Review Article

Acute respiratory distress syndrome : a tale of the sinking lungs

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Acute Respiratory distress syndrome (ARDS) is the most devastating inflammatory lung condition associated with high mortality. ARDS is triggered by injury to the alveolo-capillary membrane from a variety of insults resulting in fluid accumulation and acute respiratory failure. To date only two modalities of treatment-mechanical ventilation and extracorporeal membrane oxygenation (ECMO) have been shown to reduce mortalities in patients of ARDS.

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A Catch In Breath

Acute respiratory distress syndrome is a story of failing lungs with an escalating dyspnea, hypoxemia and uncalled for pulmonary infiltrates secondary to an array of medical and surgical disorders. Sailing down its primary description way back in 1967, a clear progress has been made in the understanding of its patho-physiology[1-4]. ARDS is a multifaceted syndrome with a wide clinicopathological phenotype, making it difficult to translate its understandings from the experimental models to the real subjects. The American- European consensus conference witnessed a simplified criteria consisting of bilateral radiographical opacities, presenting with hypoxemia, reflected by a PaO2/FiO2 ratio of less than 200 and 300 being defined as ARDS and acute lung injury (ALI), respectively[5]. This definition was accepted far and wide, but few researchers were of the opinion that this definition should clarify the level of positive end expiratory pressure(PEEP) and FiO2.The ARDS definition task force, developed the Berlin depiction which advocates the application of 3 categories of ARDS based on the degree of hypoxemia[6] (Table 1).

Table 1 — *The diagnostic criteria of ARDS*

Oxygenation-severity	Onset	Pulmonary radiography	No left arterial hypertension
(1) Mild: 200 mmHg < Pao2/Fio2 ≤300mmHg *(2) Moderate:* 100 mmHg < Pao2/Fio2 ≤200 mmHg *(3) Severe:* Pao2/Fio2 ≤100 mmHg	Within 1 week of clinical injury or a deteriorating respiratory symptoms	Bilateral opacities consistent with pulmonary oedema, but which cannot be explained by lobar pneumonia, pleural effusion, or nodes	Respiratory failure is not due to hydrostatic oedema.

A Badly Inflicted Trauma :

Prior researchers were confined to mechanically ventilated patients of ALI/ARDS, but newer advances have been targeting the diagnosis of these entities in the spontaneously breathing patients[7,8] allowing the sidelining and bombarding the patients with treating methodologies which might be in the need of ventilator support.The ARDS can be caused by direct pulmonary affliction or by an indirect lung injury. Pneumonia of bacterial or viral etiology, aspiration, trauma, shock or near drowning pushes the patient towards this treacherous lung injury. Table 2 enumerates the common causes of acute respiratory distress syndrome.

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ARDS : See You at the ICU :

The yearly frequency of ARDS is estimated to be as high as 60/100,000 population. Approximately 10% of all intensive careunit (ICU) admissions involve patients with ARDS. The children are involved in ARDS with a fumingly high frequency[9,10]. Fortunately with an increased lung salvaging ventilatory support, lesser nosocomial infections and a guideline based use of blood products, there has

Table 2 — *Common conditions associated with Acute respiratory distress syndrome*

Direct Lung affliction	Indirect lung affliction
Bacterial and Viral pneumonia, Aspiration,lung contusion Near drowning Toxic inhalational injury	Sepsis,Trauma, Multiple transfusions, Drug overdose, Pancreatitis, Post cardiopulmonary bypass

been a slight downward deflection of its incidence[11,12]. Co-morbidities including a dysfunctional liver or kidney function, shock, older individuals above 60 years, or PaO2/FiO2<100 are said to boast a shoddier outcomes[13-16]. A newer network clinical trial has delineated a 60 day morality of less than a quarter of adult patients despite of a bad APACHE score.

Smoke and Drinks :

Studies have focused on the genetic and ecological factors which might help the propensity and sternness of ARDS. Smokers, defined by the plasma levels of nicotine, have been autonomously earmarked to be susceptible to the development of ARDS after a severe blunt trauma. The stylish cigarette disfigures the lung alveolar endothelium and invites the inflammatory cells[17-19]. Similarly the alcohol is the found to increase the risk of lung injury.

It's in the Genes :

Like many other diseases the ARDS has been found to be influenced by the altercation in 25 genes[20]. Most of the criminal genes are those which are normally involved in lung damage and repair, and those regulating coagulation, inflammation, apoptosis and playing with reacting oxygen species[21-25]. Despite of this captivating connection, the alleged causal genes require more substantiation, before adjudging them for this heinous link. One such intriguing study has identified PPFIA1 (encodes liprin alpha, which is involved in cell-matrix interaction) as a predictor of ARDS after a major lung trauma.

Clinical Journey :

The natural history of ARDS is earmarked by three basic phases, each having distinguishing pathological and clinical features.

Exudative Phase : Sinking Boat in a Muddy Island :

This phase is defined by injury to the Type I pneumocytes and alveolar capillary endothelium with consequential trouncing of the tight barrier which was there for the macromolecules and fluids. This loss allows the fluid rich in protein, to make home in the alveolar and interstitial spaces. The cytokines that ignite the inflammation (IL-1, IL-8, TNF-α) and the leukotriene B4, proliferate in this phase and are finely tuned to recruit the leukocytes into the lung interstitium and alveolus[26-31] (Fig 1). Fresh studies have concludedthat molecular proceedings that oversee the balance between angiotensin converting enzymes 1 and 2, may control the degree of inflammatory lung injury following a viral infection and sepsis[32,33]. Likewise, recently acknowledged lipid modifications may contribute to healing of lung inflammation[34].

Wrecked Airways :

Apart from this, the conglomerated plasma proteins in the alveoli along with cellular waste and surfactants form the hyaline membrane whorls. The lungs are also prone to the injury due to an early vascular annihilation by the microthrombus and the cellular fibrous proliferation[35-41]. Edema ensues in the basal or depending areas of the lungs leading to a diminished air entry or even collapse which further compromises the lung compliance. The inadvertent hypoxemia develops resulting in inevitable dyspnea. The altercation in the alveolar spaces are further downplayed by the microvascular occlusion that kills the pulmonary arterial flow of blood and expands the pulmonary dead space which results in hypercapnia in addition to hypoxemia. This phase displays its effects within 12-36 hours of initial insult and lasts for 1 week after the exposure to the precipitant. Hunger for air generates dyspnea and tachypnea frequently culminating in respiratory fatigue and failure. The investigative values represents nothing but the underlying clinical entity but the chest roentgenogram displays bilateral opacities involving at

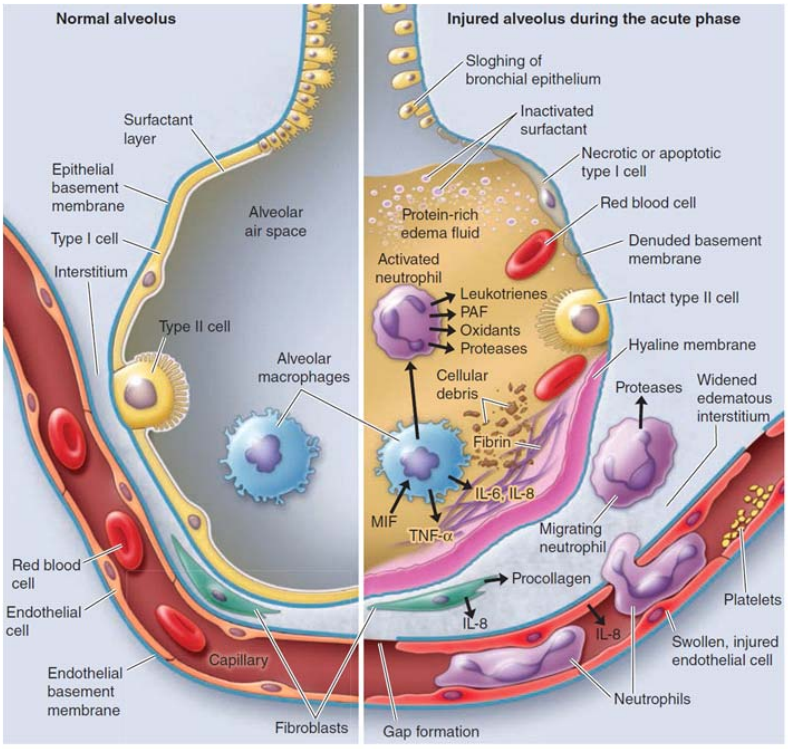

Fig 1 — Injured Alveolus in Acute Lung Injury

least 75% of lung fields, consistent with pulmonary edema but indistinguishable from cardiogenic cause of pulmonary edema (Fig 2). A film devoid of the features of pleural effusion, cardiomegaly and pulmonary vascular redeployment, disagree with the cardiogenic nature, still, a thorough cardiac evaluation is mandated to exclude hydrostatic-cardiac edema. A chest CT could further consolidate the findings of X-ray in demonstrating the heterogeneous pulmonary infiltration. Despite of the meticulous imaging, the cardiogenic, pneumonic infiltrates should be kept in differentials along with alveolar hemorrhage. Not as much universally, the acute interistitial pneumonitis, hypersensitivity pneumonitis, radiational or other toxic injury and neurogenic pulmonary oedema also seek some consideration.

Proliferative Phase :

Starting at the end of 1 week it lasts for up to 3 weeks, it witnesses the recovery and ex-tubation from mechanical ventilation. Histological resolution manifests in this phase with stitching up of lungs by reorganization of alveolar exudates and exchange of lymphocytic infiltrate in place of neutrophilic infiltratres. The basement membrane harness the type II pneumocytes which synthesize the surfactant afresh and further differentiate into type I pneumocytes. Notwithstanding this improvement, many patients still come across the symptoms of dyspnea, hypoxemia and tachypnea. Some even progress to deteriorating lung injury and premonitory changes of pulmonary fibrosis.

Fibrotic Phase :

Apart from the several patients who recover within 3-4 weeks after the primary pulmonary injury, some slip into a redundant fibrotic phase that may mandate a long term supplemental oxygen or mechanical ventilatory support.

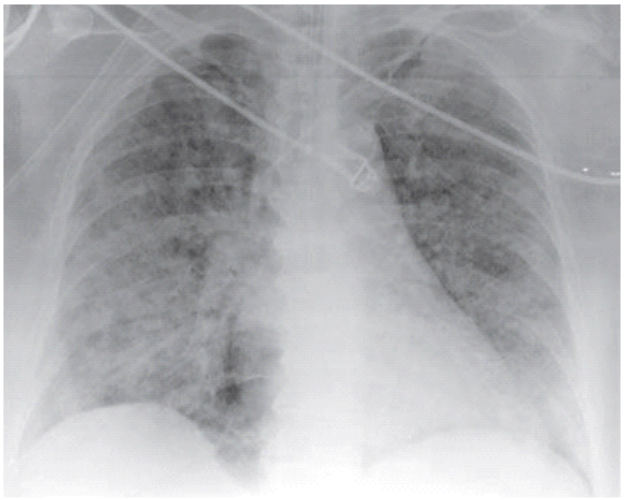

Fig 2 — X-ray in the Exudative phase of ARDS

The edema that accumulated during the exudative phase materializes to fibrosing structures in the alveoli and interstitium. The disrupted acinar construction paves way for the emphysematous changes some coalescing to form bullous lesions. The microvascular structures endure intimal proliferation which moves on to occlude them and aggravate the pulmonary hypertension. These changes could manifest as a fallen lung compliance, increased pulmonary dead space and pneumothorax. This reinstalls the burden of morbidity and mortality.

The Remedy :

The management of the patients with ARDS needs general care before jumping into targeted therapy. Treatment of the primordial causative factor is imperative with minimal use of unwanted procedures that might be associated with complications of their own soil. Blanket care from thrombo-embolic phenomenon, aspiration, excessive sedation, unnecessary long-drawn-out mechanical ventilation, central or peripheral venous catheter site infection goes without mention but holds immeasurable significance. A nosocomial infection should be caught soon keeping in mind the nutritive requirement of the patient.

Lungs Need Air not a Blower :

Fatigue from an escalated work of breathing necessitates the deployment of mechanical ventilation. This artificial breathe of life, despite of being the savior can predispose the patient to "volutrauma" and "atelecrauma" resulting from alveolar over distension and collapse respectively. The compliance differs in the inhomogenously involved lung fields; the use of higher tidal volume could over distend and injure the normal areas of lung. The large scale trial by the ARDS network compared 6ml/kg tidal volume versus the regular 12ml/kg and demonstrated significantly lower mortality rates in patients with low tidal volumes[42-46].

Comply with the Compliance :

ARDS is a condition of reduced pulmonary compliance secondary to the loss of surfactant along with alveolar and interstitial infiltration. The end of expiration in the background of decreased end-expiratory pressure can lead to noteworthy alveolar collapse and compromised oxygenation. In a good numberof clinical establishments, positive end-expiratory pressure is attuned to curtail FiO2 and provide adequate PaO2 without leading to alveolar over-distention. At present, there is noaccord on the most favorable method to set PEEP, because numerous trials have proven to beproving nothing. In anticipation of more consolidated data, the clinicians use the sensible approach of empirically measuring the bedside optimum PEEP which

would depress the alveolar distension and provide ample PaO2 while minimizing FiO2.

Priority to the Prone :

More than a few preceding trials have established that mechanical ventilation in the prone position enhanced arterial oxygenation without a mortality benefit, a new trial confirmed statistically significant fall in mortality with lying face down in patients with severe ARDS. *Recruitment maneuvers* that fleetingly increase PEEP to elevated level can boost oxygenation, but a mortality advantage could not be seen. Newer modalities of ventilation such as high frequency oscillatory ventilation and airway pressure release ventilation have been found to be no better than the conventional forms. Artificial lung replacement therapy with extra corporeal membrane oxygenation has shown some ray of hope in improving the mortality of the patients.

Keep the Heart Pressure Free :

A balanced left atrial filling pressure keeps a check on the pulmonary edema and walls off the further fall in compliance and arterial oxygenation; this not only improves pulmonary dynamics but also cuts down the duration of hospital stay. This advocates the aggressive reduction in left atrial pressure by the apt use of diuretics and restricting the fluid intake. To protect the lungs during ventilation, a synchrony needs to be established between the ventilator and the patient, which could be achieved not only by use of appropriate sedatives but also by coupling it with a rightly administered neuromuscular blocker. Despite of innumerable researches the current evidences fail to find any benefit of routine use of glucocorticoids in the care of patients with ARDS. Similarly the trials disproved the use of surfactant replacement, ketoconazole, PGE1 (they transiently improve the oxygenation but fail to improve survival), and NSAIDs.

A whole host of clinical trials have been deployed with primary goal of modifying the clinical course of ARDS but unfortunately most have failed to do so. Although, these could be woven together to form a comprehensive evidence based recommendation an algorithm for the same is depicted in Fig 3.

The Future Perfect :

Therapies involving allogenic human MSCs have shown early promises because it has bee found to be having effect on anti-inflammatory cytokines, growth factors and antimicrobial peptides[47-52]. Statins have found a place in several trials backed by its propensity to modulate inflammation and reinstate the barrier integrity. Aspirin is in talks to extend its helping hand in preventing transfusion associated and acid induced ARDS. With ever increasing interest and commitment in fighting ARDS an array of therapeutic display is in the verge of pipeline.

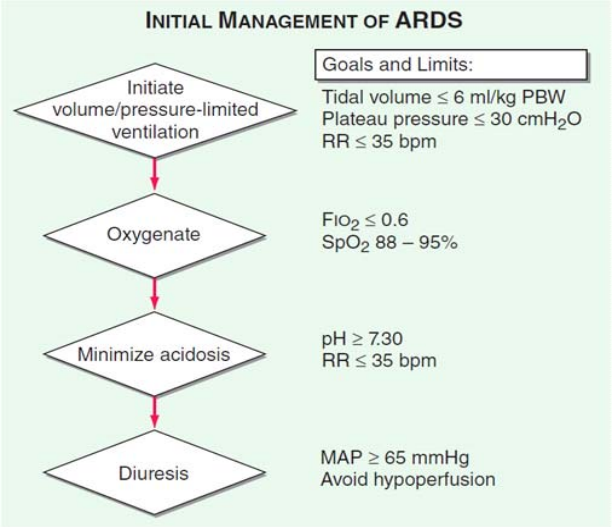

Fig 3 — Initial management of ARDS

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