REVIEW ARTICLE

Acute Respiratory Distress Syndrome

PRIYA PRABHAKARAN

From Division of Pediatric Critical Care, University of Alabama, Birmingham, AL ,USA.

Correspondence to: Priya Prabhakaran, Suite 504, ACC Building, 1600, 7th Avenue S, Birmingham, AL 35233, USA. pprabhakaran@peds.uab.edu

Background: Acute respiratory distress syndrome (ARDS) is a common diagnosis among children admitted to pediatric intensive care units. This heterogeneous disorder has numerous pulmonary and non-pulmonary causes and is associated with a significant risk of mortality. Many supportive therapies exist for ARDS.

Search: Literature search was performed by using the key words ARDS and related topics on the Pubmed search engine maintained by the National Heart, Lung, Blood Institute. Pediatric randomized controlled trials that have been published in the last 10 years were included. Emphasis was placed on pediatric literature, although sentinel adult studies have been included. Most of the evidence presented is of levels I and II.

Results: Low tidal volume is the only strategy that has consistently improved outcome in ARDS. A tidal volume of ≤6mL/kg predicted body weight should be used. Ventilator induced lung injury may result in systemic effects with multi-system organ failure, and all efforts should be made to minimize this. Positive end-expiratory pressure should be used to judiciously maintain lung recruitment. There is insufficient evidence to routinely use high frequency ventilation, prone positioning, or inhaled nitric oxide. Calfactant therapy is promising and may be considered in children with direct lung injury and ARDS. Current literature does not support routine use of corticosteroids for non-resolving ARDS.

Key words: *Acute respiratory distress syndrome, Pediatric, Surfactant, Ventilation.*

Since its description in 1967 by Ashbaugh(1), acute respiratory distress syndrome (ARDS) has been the subject of intense investigation. This heterogeneous disorder has an incidence of 8.5-16 cases/1,000 pediatric intensive care unit (PICU) admissions(2). While the outcome of pediatric ARDS has improved, the mortality rate remains high at about 22%(3).

DEFINITION

Based on the 1994 American European Consensus Criteria, ARDS is defined as (1) having acute onset (2) severe arterial hypoxemia ($PaO_2/FiO_2 \leq 200$ torr) for ARDS and <300 torr for acute lung injury (ALI), (3) bilateral radiographic infiltrates, and (4) no evidence of left atrial hypertension(4). Although the simplicity of this definition is attractive, it does not take into account the etiology or severity of ARDS, which are determinants of natural history and outcome.

ETIOLOGY AND PATHOGENESIS

Several primary pulmonary and systemic disorders injure alveolar epithelium and increase permeability of the alveolar-capillary barrier. Primary lung disorders that cause ARDS include pneumonia, aspiration, inhalation injuries, near-drowning and contusions from trauma. Sepsis, shock, burns, and pancreatitis are systemic disorders that can cause ARDS. Exudation of protein-rich fluid into alveolar spaces follows with decrease in aerated lung and lung compliance. Injury to type II pneumocytes decreases alveolar fluid clearance, impairs surfactant production and turnover. Inactivation of surfactant by alveolar fluid and inflammatory mediators exacerbates alveolar instability.

The neutrophil influx that follows amplifies the inflammation and causes systemic effects by increasing the production of cytokines such as

interleukins (IL) -1, -6, and -8, tumor necrosis factor-α (TNF-α), proteases, leukotrienes, and platelet activating factor (PAF). Several pathways involving inflammatory and anti-inflammatory pathways interact in the pathogenesis and resolution of this process.

The acute phase of ARDS is followed either by resolution of lung injury or by fibrosing alveolitis and chronic lung disease. The clinical correlate of the fibrotic phase is nonresolving ARDS beyond 7 days(5).

VENTILATION

Mechanical ventilation merely supports gas exchange while the disease process runs its course. However, mechanical ventilation can contribute to lung injury(6,7). The goal of mechanical ventilation should be to maintain adequate rather than "normal" gas exchange while minimizing lung injury. This is the premise on which permissive hypoxemia and hypercarbia are based. Adequate oxygen delivery should be maintained by optimizing cardiac output and hemoglobin concentration in addition to arterial oxygen saturation.

Non invasive Ventilation

There is a limited role for the use of non invasive ventilation (NIV) in a select population of pediatric ARDS. There are no large randomized controlled trials (RCTs) examining NIV in pediatric ARDS. NIV through face mask or helmet was used in a series of 23 immunocompromised children with ARDS. Early and sustained improvements in oxyge-nation were noted in 82% and 74%, respectively. 54.5% avoided intubation, and responders to NIV had a significantly lower mortality and shorter ICU stay than non-responders(8). NIV is more likely to be successful in avoiding the need for intubation in children with acute respiratory failure (ARF) due to hypoventilation rather than due to ventilation-perfusion (V/Q) mismatch. Higher Pediatric Risk of Mortality (PRISM) score(9), and failure of the fractional inspired concentration of oxygen (FiO2) to decrease after the initiation of NIV(10) were predictive of failure of NIV in pediatric ARF. While a short trial of NIV may be acceptable and feasible in alert, hemodynamically stable children with ARDS, improvement in gas exchange and respiratory mechanics should be monitored to avoid a delay in intubation.

Conventional Ventilation

Ventilation with large tidal volume (TV) over-distends the relatively compliant parts of the heterogeneously involved lung. This disrupts the alveolar epithelium and the capillary endothelium and promotes the release of cytokines such as IL-6, and TNF-α. Further lung inflammation and Ventilator associated lung injury (VILI) follow. The cytokine release with systemic effects at sites remote from the lung has been demonstrated in animal models of injurious ventilator strategies(11). Release of adhesion molecules by large TV(12) as well as the generation of more oxidant stress with higher TV(13) are also important factors in creating VILI and perpetuating the systemic inflammatory state. In clinical practice, multi-system organ failure (MSOF) ensues and is frequently the cause of death.

Low tidal volume ventilation (TV ≤6 mL/kg ideal body weight) is the only ventilatory strategy that has improved survival from ARDS in adults in a RCT(14). Ventilation with TV of 6 mL/kg versus 12 mL/kg (mean plateau pressure 25 cms H_20 *vs* 33 cms H_20) reduced mortality in adults with ARDS (31% versus 39.8%, *P*=0.007). Increase in number of ventilator free days (12 ± 11 *vs* 10 ± 11, *P* + 0.007) and the number of days free from non-pulmonary organ failures (15 ± 11 *vs* 12 ± 11, *P* = 0.006) were demonstrated.

A pediatric RCT on this subject is precluded because of lack of another clinical therapy that can be considered equivalent(15). Low TV ventilation has already become standard of care for pediatric ARDS. Results of trials comparing low TV ventilation to historical controls support the use of this strategy in children with ARDS and may explain the slight improvement in recent outcomes(16,17). Based on expert opinion, children with ARDS should be ventilated with the following parameters: avoiding TV ≥10 mL/kg, limiting plateau pressure to ≤ 30 cm H2O, and maintaining arterial pH 7.3-7.45, PaO2 60-80 torr (SpO2 ≥90%)(18).

Modest to severe hypercapnia often develops in the setting of ventilation with reduced TV. Hypercapnia, especially that which develops over time is well tolerated by most children(19). There is some evidence that hypercapnia should be limited to a degree that allows arterial pH to be >7.2(18). Permissive hypercapnia is contraindicated in patients with intracranial hypertension, pulmonary hypertension, and severe cardiac dysfunction.

In adult patients without ARDS who were ventilated for over 48 hours, high TV and high peak inspiratory pressure (PIP) were both significantly associated with the development of ARDS(20).This highlights the importance of lung protective ventilation in all children, regardless of the presence or absence of lung injury.

Positive end-expiratory pressure (PEEP) is an essential component of ventilation in ARDS. PEEP keeps alveoli expanded, raises the lung volume towards functional residual capacity (FRC), improves lung compliance, and decreases ventilation -perfusion (V/Q) mismatch. The best PEEP and the strategy of choosing it remain unresolved. A RCT of high (mean 13.2 ± 3.5cm H_20) versus low (mean 8.3 ± 3.2cm H_20) PEEP in adults with ARDS, all of whom were ventilated with low TV, showed no benefit in mortality, organ failures, or duration of mechanical ventilation in the high PEEP group, although the patients who received higher PEEP had improved oxygenation. The concentrations of plasma inflammatory biomarkers in the two groups were not different(21). Two subsequent RCTs in adults also showed similar results(22,23). There are no pediatric RCTs on this subject. Titrating PEEP to the best static lung compliance compatible with a plateau pressure of ≤ 28-30 cm H_2O with TV ≤ 6mL/kg may be reasonable in children.

High Frequency Oscillatory Ventilation (HFOV)

HFOV is an alternative form of ventilation characterized by very high respiratory rates (3-12 Hz) and very small TV, often less than dead space, achieving higher mean airway pressure (mPaw) at lower PIP than conventional ventilation. The theoretical advantage of HFOV in ARDS is that the lungs are kept recruited or "open" without cyclic inflation and deflation in tidal ventilation. The only RCT of HFOV in the management of pediatric RDS has not shown a mortality benefit despite improvement in oxygenation and mechanics(24). HFOV cannot be recommended for routine use in pediatric ARDS. Despite this there is a wide variation in the use HFOV in the management of pediatric ARDS(25). This modality may have a place in managing children with severe disease who require very high mPaw on conventional ventilation (>20-25 cm H_2O) and should be considered early on in the management of children with large air leaks.

PRONE POSITIONING

Prone positioning improves VQ matching and secretion clearance. Dependent lung units are better ventilated in the prone position. These have been proposed as mechanisms by which prone positioning might improve oxygenation. In a RCT on 102 children with ARDS, no benefit in mortality or duration of ventilation was demonstrated in the group that was placed prone early in the course of their illness and for a significant portion of the day (20 hours) despite the fact the patients in the prone group did show an improvement in oxygenation(26). Prone positioning was well tolerated. Similar findings were shown in 18 of 23 children with ARDS studied prospectively by Casado-Flores and colleagues(27). Prone positioning cannot be recommended routinely, but may be considered in the patient with severe ARDS and refractory hypoxemia(28).

NITRIC OXIDE

Inhaled nitric oxide (iNO) is a selective pulmonary vasodilator with minimal systemic effects. Theoretically, iNO selectively increases perfusion of ventilated lung units, reducing V/Q mismatch. A RCT on 108 children with ARF of iNO 10ppm versus conventional ventilation alone showed an improvement in oxygenation without reduced mortality in the study group. The effect was more sustained among immunocompromised children and those with entry oxygenation index (OI) >25(29). Further improvement has been shown in combination with HFOV due to better lung recruitment(30). A meta-analysis of multiple trials in adults and children with ARDS showed that iNO improves oxygenation in

patients with ARDS without changing mortality(31). There is insufficient data to support the routine use of iNO in children with ARDS.

SURFACTANT

Secondary surfactant deficiency contributes to the pathogenesis of ARDS. Additionally, in ARDS, surfactant is inactivated and its function inhibited by inflammatory mediators, plasma proteins that have exuded into the alveolar space, and cellular debris(32). This has posed some unique challenges in successful surfactant replacement therapy in adults with ARDS and potentially explains un-successful trials of surfactant in adult ARDS. These trials used synthetic, semi-synthetic or recombinant surfactant preparations(33,34). There has been speculation that surfactant may be more efficacious in patients with direct lung injury(35).

Calfactant is a modified natural surfactant whose ratio of phospholipids to apoprotein surfactant protein B (SP-B) is similar to bovine surfactant. It also resists degradation and inhibition by proteins associated with lung injury. In a RCT of intra-tracheally administered calfactant versus placebo in children with respiratory failure, the primary outcome, which was number of ventilator free days at 28 days, was not different in the two groups. The mortality rate was significantly greater in the placebo group as opposed to the treatment group (27/75 *vs* 15/77, OR 2.32, 95% CI 1.15-4.85)(36). Infants younger than 12 months in the placebo group had an almost threefold higher mortality than those in the treatment group (9/19 *vs* 23/21, $P = 0.01$)(36). However, immunocompromized children were unevenly distributed in the two groups, and there were insufficient numbers for subgroup analysis. Children with respiratory failure from direct lung injury were more likely to benefit from surfactant than those with indirect lung injury such a sepsis. There may be a role for Calfactant in children with ARDS, caused by direct lung injury. There is still uncertainty regarding the role of surfactant in pedia-tric ARDS. RCTs of Calfactant and a synthetic sur-factant Lucinactant are ongoing in children with ALI.

SURVEILLANCE AND TREATMENT OF INFECTIONS

Sepsis and pneumonia have been shown to be the cause of ALI or ARDS in 35-55% of children in different series(37) Tracheal aspirates obtained early in the illness might provide useful information to help guide the choice of antimicrobials. Furthermore, children with ARDS regardless of the cause, are prone to develop nosocomial infections, particularly ventilator associated pneumonia (VAP). While the ideal method of diagnosing VAP remains controversial, the possibility of an infection should always be considered in the event of a new fever with change/increase in secretions from the lower res-piratory tract, radiographic changes, and microbio-logic data of respiratory secretions. Non-bacterial etiologies of infection must be considered, parti-cularly in children with risk factors such as neutropenia, immune suppression, or organ/bone marrow transplant recipients. Diagnostic broncho-scopy should be considered in evaluating immune compromised children with ARDS and in immune-competent children where no cause infectious or non infectious cause for the ARDS is evident. Prompt empirical therapy based on knowledge of the local antibiogram should be instituted when an infection is suspected. De-escalation of therapy must occur as soon as feasible.

The permeability of the alveolar capillary barrier is increased in ARDS. In the presence of high central venous pressure (CVP), and pulmonary vascular pressure, the exudation of fluid into the alveolar space is increased. A prospective RCT in adults with ARDS (FACTT Trial) that compared a conservative fluid management strategy to a liberal strategy demonstrated a significant increase in the number of ventilator-free days and ICU free days in the conservative group without an increase in non-pulmonary organ failure, shock, or requirement for renal replacement therapy(38). No association has been found in children between the cumulative fluid balance and duration of mechanical ventilator weaning(39). An association has been noted between mortality and the magnitude of fluid overload in critically ill children(40). In managing the fluid status in children with ARDS, maintenance of negative fluid balance should be attempted only after any accompanying shock has resolved(41).

Hypoproteinemia decreases plasma colloid

oncotic pressure. This increases the gradient for fluid movement into the alveoli and is predictive of RDS in adults(42). In a small RCT on 37 adults with ARDS and serum protein concentration of <5 g/L, an intervention group that received albumin with furosemide was compared to a control group who received double placebo. Patients in the intervention group showed improved oxygenation, hemodyna-mics, and fluid balance. The study was not powered to detect a difference in mortality(43). Effects of combination albumin-diuretic therapy on mortality and duration of ventilation in children remain unknown.

NUTRITION

The importance of providing adequate nutrition early to critically ill children is well established. Enteral nutrition is superior to and safer than parenetral nutrition and should be used whenever possible. A RCT of the route of enteral feeding in critically ill children showed that the delivery of food into the intestine resulted in successful delivery of greater nutrition as compared to gastric delivery(44). Despite some evidence that Omega-3 fatty acid supplementation may improve outcomes in adults with ARDS(45), there is no evidence to support specific dietary modifications in children.

CORTICOSTEROIDS

The anti-inflammatory and anti-fibritoic properties of corticosteroids suggest that they might have a role in modulating the course of ARDS. The results of numerous trials that have evaluated the role of steroids in the treatment of ARDS have been largely disappointing. A recent meta-analysis of this issue in adults with ARDS suggests that the use of steroids to treat adults with ARDS may increase ventilator free days and reduce mortality(46). No RCT addressing this issue in children has been published although anecdotal reports of improvement exist. Despite complex results from many trials, available evidence argues against the routine use of steroids in ARDS given their doubtful efficacy and their potential for causing serious adverse effects such as infection and steroid myopathy.

EXTRACORPOREAL MEMBRANE OXYGENATION (ECMO)

There are no RCTs addressing this in children. In a retrospective study of children with hypoxic ARF, including some with ARDS with predicted mortality rate of 50-75%, ECMO reduced mortality(47). ECMO may be lifesaving in critically ill children with ARDS who would otherwise die. The invasive nature of this therapy and the high risk of bleeding require than this be considered only in children in whom all other therapy has failed.

PROGNOSTIC FACTORS

The mortality in children with ARDS and ALI is decreasing. In cohorts of children with ARDS from a variety of causes, mortality rates of 20% – 30% are reported. This is significantly lower than the reported mortality rates in adults, but still very high compared to the overall mortality rates of children admitted to PICUs. The initial severity of the defect in oxygenation, non-pulmonary organ failure, and the presence of neurologic dysfunction were independent predictors of mortality in a prospective evaluation of ALI and ARDS in children. Immune compromised status also correlated positively with increased mortality(3). Sepsis syndrome and multi-organ failure are common causes of death in patients with ARDS(48). Mortality is particularly high in children who have received stem cell transplants who require mechanical ventilation(49).

SUMMARY

ARDS results from a variety of pulmonary and non-pulmonary insults. The therapy of ARDS is supportive. Low tidal volume is the only therapy that has consistently shown a mortality benefit and should be implemented in all cases. Mechanical ventilation should be titrated very carefully in order to avoid VILI, and potential multi-organ dysfunction syndrome.

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