

ADULT RESPIRATORY DISTRESS SYNDROME IN A CHILD WITH NEPHROTIC SYNDROME

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Adult respiratory distress syndrome (ARDS), a condition which is commonly seen in adults, is now well recognized in children as well. The diagnosis of ARDS is not always easy. The outcome depends upon prompt diagnosis and appropriate management. We report a case of ARDS in a child with nephrotic syndrome who was receiving immunosuppressive therapy. The clinical criteria of ARDS were met. The aim of this study was to create an awareness of ARDS in children, and review the current status of ARDS in the literature.

Case Report

A nine-year-old girl, who was known to have idiopathic nephrotic syndrome presented with high fever and respiratory distress of two days' duration. The girl had initially presented at the age of six years with generalized edema and hypertension. Her initial investigations were compatible with idiopathic nephrotic syndrome, which was initially steroid resistant. Kidney biopsy revealed membranoproliferative glomerulonephritis. She had received steroids and cyclophosphamide in the past, and was on cyclosporin and prednisolone during this latter episode. The girl achieved had remission of proteinuria and had maintained stable renal function prior to this illness.

Our initial impression after examination was pneumonia, but 12 hours after admission, the respiratory distress increased. Breath sounds became more diminished and there were diffused inspiratory crepitations bilaterally. Chest x-ray showed bilateral infiltrations of lung fields, and there was no cardiomegaly (Figure 1). Her condition progressively deteriorated and she was transferred to the intensive care unit. Arterial blood gases revealed severe hypoxemia. Despite increasing the fraction of inspired oxygen (FiO_2), the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$ ratio) remained at 200 mm Hg. The serum creatinine at this time was $138 \mu\text{mol/L}$ and the electrolytes were normal. The

urine output was good, the jugular venous pressure was not raised, and the blood pressure was well controlled.

With the presence of diffuse bilateral pulmonary infiltrates and the poor oxygenation seen on arterial blood gases, we were confronted with various possibilities, such as cardiogenic pulmonary edema, fluid overload, and ARDS. With no evidence of fluid overload, the absence of a structural heart lesion on echocardiogram, the persistence of the above mentioned x-ray picture, and a $\text{PaO}_2/\text{FiO}_2$ ratio of 200 mm Hg, our final diagnosis was ARDS. Based on the clinical presentation, the most likely cause was sepsis, although no organism was isolated from any body culture including a bronchial aspirate for *Pneumocystis carinii*. Viral studies including cytomegalovirus titers were normal.

The mainstay of therapy in this case was mechanical ventilation with a high positive end-expiratory pressure (PEEP) to improve oxygenation. The PEEP was constantly but gradually increased depending upon her clinical condition. In our patient, the initial PEEP was 5 cm of H_2O , and it was gradually increased to a maximum of 10 cm. No barotrauma was observed. Besides ventilation, the patient received an adequate cover of IV antibiotics (cefotaxime, vancomycin and erythromycin). IV hydrocortisone was given instead of oral prednisolone to maintain her in remission. Cyclosporin was discontinued. She improved gradually over a period of four weeks, with complete resolution of pulmonary infiltrates (Figure 2). The serum creatinine at the time was $83 \mu\text{mol/L}$, and she was discharged on prednisolone on alternate days plus hydralazine, long-acting nifedipine and captopril.

Discussion

Adult respiratory distress syndrome was first reported in 1968. To date, more than 500 cases have been reported in the literature.^{1,2} A recent consensus conference sponsored by the American Thoracic Society and the European Society of Intensive Care Medicine (ATS-ESICM) recommended that "acute lung injury" (ALI) be defined as a syndrome of inflammation and increasing permeability that is associated with a constellation of clinical, radiological and physiological abnormalities that cannot be explained by, but may co-exist with, left atrial or pulmonary capillary hypertension.³ ARDS was simply

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FIGURE 1. Chest x-ray showing bilateral infiltrations of the lung fields.

FIGURE 2. Chest x-ray showing complete resolution of pulmonary infiltrates.

defined as a more severe form of ALI. Thus, ARDS is an example of a specific type of lung injury, characterized by pathologic structural changes termed “diffuse alveolar damage” that are associated with a breakdown in the barrier and gas exchange functions of the lung. The result is proteinaceous alveolar edema and severe hypoxemia—both clinical hallmarks of ARDS.

The ATS-EISCM operational criteria for the diagnosis of ARDS include the following:⁴ 1) significantly increased vascular permeability; 2) appropriate clinical setting; 3) identifiable cause or associated condition; 4) dyspnea (usually severe); 5) hypoxemia (usually refractory to supplemental oxygen); 6) Pao₂/FiO₂ ratio <200 mm Hg; 7) bilateral radiographic infiltrates (interstitial and alveolar); 8) reduced respiratory system compliance (optional); and 9) no evidence of cardiac factors as the principal cause of pulmonary edema.

A long list of agents, mediators and conditions are associated with ARDS. The causes of ARDS are categorized as “direct” or “indirect.” Table 1 depicts acute disease or injuries associated with ARDS. In 98 children (80%) the cause was known, while in 25 (20%) the cause was unknown.² In children, sepsis has been reported to cause 20% of ARDS.¹ The pathology of diffuse alveolar damage changes dynamically as ARDS evolves and resolves.^{5,6} The changes that develop are conveniently divided into three phases: exudative (days 1 to 3), proliferative (days 3 to 7) and fibrotic (after 1 week). These times, of course are approximate, and characteristic features in each phase often overlap.

The onset of ARDS is usually heralded by severe dyspnea and hypoxemia. The principal cause of hypoxemia is extensive right-to-left intra-pulmonary shunting of blood. In ARDS, a shunt may involve 25% to 50% of the cardiac output. Because blood flowing through the shunt is not exposed to alveolar gas, supplemental oxygen perse is of little value, thus accounting for the “refractory” nature of hypoxemia in ARDS.

For the therapy of ARDS, a “lung-protective” strategy⁷ has been devised. The key elements of this strategy are: 1) to recruit as many functional units as possible; 2) to maintain their patency throughout the respiratory cycles; and 4) to avoid alveolar over distension.

The main aim of all current therapies is to improve oxygenation in ARDS. Present therapies can be conveniently divided into non-pharmacological and pharmacological therapies.

Non-Pharmacological Therapies

Mechanical ventilation is initiated with a volume-cycled ventilator in the assist-control (AC) mode. Alternatively, the intermittent mandatory ventilation (IMV) mode can be used. According to Marini et al.,⁷ the initial ventilatory settings should be as follows: FiO₂: 1.0, tidal volume 10 ml/kg; PEEP 5 cm H₂O; peak inspiratory flow rate 60 l/min; and inspiratory flow pattern, decelerating waveform.

The same authors recommend two strategies for the administration of PEEP.

1. PEEP is applied in increments of 3 to 5 mm Hg (not exceeding a maximum of 15 cm of H₂O. The goal is acceptable arterial oxygenation (i.e., SaO₂ of 0.9 or greater), relatively non-toxic levels of FI O₂ (i.e., FI O₂ of 0.6 or less), acceptable airway pressures, and an improvement (or at least no reduction) in systemic oxygen delivery.
2. The alternative approach seeks to keep the end expiratory lung volume above the inflection point of the static-volume curve. In most patients, this goal is achieved with PEEP levels between 8 and 15 cm H₂O, although levels above these may be necessary in some patients.

In patients with ARDS, ventilatory rates greater than 20 to 25 breaths per minute are often required to normalize PaO₂ and PH. However, if oxygenation and FiO₂ goals are not being met and the major problem is excessive airway pressure (with or without auto PEEP), so-called controlled

TABLE 1. Acute diseases or injuries associated with ARDS

Direct mechanism of lung injury	65
Infectious pneumonia	41
Virus	24
Pneumocystis carinii	10
Other	
Non infectious	24
Near drowning	7
Aspiration	4
Pulmonary trauma	3
Smoke, CO	3
Other	7
Indirect mechanism of lung injury	33
Sepsis syndrome	16
Massive blood transfusion	4
Coma	4
Burn	3
Trauma	2
Hypovolemic shock	2
Other	2
Unknown	25

hypoventilation with permissive hypercapnia is another strategy that could be controlled.⁷ Airway pressure release ventilation (APRV) and high-frequency ventilation (HFV) are additional methods of mechanical support with the goal of recurring and stabilizing collapsed units. In a recent review, statistically significant reduction in mortality (58.8% vs. 12.5%) was seen with the early use of high-

frequency oscillatory ventilation within the 24 hours of acute hypoxic respiratory failure in pediatric patients.⁸ Tracheal gas insufflation (TGI) is a supplementary technique, especially if low ventilatory rates are being used, to improve the ventilatory efficiency of small tidal volumes delivered by conventional techniques (by washing out the "dead space").⁹ Alternatively, perfluorocarbon-associated gas exchange (i.e., partial liquid ventilation) is a technique in which the gaseous residual capacity of the lung is replaced with perfluorocarbon, and tidal breaths are delivered by a conventional ventilator.¹⁰ In a recent report, statistically significant increase of pH (7.22 vs. 7.34 $P<0.01$) and decrease of FiO_2 (82% vs. 64%, $P<0.05$) and oxygen index (23 vs. 17, $P<0.05$) occurred during three hours of partial liquid ventilation in patients with ARDS.¹¹

Two forms of extracorporeal respiratory support have been evaluated in patients with ARDS. Extracorporeal membrane oxygenation (ECMO)¹² failed to show any survival benefit when compared with conventional mechanical ventilation, although it is still used in some centers for support of the most severely affected patients with ARDS. Even though extracorporeal CO_2 removal (ECCO₂ R) is still frequently used in Europe, in the US, no survival advantage was found for an ECCO₂ R treated group of patients with ARDS.

Because lung infiltrates in ARDS can be distributed non-uniformly, positional changes can improve oxygenation at times by changing the distribution of perfusion. Indeed, despite the obvious clinical impracticality, the prone position significantly improves oxygenation in some patients with ARDS.¹³ Several clinical studies indicate that pulmonary function and outcome are better in patients who lose weight or in whom the wedge pressure falls as a result of diuresis or fluid restriction.

Pharmacological Therapies

Although the routine use of exogenous surfactant in ARDS has not yet been recommended, its replacement in ARDS might improve airspace stability and reduce atelectasis. Prospective multicenter placebo control studies have shown that patients with ARDS do not benefit from the use of high-dose corticosteroids early in the disease process.¹⁴ Ketoconazole is a potent inhibitor of thromboxane synthesis and inhibits the synthesis of leucotrienes. Two preliminary studies involving relatively small number of patients showed that ketoconazole may prevent ARDS in patients who are at risk¹⁵ (those with sepsis or multiple trauma).

It was recently reported that a combination of inhaled nitric oxide and 10 cm H₂O PEEP significantly enhanced oxygenation in patients with ARDS.¹⁶ In ARDS, inhaled nitric oxide can reduce pulmonary artery pressure and intrapulmonary shunting. It can increase $\text{PaO}_2/\text{FiO}_2$ and leave the mean arterial pressure and cardiac output unchanged.¹⁷ In yet another recent study, 21 ARDS patients secondary to trauma and/or sepsis who failed to respond to

mechanical ventilation and PEEP were treated with plasminogen activators. The basis of this treatment was that disseminated intravascular coagulation (DIC) initiates ARDS by the microcirculation with microclots. The patients responded with a significant improvement in partial pressure of oxygen in arterial blood. No bleeding occurred and clotting parameters remained normal.¹⁸ Above all, therapies for ARDS, treatment of the underlying cause is of paramount importance.

The outcome for an individual patient with ARDS is difficult to predict. For almost two decades after the first report of ARDS, the mortality remained constant at 60% to 70%. Most recent reports, however, suggest that mortality may be falling to about 40%.¹⁹ Mortality remains high among children with ARDS, particularly when serious lung conditions co-exist, when sepsis occurs and when there is multi-organ failure. Lung function improves with time among survivors, but pulmonary fibrosis may persist. More specific predictors of outcome for ARDS have been sought by measuring various serum and lung lavage factors like Von Willibrand factor antigen in serum, neutrophil-activating factor type I/inteleukin-8 in air space lavage fluid and pro collagen peptide in BAL fluid. The integrity of the epithelial barrier in relation to resolution of alveolar edema also appears to be a determinant of outcome in patients with ARDS.²⁰ Patients who can concentrate the protein in the edema fluid during the 1st 12 hours of illness (indicating an intact epithelial barrier with the ability to actively transport fluid out of the alveoli) are more likely to recover than those who cannot do so. Interventions that reduce alveolar inflammation enhance alveolar fluid removal, and reduce pulmonary fibrosis will further improve survival and recovery from ARDS in the future. The long-term functional outlook for survivors of ARDS is generally good.²¹

The aim of this report to create awareness among physicians of the possibility of ARDS. The message we would like to emphasize is that not every respiratory distress in a patient with renal impairment is due to fluid overload. A prompt diagnosis, quick institution of mechanical ventilation and treatment of the underlying cause could lead to a better outcome in ARDS, as was seen in our case.

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