INTRODUCTION

The description of acute respiratory distress syndrome (ARDS) as a distinct entity was first reported by **Ashbaugh and colleagues in 1967**, defined as a clinical pattern including "severe dyspnea, tachypnea, cyanosis that is refractory to oxygen therapy, loss of lung compliance, and diffuse alveolar infiltration seen on chest x-ray."

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are characterized by rapid-onset respiratory failure following a variety of direct and indirect insults to the parenchyma or vasculature of the lungs. ***(Raghavendran and Napolitano, 2011).***

Alveolar fibrin deposition is an important feature of ALI/ARDS and pulmonary infection. The mechanisms that contribute to disturbed alveolar fibrin turnover are localized tissue factor-mediated thrombin generation and depression of bronchoalveolar urokinase plasminogen activator-mediated fibrinolysis, caused by the increase of plasminogen activator inhibitors ***(Schultz et al., 2006).***

AIM OF THE STUDY

Assessment of urokinase activity in bronchoalveolar lavage fluid in pediatric critically ill patients with acute respiratory distress syndrome.

ACUTE LUNG INJURY AND ACUTE RESPIRATORY DISTRESS SYNDROME

Definition of ALI/ARDS:

Acute lung injury (ALI) and its more severe form, the acute respiratory distress syndrome (ARDS), are syndromes of acute respiratory failure, which was defined by radiological (bilateral lung field infiltrates) and physiological (The ratio of arterial oxygen pressure and the inspiratory oxygen concentration PaO2/ FiO2 <300 mmflg for ALI and <200 mmHg for ARDS) criteria in which wide spread damage to cells and structures of alveolar capillary membrane occurs within hours to days ***(Luh and Chiang, 2007).***

History

ARDS was first described in 12 patients in 1967 by ***Ashbaugh et al. (1967),*** and characterized by acute respiratory distress, cyanosis refractory to oxygen, decreased pulmonary compliance, and diffuse alveolar infiltrates on chest radiograph. Due to the lack of specific criteria used to identify cases, an expanded definition was developed in 1988 by ***Murray et al (1988)*** that quantified the degree of disease

by means of a scoring system based on physiologic measures, radiographic features, and clinical cause. In 1994, the American European Consensus Conference of ARDS developed uniform definitions to improve the standardization of patient care, clinical research, and trials of potential therapies for the disease ***(Jama J. 2012).***

The consensus definition characterizes the illness as: developing with an acute onset; a PaO2/FiO2 <300 for ALl and <200 for ARDS; bilateral infiltrates on chest radiograph; and a pulmonary artery occlusion pressure <18 mm Hg or the absence of clinical evidence of left atrial hypertension. This definition has found widespread acceptance, and has been used extensively to identify patient populations for many clinical investigations ***(Raghavendran and Napolitano, 2011).***

Table (1): The Berlin Definition of Acute Respiratory Distress Syndrome ***(Ranieri et al., 2012).***

Acute Respiratory Distress Syndrome		
Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms.	
Chest imaging	Bilateral opacities-not fully explained by effusion, lobar/lung collapse, or nodules	
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g, echocardiography) to exclude hydrostatic edema if no risk factor present.	
Oxygenation	Mild	200mm Hg $< Pao_2/Fio_2 \leq$ 300mm hg with PEEP or CPAP $\geq$5cm H_2O
	Moderate	100mm Hg $< Pao_2/Fio_2 \leq$ 200mm Hg with PEEP $\geq$5 cm H_2o
	Severe	$Pao_2/Fio_2 \leq$ 100mm Hg with PEEP $\geq$5 cm H_2o

Epidemiology of ALI/ARDS

The Incidence:

One of the first estimates of the incidence of ARDS in the United States is from a National Heart, Lung and Blood Institute workshop organized in 1976. It estimated that there are 150, 000 cases of ARDS per year in the United States, an

incidence of about 75 cases per 100, 000 persons ***(Jaime et al., 2006).***

In ***1999, Rubenfeld and colleagues*** recorded an incidence of ALI of almost 80 cases per 100, 000 population per year. In 2009, a study on pediatric patients six months to 15 years of age, the reported incidences of ALI and ARDS were 9.5 and 12.8 per 100.000 person-years, respectively, with a combined in-hospital mortality rate of 18 percent ***(Zimmerman et al., 2012)***

Mortality/Morbidity:

No age, gender, social class, or residence predilection recorded for occurrence of ALI. Mortality rates have varied between 2o-75% among several studies, but they are difficult to interpret because of inconsistent diagnostic criteria**.** ***Abdel-Gawad, et al., 2006,*** have reported a mortality rate of 71.4% in a study done on 35 pediatric patients with ALI in PICU of Ain Shams University children's hospital.

Risk factors associated with mortality:

Poor prognostic indicators were associated independently with (1) the initial severity of hypoxemia (2) the presence of non-pulmonary organ system failure,

especially with 2 or more organ systems; and (3) the presence of central nervous system dysfunction. Higher mortality rates occurred in patients with near- drowning, heart disease, and sepsis ***(Flori et al, 2005).***

Causes of acute respiratory distress syndrome

Causes of ARDS include causes of direct and indirect lung injury. Sepsis syndrome, trauma, pneumonia, and aspiration of gastric contents are found to be the common clinical conditions associated with the development of ARDS. Approximately 32% of patients with sepsis, whether the source is gram-negative or gram-positive organisms, experience ARDS. In children, 30% to two-thirds of cases originate with pneumonia and sepsis ***(Timmon et al, 2006).***

Most pediatric victims of ARDS have chronic morbid conditions, although one-third of cases occur in previously normal children. The most common predisposing condition is immune suppression. When the history and physical examination suggest infection, the workup should progress simultaneous to the resuscitation so empiric treatment is not delayed. Blood, urine, and infected *soft* tissue should be sampled ***(Timmon et al., 2006).***

A study done by ***Abdel-Gawad, et al.,*** **pneumonia** had the highest incidence as a cause of direct injury to the lung 37%, while; sepsis was the most common cause of indirect lung injury in ARDS patients 22% ***(Abdel-Gawad, et al., 2006).*** Detailed causes of direct and indirect lung injury causing ARDS are listed in **table (2).**

Table (2): Clinical disorders associated with the development of ARDS according to occurrence ***(Luh and Chiang, 2007).***

Direct Lung Injury	Indirect Lung Injury
Common causes: - Pneumonia. - Aspiration of gastric contents. **Less common causes** - Pulmonary contusion - Fat emboli - Near-drowning. - Inhalational injury - Reperfusion pulmonary edema after lung transplantation or pulmonary embolectomy.	**Common causes:** - Sepsis. - Severe trauma with shock and multiple transfusions. **Less common causes** - Cardiopulmonary bypass - Drug overdose - Acute pancreatitis - Transfusions of blood products.

Pathogenesis of ARDS:

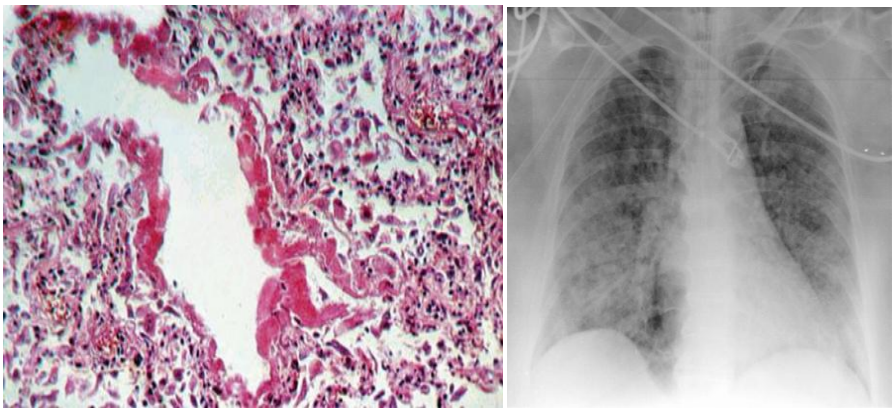
Histopathologic stages:

ARDS has generally been characterized into three stages:

I - Exudative stage:

The exudative phase starts over the first 2 to 4 days after onset of lung injury. The exudative phase occupies approximately the first week after the onset of respiratory failure. Characterized by accumulation in the alveoli of excessive fluid, protein and inflammatory cells. The parenchymal surface of the lung is hemorrhagic, with a firm, airless consistency. Unlike the picture in cardiogenic pulmonary edema, it does not exude frothy fluid ***(Castro et al, 2006).***

The influx of protein-rich edema fluid into the air spaces occurs as a consequence of increased permeability of the alveolar—capillary barrier. The importance of endothelial injury and increased vascular permeability to the formation of pulmonary edema in this disorder has been well established. Endothelial activation may occur in response to a wide range of stimuli including cytokines, thrombin, lipopolysaccharide, and other microbial products, and extreme changes in blood pressure. This phase may resolve completely or pass to next stage ***(Suratt and Paron, 2006).***



(A) (B)

Fig. (1): ARDS exudative phase (A) which involves a loss of alveolar epithelial cells and presents alveolar hyaline and neutrophil membranes. (B): A representative anteroposterior (AP) chest x-ray in the exudative phase of ARDS that shows diffuse interstitial and alveolar infiltrates, which can be difficult to distinguish from left ventricular failure.

II -Proliferative Phase:

This stage occurs 1 to 2 weeks after injury. On gross examination the lungs are densely consolidated with patchy red—brown or yellow—gray discoloration. The histologic picture is characterized by the formation of organized granulation tissue (proliferation of fibroblast and myofibroblasts admixed with scattered mononuclear inflammatory cells). Hyaline membranes are not prominent ***(Castro et al., 2006).***

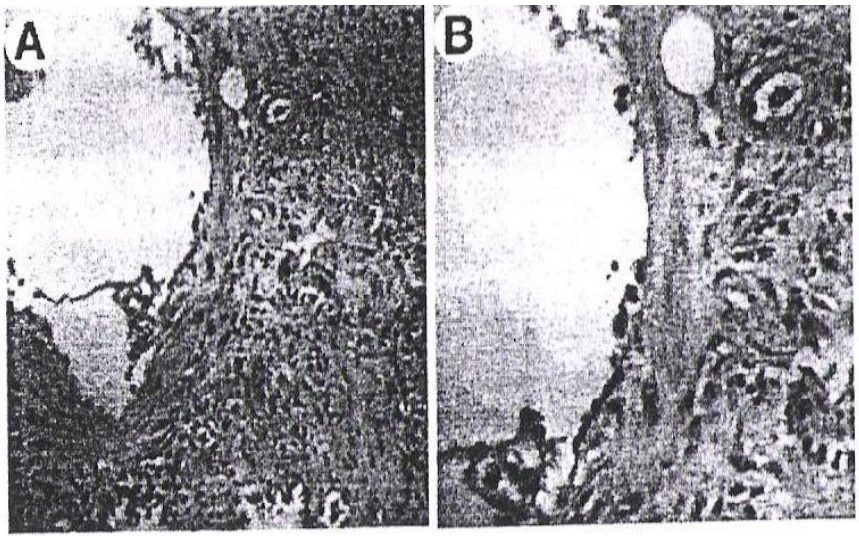


Fig. (2): Proliferative phase (A) Extensive interstitial fibroblastic proliferation (granulation tissue) producing marked thickening of the alveolar septa. (B)Thickened alveolar septa due a fibroblastic proliferation associated with hyperplastic alveolar pneumocytes ***(Castro et al., 2006).***

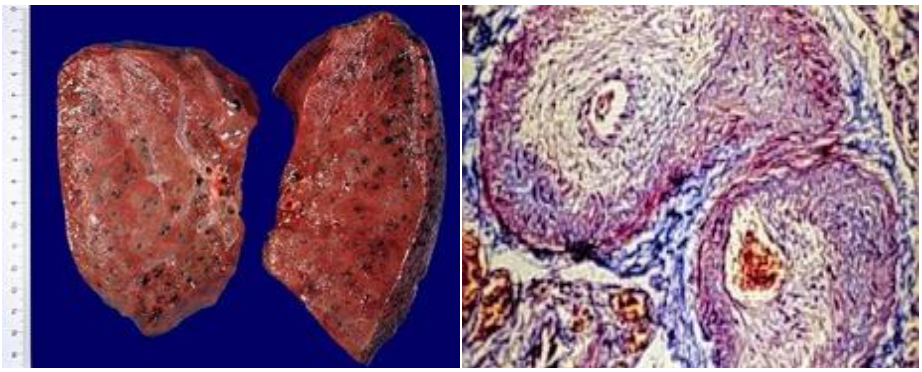
Vascular macroscopic and microscopic thromboemboli are common and are present in up to 95% of patients. Peripheral infarcts may be seen, some wedge-shaped and subpleural, others may have unusual patterns including bandlike or intermittent lobular necrosis. At the end of this phase some patients have progression to fibrotic lung injury ***(Castro et al., 2006).***

III-The Fibrotic Phase:

This phase is seen in patients after 3 to 4 weeks on ventilator. The lung is completely remodeled by granulation tissue. During this stage, the lung reorganizes and recovers.

Lung function may continue to improve for as long as 6-12 months and sometimes longer, depending on the precipitating condition and severity of the injury. It is important to remember that there are different levels of pulmonary recovery amongst individuals who suffer from ARDS. ***(Castro et al, 2006).***

The alveolar space becomes filled with mesenchymal cells and their products, along with new blood vessels. The finding of fibrosing alveolitis on histologic analysis correlates with an increased risk of death, and patients who die of the condition have a marked accumulation of collagen and fibronectin in the lung at autopsy ***(Calfee et al, 2011).***



(A) **(B)**

Fig. (3): The Fibrotic Phase (A): Image of lungs with DAD in the fibrotic stage. Dense, airless, heavy lungs that look like meat. "Carnification". (B): Lung fibrosis in ARDS

Table (3): Pathological Phases in ARDS ***(Vasudevan et al., 2004):***

Phase	Macro-scopic	Microscopic	Vasculatures
Exudative (0-7 days)	Heavy, rigid, dark lungs	• Diffuse alveolar damage • Proteinaceouse and hemorrhagic alveolar interstitial edema • Formation of hyaline membrane (eosinophilic fibrin, immunoglobulin and complement) • Neutrophilic infiltrate • Epithelial>endothelial damage	• Local thrombus
Proliferative (7-21 days)	Heavy, solid, gray lungs	• Organization of exudates/fibrosis • Interstitial spaces dilated • Necrosis of type I pnenmocytes • Appearance of fibroblasts • Extreme narrowing even obliteration of air space • Beginning of fibrosis in the intraalveolar space	• Capillary network damaged • Pulmonary hypertention
Fibrotic phase (day 10 onwards)	Cobblestone appearance due to scarring	• Relative accumulation of lymphocytes and macrophages • Fibrosis • Deranged acinar architecture • Patchy emphysematous changes	• Vasculare grossly deranged • Tortuous vessels

Resolution of ARDS:

After the acute phase of acute lung injury and the acute respiratory distress syndrome, some patients have an

uncomplicated course and rapid resolution of the disorder occur. Liquid is gradually cleared from airspaces driven water movement across the alveolar epithelium via membrane water channels. Repair of the injured lung requires an intact epithelial basal lamina which facilitates restoration of the epithelial barrier and may thus further promote clearance of edema. Lung lymph flow, a much ignored subject, may also contribute to the clearance of pulmonary edema ***(Ware et al., 2010).***

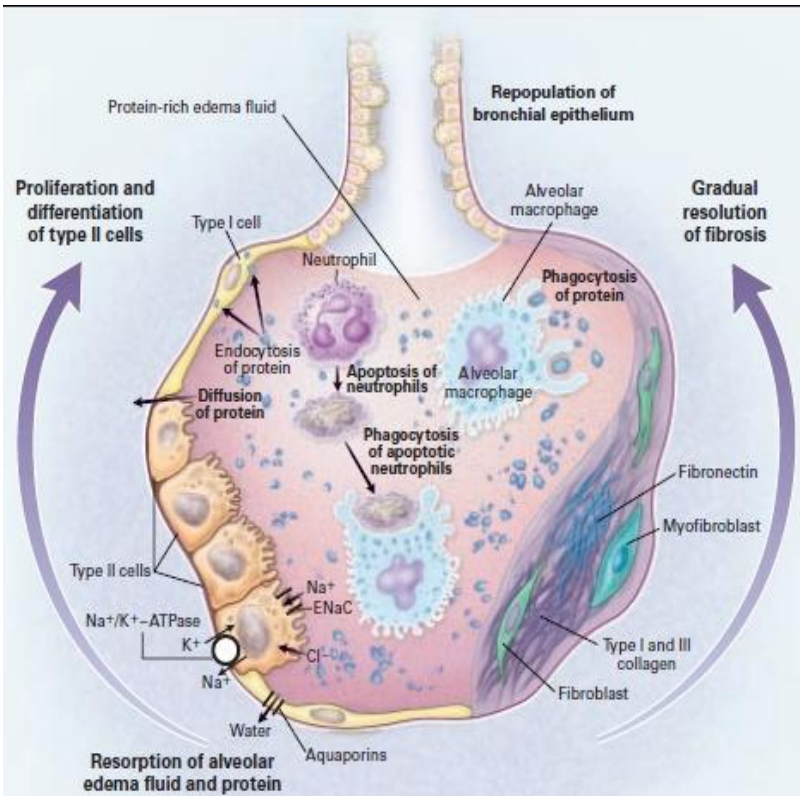


Fig. (4): Mechanisms Important in the Resolution of Acute Lung Injury and the Acute Respiratory Distress Syndrome **(Suratt and Paron, 2006).**

Clinical picture of ARDS:

In 1994, ***American—European Consensus conference (AECC)*** agreed on a set of clinical and radiologic diagnostic criteria for ARDS as the gold standard test to confirm the diagnosis. The agreed criteria include: (1) acute onset; (2) bilateral chest radiographic infiltrates; (3)a pulmonary artery occlusion pressure<18 mm Hg or no evidence of left atrial hypertension; and (4) impaired oxygenation regardless of the PEEP concentration with a PaO2/ FiO2 ratio <300 mmHg for ALI and <200 mmHg for ARDS ***(Castro et al, 2006).***

The usual way to describe the severity of pulmonary dysfunction in ventilated ICU patients is by using the PaO_2/FiO_2 ratio (PF). The PF may be adjusted by the ventilator pressure settings in order to reduce inspiratory oxygen fraction but the PF does not take the mean airway pressure (MAP) into account. As such, the OI is a better representative of oxygenation dysfunction ***(Ortize, et al. 2013)***

The **oxygenation index** is a calculation used in intensive care medicine to measure the fraction of inspired oxygen (FiO2) and its usage within the body. OI ***specifically*** takes into account mean airway pressure (MAP), which is an