilation methods utilized greater tidal loads to decrease alveolar tension and boost arterial oxygen concentration. The alveolar endothelium is disrupted by the innate inflammatory response, which prolongs and enhances the overall process of complex ARDS. Low tidal volume (6 ml/kg projected body weight) has been shown to reduce alveolar distension injury and improve survival in the Antireflux Mucosal Ablation (ARMA) protocol, which was developed from the ARDSNet experiment and subsequently used as a respiratory treatment platform for progressive acute respiratory distress syndrome.[1]

2. Prone ventilation

Mechanical ventilation is administered to a patient on their back position, known as prone ventilation. Following a stabilization period of 12 to 24 hours and severity criteria, randomized controlled trial was conducted with PaO_2/FIO_2 being tested at 150 mmHg at positive end-expiratory pressure of 5 cmH_2O. This was confirmed recently in patients with ARDS. According to this study, the mortality rate decreased significantly, from 32.8% in the supine group to 16% in the prone position group.

The cause of this substantial surge is uncertain, but the prone position may aid in reducing ventilator-induced lung damage, as evidenced by numerous studies. The effectiveness of early morning stretching exercises at day 28 and 90 in the PROSEVA trial has been demonstrated to significantly reduce mortality rates.[3]

3. Neuromuscular blockade

Neuromuscular blockade may be utilized as a ventilator support method for patients with ARDS to minimize lung injury caused by patient-ventilator dyssynchrony and strong spontaneous respiratory effort. Whether neuromuscular blockade (NMB) is effective in treating patients with ARDS remains uncertain., however. The ACURASYS trial investigated the initial administration of neuromuscular blockers in ARDS patients who were receiving lung-protective ventilation. This study suggests that neuromuscular blockade leads to an increase in ventilator-free days and 90-day mortality. [4]

The ROSE trial was conducted to evaluate the use of Neuromuscular blockade in patients with moderate to severe ARDS. The trial involved early continuous infusion of cistatracurium for the intervention group, while patients in the control group received a lighter sedation target. During the course of the neuromuscular blockade, there was evidence that at 48 hours it reduced barotrauma rates and provided more oxygenation without increasing ICU-associated muscle weakness. The finding that NMB has been effective in a specific group of patients who require more sedative assistance may have contributed to this outcome.[5]

4. High frequency oscillatory ventilation (HFOV)

High-frequency oscillatory ventilation (HFOV), a type of mechanical ventilation, employs supraphysiological frequencies to deliver modest tidal volumes with minimal phase pressure variation. Despite being conducted in two major randomized controlled trials for acute respiratory distress syndrome in adults, the physiological benefits were not translated into clinical benefits for ARDS. The in-hospital mortality rate of HFOV was found to be higher than that of the control group, therefore, the OSCILLATE experiment with 548 patients was concluded and terminated early. [6] In the OSCAR trial with 795 patients, there was no difference in 30-day mortality. There were notable differences in conventional mechanical ventilation when it came to 30-day mortality or in-hospital mortality. The use of HFOV leads to more negative effects, including the need for additional sedatives and vasopressors. [7]

5. Non-invasive Ventilation

NIV is a crucial method for treating hypercapnic respiratory failure, but there is still controversy surrounding its utilization in treating ARDS and acute hypoxic respiratory failure. However, it remains controversial. The aim of NIV is to avoid intubation and its consequences in individuals with ARDS and other respiratory failure. In the past few years, Noninvasive ventilation has been increasingly used to treat acute respiratory failure, with a notable decrease in complications caused by intubation and invasive mechanical ventilation. This also has the potential to decrease mortality rates in those with acute or chronic respiratory failure. [8]

6. Extracorporeal Membranous Oxygenation

A revised cardiopulmonary bypass circuit, extracorporeal membranous oxygenation is utilized to facilitate gas exchange and fluid delivery in cases of unresponsiveness to ventilation therapy, ultimately saving the patient's life. By decreasing the need for high airway pressure, the lungs can be restrained and the effects of high atmospheric pressure are prevented. [9]

In patients with refractory ARDS, the risk of ECMO-related complications may include coagulopathy, infection and hypoxia, as well as other conditions such as ischemia or multiorgan failure. ECMO was found to reduce the mortality of 28 and 90 days in patients compared to those in the mechanical ventilation group through a meta-analysis of 12 studies conducted by Shrestha DB et al. The results were significant. In addition, the ECMO group demonstrated that they had to spend more time in the ICU. [10]

Futuristic direction and Latest Pharmacological interventions for treatment of ARDS

Mesenchymal Stromal Cell

A novel approach to treating ARDS can be employed with mesenchymal stromal cells. The immunomodulatory, restorative and antibacterial effects of these plastic-adherent multipotent cells are versatile; they can arise from a variety of tissues, including bone marrow or umbilical cord, or derived from the cell wall. Although 104 RCTs of ARDS and COVID-19 have been investigated, the efficacy of mesenchymal stromal cells has not been proven. The biological environment of ARDS can affect the responses of mesenchymal stromal cells, which may lead to different therapeutic pathways targeting individual patients. However, there is a growing interest in targeting multiple pathways in this disease. [11]

During a phase 1 trial of dose escalation in 2015, nine patients with moderate to severe ARDS were able to tolerate recurrent MSCs from allogeneic bone marrow in vivo. In the next phase of the study, 60 participants were included and the results were not improved by the mesenchymal stem cell treatment. Patients who received mesenchymal stem cell therapy were more susceptible to illness at the beginning of treatment, but their efficacy may have been compromised by inconsistent mesenchymal stromal cell viability. During the phase 1 study on an MSC-derived cell transplantation in moderate-severe ARDS, safety and potential immunomodulatory effects were observed.[12]

Ulinastatin

Urinary glycoprotein and protease inhibitor ulinastatin has anti-inflammatory properties, as well as antioxidant activity. Patients with ARDS (rared endatrophic syndrome) who received ulinastatin injections for 12 hours over 14 days in a modest phase 2 trial with 40 patients per group demonstrated that the dose-based trial resulted in improved lung function, oxygenation, reduced mechanical ventilation time, and shorter hospital stays. Moreover, the use of ulinastatin can result in diminished inflammatory cytokines and enhanced antioxidant activity. Several other protease inhibitors are also being tested in preclinical studies, and further phase 2 trials of ulinastatin are currently recruiting participants.

Multiple clinical studies conducted on patients with ARDS did not yield positive outcomes for their pharmacological treatments. Among the pharmaceuticals that have not yielded positive outcomes are inhaled prostaglandins, statins (such as corticosteroids), aspirin and surfactants; activated protein C (monoestrigin); and Sivelestat. Beta-2 agonists, keratinocyte growth factor, immunomodulatory therapies, interferons and other agents that target the epithelium and endothelium, are being subjected to rigorous testing with promising preclinical results.[13]

CONCLUSION

Acute Respiratory Distress Syndrome continues to be clinically and biologically a heterogeneous disorder with alarming mortality rates, pre and post pandemic Era. Management and timely intervention of ARDS holds its own significant importance.

Our patient did not show improvement in her condition on the first round of her treatment on oxygen and crystalloid infusion, inhalation therapy and hence the treatment was made more intensive and had to put her on corticosteroids as well, along with symptomatic treatment. In consideration the patient was placed in Intensive care ward of the department of Internal Medicine. Monitoring of vital parameters and body temperature continued but the general condition of the patient remained severe and signs of respiratory failure was observed.; tachypnea, orthopnea, desaturation, spasmodic cough on constant oxygenation. Thus, it was highly essential to incorporate combinations of intensive treatment and thereafter the patient's condition got stable and after few days of cardio monitoring, patient was discharged under strict outpatient supervision.

Although the field has made great progress, the mortality rate for this disease is still high. The most critical component of treating individuals with ARDS continues to be mechanical ventilation. The ventilatory therapy of ARDS requires extensive understanding of lung protective ventilation, ideal PEEP methods, modalities of breathing, and recruitment maneuvers. Although new studies are continually being published, guidelines are updated, and more information from RCTs is required for the early and late phases of ARDS, particularly severe ARDS, as the management of ARDS is constantly evolving.

Declaration by Authors

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