Acute Lung Injury and Acute Respiratory Distress Syndrome

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Abstract. Acute lung injury and acute respiratory distress syndrome are an important challenge for pediatric intensive care units. These disorders are characterized by a significant inflammatory response to a local (pulmonary) or remote (systemic) insult resulting in injury to alveolar epithelial and endothelial barriers of the lung, acute inflammation and protein rich pulmonary edema. The reported rates in children vary from 8.5 to 16 cases / 1000 pediatric intensive care unit (PICU) admissions. The pathological features of ARDS are described as passing through three overlapping phases – an inflammatory or exudative phase (0-7 days), a proliferative phase (7-21 days) and lastly a fibrotic phase (from day 10). The treatment of ARDS rests on good supportive care and control of initiating cause. The goal of ventilating patients with ALI/ARDS should be to maintain adequate gas exchange with minimal ventilator induced lung injury. This can be achieved by use of optimum PEEP, low tidal volume and appropriate FiO_2. High frequency ventilation can improve oxygenation but does affect the outcomes. Prone positioning is a useful strategy to improve oxygenation. Pharmacological strategies have not made any significant impact on the outcomes. Preliminary data suggests some role for use of corticosteroids in non-resolving ARDS. The mortality rates have declined over the last decade chiefly due to the advances in supporting critically ill patients.
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Acute lung injury (ALI)/Acute respiratory distress syndrome (ARDS) are disorders marked by a significant inflammatory response to a local (pulmonary) or remote (systemic) insult resulting in injury to alveolar epithelial and endothelial barriers of the lung, acute inflammation and protein rich pulmonary edema. ARDS is the more severe form of ALI. These changes was first described by Ashbaugh *et al* in 1967.[1] Four decades after the first description of ARDS, clinicians are still faced with the challenge of managing children affected by this disease. Considerable advances have been made in the understanding of the pathophysiology and pathology of ARDS. Even though no specific pharmacological treatment has emerged, many support therapies have been developed which are capable of improving the outcome of patients with ARDS. However, management of ARDS continues to be team based with meticulous, multidisciplinary intensive care team approach. Our understanding of epidemiology and effect of treatment have been hampered by lack of uniform definitions and also due to the fact that patients with ARDS form an extremely heterogenous population. The availability of data on pediatric ARDS is even more limited due to lack of controlled studies in this population. Hence, many of the therapeutic strategies employed for management of

pediatric ARDS have been extrapolated or adapted from adult studies.

DEFINITIONS

Since the first description in 1967, the definition of ARDS has changed in several ways. The term "adult respiratory distress syndrome" was replaced by "acute respiratory distress syndrome" because both children and adults are affected by this serious disease. In 1988, Murray *et al* proposed an expanded definition of ARDS which included the duration of the syndrome (acute or chronic), the physiological severity of pulmonary injury and the primary insult associated with development of lung injury.[2] In 1994, in an attempt to develop a simple uniform definition that could be used to enroll patient in clinical studies, the North American European Consensus Conference (NAECC) on ARDS proposed a revised definition for acute lung injury (ALI) and ARDS (Table 1).[3] A recent review compared and contrasted the three most recent definitions of ARDS (Table 2).[4]

EPIDEMIOLOGY

The incidence of ALI and ARDS has been difficult to establish. Based on the NAECC criteria, it is estimated that ARDS has an incidence of 13.5 cases per 100,000 people and that ALI affects 17.9 of every 100,000 people.[5] A definitive study using NAECC definition has been

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TABLE 1. 1994 Consensus Conference Definitions of ALI and ARDS[3]

Onset	:	Acute and persistent
Oxygenation criteria	:	$PaO_2/FiO_2 \leq 300$ for ALI; ≤ 200 for ARDS
Radiographic criteria	:	Bilateral infiltrates
Exclusion criteria	:	Pulmonary artery occlusion pressures ≥ 18 mmHg Clinical evidence of left atrial hypertension

completed at the University of Washington and preliminary results suggest that the original NIH estimate of 75 cases of ARDS per 100,000 people per year may have been reasonable.[6]

In children, no population based data is available. However, the reported rates vary from 8.5 to 10.4 cases / 1000 pediatric intensive care unit (PICU) admission.[7,8,9] In our centre the incidence of ARDS was 16/1000 PICU admissions.[10] Patients with sepsis, severe trauma, pneumonia and multiple transfusions of blood products makes up the largest percentage of ARDS cases.[11-13] Overall, approximately 20-40% of patients with well established risk factors and respiratory failure develop ARDS, and the more risk factors in any individual, the greater the likelihood of developing ARDS[14-16] (Table 3). What is encouraging is the fact that mortality has decreased over the past decade with most series reporting 30-50% depending on underlying health status.[5,13,17,18]

PATHOLOGY AND PATHOGENESIS

ALI/ARDS are the end result of an aggressive inflammatory process and the end organ affected by the inflammatory cascade is the lungs. The reason for lungs being the target organ is not known. The pulmonary response occurs to a broad range of injuries occurring either directly to the lungs or as a consequence of injury or inflammation at other sites in the body.

Much has been learned about the pathogenesis of ARDS and central to the pathogenesis are an explosive inflammatory process and the reparative response invoked in an attempt to heal this.

Pathology

Lung injury is a dynamic condition and the pathological features of ARDS are described as passing through three overlapping phases (Table 4) – an inflammatory or exudative phase (0-7 days), a proliferative phase (7-21 days) and lastly a fibrotic phase (from day 10). The initiating insults themselves may influence the pathophysiological picture. Recent evidences suggest that there may be a considerable overlap of the inflammatory and fibroproliferative phases. N-terminal procallagen III peptide levels (marker for collagen turnover) is raised in BAL fluid within 24 hours of ventilation for ARDS.[19] Myofibroblast cells also show an early increase within 48 hours of diagnosis and is intensely mitogenic for fibroblasts. These events suggest that process of fibrosis may be switched on at a very early stage and thus offering the possibility for early directed treatment against fibrosis independent of the effects on inflammation.

Pathogenesis

There is no uniform response to injury (direct or indirect). Some develop ARDS, some ALI, and some do not develop pulmonary symptoms at all. The main players in the inflammatory process are neutrophils and multiple mediator cascades.[21] The fibroblast is key in the fibroproliferative phase and is the target of regulators of matrix deposition.[22] A complex interplay of regulatory cytokines conteracts the inflammatory mediators. Even though lung injury is triggered off by a specific insult, it can be exacerbated by inappropriate mechanical ventilatory strategies. Alveolar over-distension, repetitive opening and closing of alveoli through use of inappropriate PEEP and high FiO_2 can generate a proinflammatory response.

With initiation of inflammation, there is increased leucocyte production and rapid recruitment to the inflamed site. There is also activation of mediator cascades. The neutrophil is the dominant leucocyte which causes cell damage through production of free radicals, inflammatory mediators and proteases.[23-25] Recent animal studies suggest that enzyme neutrophil elastase may be an important mediator of damage to alveolar epithelium

TABLE 2. Comparisons of Different Definitions of ARDS

Author	Advantages	Disadvantages
Petty and Ashbaug (1971)[1]	• First description • Detailed clinical description which summarized clinical features well	• No specific criteria for identification of patients
Murray *et al* (1988)[2]	• Evaluates severity of lung injury by 4 point scoring system	• Lung injury score not predictive of outcome • Specifies cause of lung injury • No specific criteria to exclude cardiogenic pulmonary edema
NAECC (1994)[3]	• Simple criteria which are easy to apply in clinical setting • Identifies two clinical spectrum (ALI and ARDS)	• Radiographic criteria non specific • Does not specify cause

TABLE 3. Clinical Conditions Associated with Development of ALI/ARDS[19]

Direct	Indirect
Usual	**Usual**
• Pneumonia	• Sepsis
• Aspiration pneumonia	• Severe trauma
Rare	• Multiple transfusions of blood
• Inhalational injury	products
• Pulmonary contusion	**Rare**
• Near drowning	• Acute pancreatitis
• Reperfusion injury	• Drug overdose
	• DIC
	• Burns
	• Head injury

and progression to fibrosis.[26] Adhesion molecules, notably β2 integrins mediate neutrophil binding to pulmonary endothelium and also modulate activation and mediator release by neutrophils.[27] However, ARDS can develop in neutropenic patients hence neutrophils are believed to be an important but not essential component of the inflammatory response.[28]

The inflammatory process is driven in part by cytokines including TNF-α, IL-1β, IL-6 and IL-8.[29-30] They are produced by inflammatory cells and promote neutrophil-endothelial adhesion, microvascular leakages and amplification of other proinflammatory response. The other mechanisms responsible for barrier dysfunction during inflammatory phase includes production of nitric oxide, activation of platelet activating factor (PAF) and dysregulation and delayed apoptosis.[31-32]

In patients of ARDS, there is loss of normal control of pulmonary vasomotor tone due to refractory hypoxemia resulting in mild pulmonary hypertension. Increased expression of potent vasoconstrictor endothelin and

microthromboembolism may also contribute.[33]

Inflammation leads to surfactant dysfunction in ARDS.[34] There is loss of type II cells leading to decreased synthesis and recirculation of surfactant. The functional capacity of surfactants are also reduced in presence of protein rich edema. There is increase in ratio of minor phospholipids to phosphatidylcholine in lung injury. The degree to which surfactant dysfunction contributes to the pathogenesis of ARDS is currently not clear.

Alveolar type II cell proliferation and enhanced fibroproliferation are key steps in attempts at repair in the lung. The fibrotic response is stimulated by mediators like TNF-α, IL-1β which causes local fibroblasts to migrate, replicate and produce excessive connective tissue.[35] Other profibrotic factors include fibrin, thrombosis and factor Xa. Studies in animals and in humans suggest that TGF-β is important in the pathogenesis of pulmonary fibrosis.[36]

The resolution phase of ARDS has been least clearly documented. In the majority of survivors, lung mechanics fully recover suggesting that the pulmonary fibrosis in ARDS is reversible.[37] In those patients in whom fibrosis does not completely resolve, persisting pulmonary abnormalities on long term follow up have been found.

THERAPEUTIC STRATEGIES IN ARDS

ARDS has no specific pharmacological treatment. A number of support therapies based on the advances in our understanding of pathophysiology and pathogenesis of ARDS have been developed. Not all therapies have been effective in modifying the course of this condition because patient with ARDS form an extremely heterogenous population. The therapeutic strategies that may be used in ARDS are outlined in Table 5.

TABLE 4. Pathological Phases in ARDS

Phase	Macroscopic	Microscopic	Vasculature
Exudative (0-7 days)	Heavy, rigid, dark lungs	• Diffuse alveolar damage • Proteinaceous 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 pneumocytes • Appearance of fibroblasts • Extreme narrowing even obliteration of air space • Beginning of fibrosis in the intraalveolar space	• Capillary network damaged • Pulmonary hypertension
Fibrotic phase (day 10 onwards)	Cobblestone appearance due to scarring	• Relative accumulation of lymphocytes and macrophages • Fibrosis • Deranged acinar architecture • Patchy emphysematous changes	• Vasculature grossly deranged • Tortuous vessels

TABLE 5. Therapeutic Strategies in ARDS[38]

Control of causative factors (sepsis, shock, etc)
Mechanical ventilation
  • Controlled oxygen exposure (FiO_2)
  • Avoidance of volutrauma (low V_T)
  • Avoidance of atelectrauma (appropriate PEEP)
Non-conventional ventilation
  • High frequency ventilation
  • Liquid ventilation
Careful fluid administration
Drug-based therapies
  • Nitric oxide
  • Surfactant
  • Corticosteroids and other anti-inflammatory agents
Positioning (Prone ventilation)
Supportive therapy
  • Analgesia and sedation
  • Nutrition/Immunonutrition
  • Psychosocial support

TABLE 6. Risk Factors Predictive of Increased Mortality in Multivariate Analysis of Patients With ALI /ARDS[17,72,73]

• Liver dysfunction / cirrhosis
• Sepsis
• Non-pulmonary organ dysfunction
• Age
• Organ transplantation
• HIV infection
• Active malignancy
• Length of mechanical ventilation prior to ARDS
• Oxygenation index
• Mechanism of lung injury
• Right ventricular dysfunction
• $PaO_2/FiO_2 < 100$

Control of Causative Factor

The factors causing and exacerbating the disease process must be treated or controlled. Patients with infection should be treated with appropriate antibiotics. Intravascular volume expansion with crystalloids and vasopressors should be used to manage patients in shock.

Ventilatory Strategies in ARDS

Mechanical ventilation has evolved from being merely a support-therapy to a therapy which can influence the progression of the lung disease. The goal of ventilating patients with ALI/ARDS should be to maintain adequate gas exchange with minimal ventilator induced lung injury. The indications of ventilation for ARDS are based on clinical, laboratory and radiological findings. But the key is to initiate ventilation at an early stage.

The heterogeneous distribution of lung disease in patients with ARDS makes mechanical ventilation a challenge to intensive care physician. The pathological distribution of aerated lung lying over areas of dense consolidation and collapse has important implications for ventilatory management. In addition, lung pathology in ARDS is also dynamic with rapid changes in compliance occurring in matter of hours as the syndrome evolves

rapidly. Thus, application of normal physiological tidal volumes and inappropriate PEEP can lead to over distention of alveoli in aerated regions, while failing to recruit consolidated dependent regions.

Ventilator induced lung injury can occur by several mechanisms: oxygen toxicity from use of high FiO_2, over distension of alveoli leading to barotrauma; repetitive opening and closing of alveoli volutrama causing shear stress and triggering further inflammation.

The most revolutionary change in the management of children with ARDS has been adoption of concept of "lung protective" ventilation where lower tidal volume (V_T) and appropriate higher positive end-expiratory pressure (PEEP) are used.

Controlled Oxygen Exposure

High FiO_2 should be avoided to minimise the risk of direct cellular toxicity and avoid reabsorption atelectasis. Even though there is no clinical evidence to suggest a threshold value, it is preferable to decrease FiO_2 below 0.6 as soon as possible.

Carbon Dioxide

Using the 'lung protective' strategy may cause hypercapnia. It is increasingly being accepted that a mild elevation of $PaCO_2$ (permissive hypercapnia) and maintaining limits on V_T and airway pressure is associated with a significantly lower mortality from ARDS.[42] There are no data to confirm the degree of acidosis that is safe. It is probably safe to maintain a pH above 7.25 with a $PaCO_2$ of less than 80 mm Hg.[43]

Tidal Volume (V_T)

A couple of large studies have evaluated the role of lung-protective (low V_T) strategy for ARDS[5,39] which has shown an improved survival rate in patients with ARDS. However, in two other studies on patients with ARDS, low VT has failed to show any benefit.[40,41] There are no randomized trial in children to support the above view. Conducting such trials would be both difficult and probably unnecessary considering the strong physiological, experimental and clinical support. Children with ARDS should be ventilated with a low V_T of ≤ 6 ml/kg. If a child is ventilated on a pressure controlled mode, the tidal volumes should be accurately monitored.

Positive End-expiratory Pressure (PEEP)

The application of adequate levels of PEEP improves oxygenation and is associated with favourable physiological outcomes.[44,45] PEEP improves oxygenation by providing movement of fluid from the alveolar to interstitial space, recruitment of small airways and collapsed alveoli and an increase in functional residual capacity. Current clinical practice in absence of routine static PV (pressure-volume) curve measurement is to keep PEEP between 8 cm H_2O and 20 cm H_2O. PEEP

should be progressively increased by 2-3 cm H_2O increments to maintain saturation between 90 and 95% with FiO_2 < 0.5. Child should be monitored for any evidence of cardiovascular compromise and hyper-inflation. If facilities for monitoring Pressure-volume loops are available, then it is desirable to keep the PEEP above the lower inflection point.

Inspiratory Time

No clinical studies have specifically addressed inspiratory time. The I:E ratio may be increased to 1:1 or 2:1 (inverse ratio ventilation) to improve oxygenation.

Mode of Ventilation

Regardless of the ventilation mode used, no one conventional ventilation mode has been shown to be superior than the other. It is the setting rather than the mode that is important. The preferred mode is time-cycled, pressure regulated, volume controlled mode to limit peak inspiratory pressure to 30-35 cm H_2O.

Recruitment Manoeuvres

There are no randomised studies to indicate whether recruitment manoeuvres like use of sigh, CPAP or BiPAP influence outcome.

Non-conventional ventilation in ARDS

High-frequency Ventilation (HFV): There has been a resurgence of interest in HFV over the last few years but the role in pediatric respiratory failure and ARDS remains a source of debate. The advantages of HFV are (a) use of low V_T and avoidance of barotrauma and (b) maintenance of near normal $PaCO_2$ with improved minute ventilation. The two most commonly used modes are high frequency oscillatory ventilation (HFOV) and high frequency jet ventilation (HFJV). Many studies in pediatric population have shown that early initiation of HFOV is associated with better oxygenation and better outcome.[46,47,48]

Liquid Ventilation : Liquid ventilation employs perfluorocarbons which removes the air-liquid interface and supports alveoli, thus preventing the collapse. In total liquid ventilation, the entire lung is filled with liquid while in partial liquid ventilation the lung is filled so as to occupy the functional residual capacity. This treatment modality has primarily been in the realms of research and cannot be recommended as a therapeutic strategy for ARDS[49].

Fluid Administration

It is essential that adequate systemic perfusion be maintained to optimize tissue oxygen delivery. Patient in shock should be aggressively resuscitated with boluses of crystalloids or colloids. Once hemodynamic stability is achieved, fluid administration should be limited in an effort to minimize the capillary leak and control pulmonary edema.[50,51] The intravascular volume can be assessed by renal and cardiac functions and by acid-base balance.

Drug Based Therapies

The use of agents with specific physiological goals has been studied in human population with ARDS.

Nitric Oxide (NO): NO is a potent endogenous vasodilator which is administered via inhalation causing pulmonary vasodilation and decrease in pulmonary hypertension. Reduced arterial load and venous tone decreases capillary pressure, reducing leakage and thereby improving gas exchange. Maximal improvement in oxygenation is sometimes achieved with 1-2 part per million (ppm) and usually not more than 10 ppm is required in most patients. The effect can be frequently seen in less than ten minutes or may take several hours. The data from various pediatric studies suggest that NO improves short-term oxygenation in children with ARDS but little change is seen in long-term oxygenation indices.[52,53] It may be used in patients for temporary rescue where hypoxemia is refractory to conventional interventions.

Surfactant Therapy : In ARDS, there is derangement in surfactant composition with alteration in phospholipid and protein composition. Few studies have shown improvement in oxygenation after using surfactant but there are no good randomized trials in pediatric ARDS to draw any definite conclusions.[54,55] New surfactant preparations are being tested in patients with ARDS.[56] Much like other drug based therapies, surfactant may be an useful adjuvant in special situations when oxygenation cannot be achieved with conventional methods. The exact selection criteria who would benefit from this therapy remains to be seen

Corticosteriods : Corticosteroids decrease the production of a number of inflammatory and profibrotic mediators by many mechanisms. The use of corticosteriod does not prevent the develop the development of ARDS, nor is it beneficial when employed during the initial phase of the clinical course.[57,58] Two meta-analyses of randomized trials investigating a short course of high dose methylprednisolone (<48 hrs) in early sepsis and ARDS found no evidence of beneficial effects.[59,60] But in a prospective, randomized controlled trial prolonged administration of methyprednisolone in adult patients with unresolving ARDS (ARDS>7 days) was associated with improvement in lung injury and MODS scores and reduced mortality.[61] In summary, corticosteroids may be used in later stages (fibrosing alveolitis) to help in weaning of the ventilator.

*Miscellaneous Therapies:*Treatment with various vasodilator like hydralazine, prostaglandin (PGE1) and prostacyclin (PGI2) have not been shown to be beneficial.[62] The use of non-steroidal drugs with anti-inflammatory effects like indomethacin, ketoconazole, ibuprofen and lisofylline have not shown any benefit in clinical studies and hence cannot be recommended.[63] Combination therapies of almitrine (vasodilator) with NO and prone positioning have demonstrated improved

oxygenation compared to use of single therapies alone.[64] Anti IL-8 antibodies is a potential target for therapy in ARDS. Antioxidants like N-acetylcysteine and haemoxygenase are currently being studied.[65]

Prone Positioning

The use of prone positioning in ARDS was reported as early as 1974.[66] The mechanism of improvement in oxygenation is complex and varied. Changes in regional lung perfusion and in regional pleural pressures and recruitment of dorsal lung have been postulated to improve oxygenation during prone positioning. In a large study in adults, prone position was not associated with any improvement in clinical outcome.[67] Data is limited in children.[68-70] Potential risks of prone positioning are increased venous pressure in head, eye damage and increased intra abdominal pressure. Prone positioning may be used in select children with ARDS as it has few risks or cost involved.

Extracorporeal Membrane Oxygenation

Even though ECMO has proven mortality benefit in neonatal ARDS, the same cannot be said of its use in pediatric ARDS. A large retrospective study has shown that patients with highest chance of dying from their diseases had the most dramatic improvement in outcomes.[71] ECMO may be reserved for the sickest children with ARDS with severe respiratory failure.

Supportive Therapies

Children with ARDS should have a comfortable stay in PICU. Analgesics and sedation should be used to minimize their physical and mental discomfort. Total parenteral nutrition or enteral nutrition should be used to optimize nutrition to improve their defense mechanism. Immunonutrition (addition of glutamine, arginine, omega-3 fatty acids) may be useful for patients with risk of or with established ARDS.[72] Care should be taken to prevent nosocomial infections. Early diagnosis and prompt treatment of these infections are crucial to their recovery. The families of such children should be counseled and psychological support must be extended to them.

PROGNOSTIC FACTORS

Several prospective trials have identified risk factors that are independent predictors of mortality (Table 6).[17,73,74] These factors may guide clinical decision and also prognosticate to the families. Patients with ALI/ARDS with sepsis, liver disease, non-pulmonary end organ dysfunction have increased mortality. In children in whom oxygenation doesn't improve after 6 days have a poor prognosis.[4] Timmons et al identified several variable that predicted worse outcome like high oxygenation index and mean airway pressure and AaDO$_2$ > 420 mmHg.[75]

Outcome

Fewer than 5% of patients with ARDS die of respiratory failure.[76] Most of them succumb to multi organ failure. No large pediatrics review of mortality in ARDS has been published since mid-90s. In various series mortality rates have varied from 75% to 60%. In our series, the mortality rate was 75%.[10] The long term outcome among survivors of pediatric ARDS appear to be good. Ben Abraham et al found that 7 of 28 survivors who were tracked had normal pulmonary function and exercise capacity.[77]

CONCLUSION

The understanding of ARDS continue to evolve as we learn more about its epidemiology and pathophysiology. It is hoped that all RCT involving ARDS will use the NAECC definition exclusively. There are no specific pharmacological treatment of ARDS and treatment may be individualized around the mechanism of injury and clinical characteristics of each patient.

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