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Acute respiratory distress syndrome: A dreadful medical condition

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***Abstract*---**There are several medical conditions that directly or indirectly lead to pulmonary destruction or acute lung injury or Acute Respiratory Distress Syndrome e.g. Sepsis, Inhalation of harmful substances, severe pneumonia, Head, chest, or another major injury, Pancreatitis (inflammation of the pancreas), massive blood transfusions and burns. Due to some incidences involved in the etiology of ARDS and limited information about the epidemiology, recognition, management, and less significant results regarding patients with acute respiratory distress

syndrome (ARDS), shows intense research on ARDS is needed. From an earlier time, this syndrome has been given many names, including congestive atelectasis, traumatic adult respiratory distress syndrome and shock lung. Recently, the new definition of ARDS has been published, and this definition suggested severity-oriented respiratory treatment by introducing three levels of severity consistent with PaO2/FiO2 and positive end-expiratory pressure. Lung-protective ventilation is still the key to a better outcome in ARDS. ARDS is said to a selection of etiologies, carries high morbidity, mortality (10to 90%), and financial cost. This review is an attempt to compile all aspects of the management of ARDS.

***Keywords*---**Acute Lung Injury, Acute Respiratory Distress Syndrome, Sepsis, Non-hydrostatic Pulmonary Edema, Positive End-Expiratory Pressure (PEEP).

Introduction

Acute respiratory distress syndrome (ARDS) is a permeability pulmonary edema characterized by acute onset, inflammatory pulmonary infiltrates, and impaired oxygenation and describes a process of non-hydrostatic pulmonary edema and hypoxemia associated with high morbidity and mortality rate (10% to 90%)[1]. The condition of shock and sepsis can be origin a syndrome of acute respiratory failure with characteristics of non-cardiogenic pulmonary edema. Over the years, this condition has been confused with acute lung injury (ALI). In 1967, Jesu´s Villar investigated the latest achievement to this syndrome and later named it the "acute respiratory distress syndrome" (ARDS)[2]. The first acknowledged explanation of ARDS discussed with the innovation of the stethoscope; in 1821 Laennec described the disgusting pathology of the heart and lungs and described idiopathic anasarca of the lungs; pulmonary edema without heart failure in “A Treatise on Diseases of the Chest” In which they described according to their anatomical characters, and their analysis established on a new standard employing acoustic instruments[3]. Though it was not until Ashbaugh et al., 1967 that introduced the term “respiratory distress syndrome” to describe the assemblage of acute onset tachypnea, hypoxemia, diffuse pulmonary infiltrates, and loss of lung compliance characterized by high short-term mortality in adults[4]. Earlier the term "Adult" was used instead of "Acute" but in 1994 definition committee of The American-European Consensus Conference on ARDS decided that there should be a come back to the original term "acute" (rather than "adult") respiratory distress syndrome in recognition of the verity that ARDS is not limited to adults, even in the first report of the syndrome. In this report, one among the 12 patients reported was 11 yr. of age[5-6]. The terms ALI and ARDS finally achieve a harmonious definition during the American–European Consensus Conference (AECC) on ARDS in 1994 (Table-1).
The American-European Consensus Conference (AECC) defined ARDS in 1994 because the acute onset of hypoxemia (partial pressure of oxygen, arterial [PaO2]/fraction of inspired oxygen [FIO2] <200 mm Hg) with new

bilateral infiltrates in the setting of either a normal pulmonary arterial wedge pressure (PAWP ≤18 mm Hg) or the absence of suspected of left atrial hypertension when PAWP was not available[7]. In case of less severe hypoxemia (<300mm/Hg), the term Acute Lung Injury (ALI) was coined. These definitions provided important tools to recognize ARDS and ALI cases but still valued some confines also e.g. "Acute" was not appropriately defined, patients with ARDS and ALI were identified based on the magnitude of the PaO_2/FIO_2 ratio (P/F ratio) changes with the application of positive end-expiratory pressure (PEEP)[8]. In addition, the presence of new bilateral infiltrates on chest radiographs was not appreciated by providers (poor inter-observer reliability). As a result, the definitions of ARDS and ALI were redefined in 2012.The new definition (The Berlin Definition) does provide a more precise definition of "acute," gives a more granular explanation of severity, and provides better direction in assessing those patients with the mechanism of both hydrostatic and non-hydrostatic pulmonary edema[9] (Table-2).

Epidemiology

Epidemiological data is an important and necessary tool to characterize the disease and to review the severity of a health problem in a particular population, it tells about sensible information of the distribution of disease and implementation of its diagnosis and therapeutic features. In ARDS, determination of incidences was very difficult as it was alleged as a rare disease. Cross-sectional studies exhibit that patients with ARDS represent approximately 5% of hospitalized, mechanically ventilated patients, before 1972, 75 cases per 100000 population **per annum** was estimated to report in USA[10]. At diverse stages of exploration by various investigators reported few incidences of ARDS Webster et al 1983, 5 incidences out of 3102500 population[11], Lewandowski et al 89 incidences out of 3440000 population[12], Luce et. al., found 70 incidences out of 109601 population[13] describe the prevalence and incidences of rare disease. Although it was also very difficult to identify the cases as the estimation was not based on the specific definition of ARDS till 1994 and final modification in 2012 (Berlin). Many pathological conditions may progress to cause ARDS or may act as a risk factor for ARDS. (Table-3)

Etiology & pathophysiology of ARDS

There is no typical ARDS patient as it is a complex phenomenon lead by many medical conditions. There are more than 50 documented conditions associated with the development of this syndrome. The threat of developing ARDS depends on the predisposing clinical condition (i.e. some measures are more likely to progress to ARDS than others) but it also increases with the number of predisposing factors[14] many factors make the pathology of syndrome intricate and unclear, although the data on the available on ARDS recommend that lung injury is a budding condition and the pathological events of ARDS are typically described in three overlapping phases (Table-3)—an inflammatory or exudative phase, a proliferative phase, and a fibrotic phase[15-18]. These phases are further made complicated by additional factors e.g. nosocomial pneumonia and the ventilator-induced lung injury, etc.

Exudative phase

The first histopathological study was made by Bachofen and Wiebel. In this stage, they describe that the diffused alveolar damage, they were heavy, rigid, and when sectioned, do not exude fluid because of its high protein content[19] progression of first 24 hr. after symptoms recognized and were marked by significant proteinaceous content and often marked by hemorrhagic interstitial and alveolar edema with hyaline membranes. The hyaline membranes are eosinophilic containing fibrin and immunoglobulin (Figure-1).

Proliferative Phase

The proliferative phase is characterized by the organization of the exudates and by fibrosis. It occurs in the second week following the onset of respiratory breakdown. The capillary network is damaged and proliferation is apparent in many small vessels further reducing the luminal area[20]. The interstitial space becomes dilated, necrosis of type I pneumocytes and the alveolar lumen fills with leucocytes, red cells, fibrin, and cell debris. These processes result in extreme contraction or even destruction of the bronchioles and alveoli. Fibrin and cell debris are progressively replaced by collagen fibrils. The main site of fibrosis is the intra-alveolar space, but it also occurs within the interstitium[21].

Fibrotic phase

This can begin from day 10 after initiating injury. Macroscopically, the lungs have a cobblestoned character due to scarring[22]. The vascularity is disgustingly unbalanced with vessels narrowed by neointimal thickening and fibrosis. BAL confirms a noticeable decline in neutrophils and a relative accretion of lymphocytes and macrophages. Total lung collagen content may double within the first 2 weeks[23]. The fibrotic phase ends the elasticity of lungs acts as the major cause of the respiratory collapse.

Progression of ARDS

Lung injury is initiated by a specific insult but can be mediated by improper mechanical ventilation. Alveolar over swelling can generate a pro-inflammatory response which is initiated by repetitive opening and closing of alveoli as occurs through the use of inappropriately low levels of positive end-expiratory pressure (PEEP) recurrent opening/closing of alveoli can also induce structural damage to the lung[24-25], in addition, the role of cellular and humoral mediators and renin-angiotensin system (RAS) has been highlighted. The RAS is thought to contribute to the pathophysiology of ARDS by increasing vascular permeability[26].
The overall response that finally causes the narrowing of the bronchial and alveolar lumen is inflammation and mediators of the inflammatory process are neutrophils and multiple mediator cascades[27-29].

Inflammation

Inflammation starts with an increase in the production of leucocytes and the activation of inflammatory mediators like cytokines, chemokines, acute phase proteins, free radicals, complement, coagulation pathway components, and focal upregulation of adhesion molecule expression.

The neutrophils

Neutrophils origins cell damage through the fabrication of free radicals, inflammatory mediators, and proteases. This is the dominant leucocyte found both in BAL fluid and histological specimens from patients with ARDS[30] it is thought to be an important but not essential component in the production of lung injury as lung injuries were also found in neutropenic patients. Recent studies on animal models of ALI and ARDS suggested that an enzyme named neutrophil elastase is an important modulator for increasing neutrophils and damage to alveolar epithelium and progression to fibrosis.

Inflammatory mediators:

Cytokines including TNF-a, IL-1b, IL-6, and IL-8 are the most significant and most common inflammatory mediators found in BAL and plasma of ARDS petients[31]. They are produced by inflammatory cells and can promote neutrophil-endothelial adhesion, micro vascular leakage, and amplify other proinflammatory responses.

TNF-α and IL-1β

Tumor necrosis factor-α (TNF-α) and interleukin- 1β (IL-1β) are derived mainly from activated macrophages and act via specific cell membrane receptors. It is now considered that TNF-α is one of the chief mediators of shock. Similarly, IL- 1β provokes neutrophils and induces up-regulation of adhesion molecules on both leukocytes and endothelium, and induces a shock-like state in animal models[32]. In sepsis, TNF-α and IL-1β are released during the first 30–90 min after exposure to LPS and in turn activate the second level of inflammatory cascades including cytokines, lipid mediators, and reactive oxygen species, also as up-regulating cell adhesion molecules.

TGF-β

Transforming growth factor (TGF)-β regulates diverse biological activities including cell growth, cell death or apoptosis, cell differentiation, and extracellular matrix synthesis. TGF-β is believed to be a key mediator of tissue fibrosis as a consequence of extracellular matrix accumulation in pathological states such as systemic sclerosis[33]. TGF-β plays a critical role in the resolution of tissue injury in multiple organs, including the lung[34]. Following acute lung injury, TGF-β has been most thoroughly evaluated during the late phases of tissue repair, where it plays a critical role in the development of pulmonary fibrosis.

Platelet-activating factor (PAF)

Platelet-activating factor (PAF: 1-o-alkyl-2-acetyl-snglycero- 3-phosphocholine) is a low-molecular-weight phospholipid that acts via specific cell surface receptors that have been identified on numerous cells and tissues including platelets, leukocytes, and endothelial cells. This bioactive phospholipid increases vascular permeability, attracts leukocytes, and primes and triggers their secretory responses[35]. Recent studies made on the animal model suggested that control mice died rapidly, after developing inflammation, pulmonary edema, and impaired oxygenation. The response was amplified in animals that over-expressed the PAF receptor. Conversely, animals that lacked a PAF receptor didn't die during the experiment and had far better oxygenation and tiny edema. These findings demonstrate the importance of the PAF receptor in the pathogenesis of acute lung injury and constitute a smoking gun that implicates PAF or PAF-like compounds in this process[36].

Substance P

Substance P is an 11-amino acid neuropeptide that's released from nerve endings in many tissues. It acts via membrane-bound NK1 receptors (NK1R) and in addition to being a mediator of pain, has been shown to play an important role in inflammatory states such as asthma, immune complex-mediated lung injury, experimental arthritis, and inflammatory bowel disease[37]. Recent research has shown that inflammatory mediators play a key role within the pathogenesis of ARDS.

Diagnosis

The diagnosis of ARDS is clinically difficult because of nonspecific features of this condition. High-lighting the complexity of ARDS diagnosis, Ferguson et al recognized that only 48% of patients with autopsy-proven ARDS had a diagnosis of ARDS. They found the accuracy of the portable chest radiograph to detect pulmonary abnormalities consistent with ARDS is significantly limited[35]. Identification of the extravascular lung water index (EVLWI) and the pulmonary vascular permeability index (PVPI)[38] using a trans pulmonary thermo dilution method likely to be a useful diagnostic tool for ARDS in patients with hypoxemic respiratory failure and radiologic infiltrates. Similar conditions like ARDS include cardiogenic pulmonary edema, acute eosinophilic pneumonia, acute interstitial pneumonitis, cryptogenic organizing pneumonia, and diffuse alveolar hemorrhage which may lead to a confusing diagnosis of ARDS. To differentiate these conditions from ARDS, a variety of diagnostic modalities are utilized, such as fine chest imaging studies, echocardiography, right-heart catheterization, and bronchoscopy. Lung biopsy has been reported to vary management in 60%–80% of select cases during which the diagnosis of ARDS remains uncertain[39-41].

Therapeutic Strategies

Therapeutic strategies for ARDS specialize in treating the underlying etiology and providing supportive care that reduces the progression of lung injury.

Our algorithm for an evidenced-based approach to ARDS is shown in the flow chart.

Flow Chart- An evidence-based approach to the management of acute lung injury and acute respiratory distress syndrome[62]. [a]If urine output > 0.5 mL/kg/hr. and mean arterial pressure > 60 mmHg with no vasopressor support. [b]Consider the utilization of ARDSNet.org positive end-expiratory pressure (PEEP) table to titrate to PEEP upwards until plateau pressure reaches 30 mmHg, or use stress index to titrate PEEP. [c]May require transfer to a tertiary care facility. Abbreviations: ARDS, acute respiratory distress syndrome; CVP, central venous pressure; ECMO: extracorporeal membrane oxygenation; HFV, high-frequency ventilation kg(kilogram);mL(milliliter).

Mechanical ventilation

Most patients with ARDS face respiratory failure and require mechanical ventilator support. Even though often a life-saving intrusion, respiratory support with a mechanical ventilator can also develop lung injury as ARDS is not a homogeneous process[42]. A précised amount of tidal volume during mechanical ventilation is delivered to more compliant, less injured regions (the so-called baby lung), and causing overstretching injury to previously functional lung[43] thus it is one of the most important tools for management of ARDS but same time it should be chosen with précised measures.

Low tidal–volume ventilation

Preclinical animal experiments suggested that using low-tidal volumes to ventilate injured lungs minimized lung injury. However, the advantages of this approach were not exposed until the first ARDS Net trial ("ARMA") was done, compared a low tidal–volume (goal 6 mL/kg of ideal body weight) and low plateau–pressure (30 cm H_2O) strategy instead of "conventional" tidal–volume and plateau–pressure (12 mL/kg per ideal body weight, 50 cm H_2O) strategy in 861 ARDS patients[44]. Patients randomized to low tidal volumes/plateau pressures experienced lower 28-day mortality (31.0% versus 38.8%; P = 0.007)[45]. These results recommended the benefits of low tidal–volume.

Positive end-expiratory pressure

one more approach for reducing injury during mechanical ventilation is the application of PEEP, which is used to trim down lung crumples at end-expiration and improve oxygenation[46-47] In a study author found decreased mortality in patients with moderate-severe ARDS (PaO_2/FiO_2, 200) who received high PEEP strategies (34.1% versus 39.1%; relative risk [RR] 0.90 [95% CI, 0.81–1.00], P = 0.049) and a trend towards increased hospital mortality in patients with mild ARDS (PaO2/FiO2 200–300) receiving high-PEEP strategies (27.2% versus 19.4%; RR 1.37, 95% CI, 0.98–1.92; P = 0.07) but there is no method which can describe how to select the optimal PEEP level that assists in lung conscription without causing lung over distention. Many approaches have been published, including the use of a PEEP-and-FiO_2[48].

High-frequency ventilation

High-frequency aeration takes the idea of low tidal–volume, open-lung ventilation to an extreme, using eminent continuous airway pressure (20–40 cm H_2O) and reduced tidal volumes at very high frequencies (3–7 Hz)[49] to oxygenate and ventilate lungs during convective gas motion[50].

Non-mechanical ventilator adjunctive therapies

Prone positioning

Repositioning to a prone position mediates lung compression from mediastinal and abdominal structures. It redistributes lung edema to fewer perfused areas (enhancing oxygenation) and reduces injurious trans-pulmonary pressures. In addition, the prone position enhances postural lung drainage and reduces the prevalence of ventilator-associated pneumonia[51].

Inhaled pulmonary vasodilator therapy

Pulmonary vasodilators (e.g. nitric oxide, prostacyclin's) are anticipated to encourage vasodilation of the pulmonary vasculature in ventilated lung to improve pulmonary-hypertension, ventilation-perfusion matching, and oxygen¬ation[52] although pulmonary vasodilators act an important role in the execution of ARDS management despite that inhaled vasodilator trials have failed to show a mortality advantage, they are a key tool in managing ARDS as they increase bronchio-alveolar lumen and reduces the hypoxemic breathing. More précised knowledge of vasodilators may act as a revolutionary discovery in the management of ARDS.

Extracorporeal membrane oxygenation (ECMO)

The method of ECMO for severe ARDS involves redirecting blood outside the body to external "lung" membranes that function to oxygenate and remove CO2 from the blood. ECMO takes the main gas-exchange function in the patient with severely damaged lungs to allow "lung rest" and avoid further chances of ventilated acute lung injury (VALI). Initiation of ECMO involves anticoagulation and therefore the surgical placement of 1 or two large-bore (21–30 Fr.) catheters that pump blood through the "lung" membranes. Early ECMO trials failed to show mortality benefit in the treatment of ARDS[53].

Corticosteroid therapy

Because inflammation is thought to be the main event of lung injury, there has been considerable interest in using anti-inflammatory medications to treat ARDS. But, trials of anti-inflammatory drugs have failed to show a significant gain. The most studied anti-inflammatory medication in the treatment of ARDS is corticosteroids, which requires more detailed dialogue. Pre-conducted trials of short-burst (e.g. 24–48 hours), high-dose corticosteroids (e.g. methylprednisolone 30 mg/kg every 6 hours) showed that corticosteroids neither reduced ARDS incidence (OR 1.55, 95% CI 0.58–4.05)[54] nor mortality (OR 0.75 [95% CI 0.41–

1.57])[55].

Fluid management

Intravenous fluid management is a significant module of the management of critically ill patients with acute respiratory failure. Fluid therapy aims to sustain intravascular volume and perfusion to critical organs in the setting of imperfect gastrointestinal intake and often compromised renal function and other fluid homeostatic mechanisms. Intravenous fluid management in patients with acute lung injury and acute respiratory distress syndrome (ALI/ARDS) can be particularly challenging. While ARDS is defined by the charisma of “noncardiogenic” pulmonary edema, 30% of patients recognized clinically as having ARDS have pulmonary artery occlusion pressures greater than 18 mmHg. Even in patients without elevated cardiac filling pressure, reducing hydrostatic forces has the potential to enhance ARDS outcomes. The ARDS Net Fluid and Catheter Treatment Trial investigated the effect of fluid management and hemodynamic monitoring strategies[56].

Future

There are plenty of opportunities to continue to improve our understanding of ARDS. This includes the development of more specialized and more specific parameters to diagnoses, more précised therapeutic strategies and methods to reliably identify ARDS in enhanced administrative databases, determination of factors associated with the large variation in the incidence of ARDS. In addition, only a minority of ARDS patients currently receive evidence-based lung-protective ventilation strategies[57-61]. Improvement in low tidal volume shows positive aspects in the management of ARDS thus is a major concern for clinical trials and researchers. More appropriate use of mechanical ventilation, Anti-inflammatory mediators, and non-pulmonary measures are needed to be enhanced and upgraded for better results. Thus, studies that evaluate existing medications with potentially beneficial anti-inflammatory side effects – like the cholesterol-lowering "statins" (NCT00979121), macrolide antibiotics 80, and aspirin (NCT01504867) – may find novel treatments for ARDS. Lastly, continued identification of specific ARDS phenotypes that may benefit from certain treatment strategies (e.g. high PEEP) may enhance our understanding of the pathophysiology of ARDS.

Conclusion

The past quarter-century has seen significant progress in our understanding of ARDS. The difficult task of establishing a consensus definition for a syndrome with multiple precipitants allowed for a coordinated clinical study that ultimately resulted in a therapeutic approach that improves mortality. Lung-protective ventilation strategies that limit further lung injury, reduce the systemic release of inflammatory mediators and attenuate multiorgan system failure currently represent the standard of care for ARDS. However, our understanding of ARDS epidemiology contains large knowledge gaps, mortality remains unacceptably high, and additional treatments are sorely

needed. Clinical epidemiologists will undoubtedly still play an outsized role in enhancing the care of patients with ARDS.

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