Update on Pediatric Acute Respiratory Distress Syndrome

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Summary

Pediatric acute respiratory distress syndrome (ARDS) remains an important challenge for the intensive care clinician. ARDS, which can result from either direct lung injury or from a “downstream” inflammatory process, is manifested by profound hypoxemia and respiratory failure. The care of pediatric ARDS is based on a meticulous, multidisciplinary, intensive care team approach. This review discusses the changing definition of ARDS and available intensive care treatment modalities, including newer lung-protective mechanical ventilation strategies and adjunct therapies. The prognosis of children suffering pediatric ARDS is examined with a look toward areas of potential future intervention in this often deadly disease. Key words: pediatric, respiratory, pulmonary, acute respiratory distress syndrome, ARDS.

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unified definition to a disease that has been plagued by changing and confusing terms (and, hopefully, allow more rational analysis of study data), a European-American Consensus Conference was held and the definitions of acute lung injury and ARDS were more accurately defined. A recent review of ARDS compared and contrasted the 3 most recent definitions of ARDS (Table 1).

ARDS can be thought of as the end result of an inflammatory process that can develop following a number of different clinical conditions. The end-organ affected by this inflammatory cascade is the lung, more specifically the capillary-alveolar unit. It is the destruction of this capillary-alveolar unit that ultimately leads to the pathophysiologic changes seen in ARDS. Though much has been learned about the inflammatory mediators that can lead to ARDS (ie, tumor necrosis factor [TNF], interferon-γ, lipopolysaccharide), efforts to squelch or control this cascade are still in their infancy. An excellent review of potential pharmacologic interventions for ARDS was recently published. However, though much has been learned about the inflammatory nature of ARDS, few clinically useful tools have been developed to control this cascade.

Patients with burns, massive transfusions, multiple trauma, and sepsis make up the largest percentage of ARDS cases. Sepsis is the diagnosis associated with the worse outcome in ARDS patients.

Since the first cases of ARDS were reported, intense research has focused on defining its underlying pathophysiologic and investigating multiple clinical interventions aimed at restoring cardiorespiratory homeostasis. What is reassuring to clinicians and researchers is that mortality from ARDS, once in the 80–90% range, is now 30–50% in most series, depending on the underlying health status of the patient. Thus, bench-to-bedside translation of research appears to have had a positive effect in the lives of ARDS patients. However, as we will see, a long road still lies ahead. We need to better understand the pathophysiologic underpinnings of ARDS and to develop prospective indicators of high-risk patients who are most likely to develop full-blown ARDS. Likewise, we need to harness our new understanding of the immune system and of end-organ targets such as the lungs, and to develop rational immunomodulating therapies.

Many excellent reviews of ARDS immunopathology have been published. This review will examine the treatment modalities currently available to the intensive care unit (ICU) clinician, with an emphasis on newer mechanical ventilation strategies and adjuncts to ARDS care. These modalities will be examined with an eye on the underlying pathophysiologic processes of ARDS and with a search for avenues of future investigation. What will become quite obvious is that care of the ARDS patient continues to benefit from a “team-based,” “meticulous attention to detail” ICU approach that has become the mainstay of respiratory, nursing, and medical ICU professionalism.

Ventilatory Management of Pediatric Acute Respiratory Distress Syndrome

Lung-Protective Strategies

Changes and improvements in the practice of pediatric critical care are often motivated by the thoughtful review of adult-focused studies. ARDS is a prime example of a disease that affects both children and adults, yet the majority of studies to date have been performed with adults. Obviously, this in part reflects the fact that ARDS is a more common diagnosis among adults than among children. However, it is important when utilizing or reviewing primarily adult-based studies to focus on stringent disease definitions and clinically useful outcomes. For example, when examining 28-day mortality in adult ARDS studies, one must be cognizant of the overall lower mortality among ICU-admitted children than among adults. However, some adult studies have shown dramatic changes in outcome and thus have motivated pediatric ICU (PICU) clinicians to alter their practices. The use of a lung-protective strategy is one such dramatic example.

Perhaps the most revolutionary change in the management of children suffering ARDS has been the adoption of techniques in which lower tidal volume (VT) and higher positive end-expiratory pressure (PEEP) are used to prevent ventilator-induced lung injury, while at the same time optimizing oxygen delivery. The old goal of maintaining P_{a\text{CO}_2} in the normal range at all costs has been replaced with the realization that large swings in VT can lead to more severe lung injury (caused by either volutrauma or barotrauma) as well as potentially increasing pro-inflammatory cytokines.

A number of large studies have examined the role of the lung-protective (low-VT) strategy for ARDS. Amato et al published a study in 1998 that compared conventional mechanical ventilation with a lung-protective strategy. Patients who received conventional ventilation had volume-controlled ventilation titrated so that their P_{a\text{CO}_2} was 35–38 mm Hg, whereas the patients receiving lung-protective ventilation had their VT kept at <6 mL/kg and plateau pressure kept at <20 cm H\text{2O} above the PEEP. Thus, an “optimal” PEEP was chosen. Inclusion criteria were based on the Murray lung injury score definition of ARDS.

The 28-day mortality was significantly better among the patients randomized to the lung-protective strategy and led to early termination of the study. Seventy-one percent of the conventionally treated patients had died at 28 days, compared to 38% of the lung-protective-strategy group (Fig. 1). And although there was less evidence of barotrauma in the lung-protective-strategy group, there was,
unfortunately, no difference in survival-to-discharge between the treatment groups.

Not all investigators have found such impressive results with a lung-protective strategy, though. Stewart et al performed a randomized trial comparing a low- VT strategy (< 8 mL/kg with peak inspiratory pressure limit of 30 cm H₂O) to a "routine arm" in which patients could receive VT of 10–15 mL/kg. The patient’s PEEP was titrated to keep the fraction of inspired oxygen (FIO₂) below 0.50. No attempt was made to quantify pressure-volume loops or identify the pressure-volume inflection point. The patient population was diverse and included patients considered at risk for ARDS as well as patients with pure sepsis who did not meet the consensus definition of ARDS. Stewart et al found no difference in 28-day mortality between the 120 patients randomized to the 2 trial arms. Further, the low-VT group had a higher incidence of renal failure and required neuromuscular blockade more often. However, this was a very diverse group of adult patients, and they were studied before the consensus conference definitions of ARDS and acute lung injury were introduced.

The largest study to date examining the use of a low-VT, lung-protective strategy was published in 2000 by the ARDS Network, in the New England Journal of Medicine. The study randomized patients with either acute lung injury or ARDS (based on the consensus conference definitions) to either traditional ventilation (VT of 12 mL/kg and peak pressure of < 50 cm H₂O) or a lung-protective strategy (VT of < 6 mL/kg and plateau pressure of < 30 cm H₂O). The primary outcome was mortality, and the secondary outcome was ventilator-free days. After randomizing 861 patients, the trial was terminated because there was significantly lower mortality among the patients randomized to the lung-protective strategy (31% vs 39.8%). Patients with worse lung compliance at randomization had the greatest reduction in mortality with the use of the low-VT strategy (Fig. 2). Likewise, the total number of ventilator-free days was higher among the patients randomized to the lung-protective strategy. Interestingly, a post-hoc analysis demonstrated that the low-VT patients had a lower incidence of end-organ complications of ARDS, including cardiac failure, renal failure, and disseminated intravascular coagulation.

Summary of Lung-Protective Strategies

Though each of the above outlined trials has strengths and weaknesses, the study by Amato et al has dramatically changed the basic management of ARDS patients. With good evidence that the combination of choosing an “optimal” PEEP and using lower VT can support oxygenation and improve outcome in ARDS patients, the use of a lung-

### Table 1. Definitions of the Acute Respiratory Distress Syndrome

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Definition or Criteria</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Petty and Ashbaugh</td>
<td>1971</td>
<td>Severe dyspnea, tachypnea, Cyanosis refractory to oxygen therapy, Decreased pulmonary compliance, Diffuse alveolar infiltrates on chest radiograph, Atelectasis, vascular congestion, hemorrhage, pulmonary edema, and hyaline membranes at autopsy</td>
<td>First description, Summarizes clinical features well</td>
<td>Lacks specific criteria to identify patients systematically</td>
</tr>
<tr>
<td>Murray et al</td>
<td>1988</td>
<td>Pre-existing direct or indirect lung injury, Mild-to-moderate or severe lung injury, Nonpulmonary organ dysfunction</td>
<td>Includes 4-point lung-injury scoring system, Specifies clinical cause of lung injury, Includes consideration of the presence or absence of systemic disease</td>
<td>Lung-injury score not predictive of outcome, Lacks specific criteria to exclude a diagnosis of cardiogenic pulmonary edema</td>
</tr>
<tr>
<td>Bernard et al</td>
<td>1994</td>
<td>Acute onset, Bilateral infiltrates on chest radiograph, Pulmonary-artery wedge pressure ≥ 18 mm Hg or the absence of clinical evidence of left atrial hypertension, Acute lung injury considered to be present if PₐO₂/FIₐO₂ ratio is ≥ 300, Acute respiratory distress syndrome considered to be present if PₐO₂/FIₐO₂ ratio is ≤ 200</td>
<td>Simple, easy-to-use, especially in clinical trials, Recognizes the spectrum of the clinical disorder</td>
<td>Does not specify cause, Does not consider the presence or absence of multiple-organ dysfunction, Radiographic findings not specific</td>
</tr>
</tbody>
</table>

FIO₂ = fraction of inspired oxygen

(Adapted from Reference 3.)
protective strategy makes sound clinical sense. The PICU clinician is faced with extrapolating primarily adult data for use in the PICU, but given the strength of the data, a randomized trial with children comparing traditional VT to a lung-protective strategy would be both difficult to perform and probably unnecessary. Though the search continues for helpful adjuncts and supportive tools for use in children with ARDS, it would appear that a mechanical ventilation strategy that aims for optimal alveolar recruitment through the use of PEEP and a low-VT approach will remain a mainstay for some time.

High-Frequency Oscillatory Ventilation

High-frequency (HF) ventilation for respiratory failure has been in use since the 1970s and has been studied in many human and animal trials. Though HF ventilation has a mainstream role in the treatment of neonatal respiratory distress syndrome, the role of HF in pediatric respiratory failure and ARDS remains a source of debate. The proposed advantages of HF ventilation therapies for ARDS include (1) the use of low VT, with improved lung recruitment and avoidance of alveolar shearing injury and (2) the maintenance of near-normal P\textsubscript{aCO\textsubscript{2}} with improved minute ventilation. Despite sound physiologic principles, the utility of HF ventilation in pediatric ARDS remains to be established.

As a follow-up to an earlier pilot study, Arnold et al published what is one of the most widely quoted pediatric studies of HF ventilation, in this case high-frequency oscillatory ventilation (HFOV). At 5 tertiary PICUs, patients with acute respiratory failure (ARF) were randomized to either HFOV with an “ideal lung recruitment” strategy or to a conventional ventilation arm in which the main ventilation goals were limiting F\textsubscript{IO\textsubscript{2}} and peak airway pressure while maintaining adequate oxygenation. Patients were managed with similar cardiovascular and oxygen delivery goals, and subjects were allowed to cross over to the other study arm if they met treatment failure criteria.

A total of 58 patients were enrolled, with 29 patients randomized to each treatment arm. Though the study examined pediatric respiratory failure from a variety of causes, 55% of the children met ARDS definition criteria. Those
patients randomized to the HFOV arm had an increase in mean airway pressure with time and had a statistically significant decrease (improvement) in oxygenation index with time (Fig. 3). Interestingly, those patients who were randomized to HFOV had better rank outcomes than the patients who completed conventional ventilation and those who crossed over to HFOV (Table 2). Thus, though the study was relatively small and not blinded, it would appear that early initiation of HFOV in pediatric respiratory failure is associated with better oxygenation and, more importantly, better outcome.

More recent but smaller case studies have also added to the bank of data supporting HFOV for older pediatric ARDS patients. A small series of 3 adolescents with ARDS and severe hypoxemia ($P_{aO_2}/FiO_2$ ratio < 100) were treated late in their courses with HFOV, and they all responded with dramatic improvement in oxygenation, and all the patients survived.24

Early trials of HF ventilation in adults have met with disappointing results. A series of 113 surgical patients randomized to either conventional ventilation or HF percussive ventilation failed to show any difference in oxygenation or clinical outcomes such as ventilator or ICU days.25 However, the use of percussive ventilation has been questioned because it may produce swings in lung volume very similar to traditional high-$V_T$ strategies.21 With the realization that higher $V_T$ may worsen outcome in ARDS patients (and thus the motivation for the use of the low-$V_T$ strategy), some groups have begun to readdress the use of HF forms of ventilation (specifically HFOV) for adult ARDS. A series of 17 adults with ARDS who were failing conventional mechanical ventilation were placed on HFOV with the goal of improving oxygenation.26 The patients had been on conventional ventilation for a variety of time periods (5.1 ± 4.3 d) and all had high Acute Physiology and Chronic Health Evaluation (APACHE) and ARDS scores (thus predicting a high mortality rate). Similar to Arnold’s study, the majority of these adult patients had improved oxygenation ($P_{aO_2}/FiO_2$ ratio and oxygenation index) after being placed on HFOV (Fig. 4), and the mortality rate in this high-risk group of patients was 53%. Of interest was the fact that the duration of conventional ventilation prior to initiation of HFOV was associated with a higher mortality rate, similar to the children in Arnold’s study.

Given the paucity of randomized, controlled trials of HFOV for pediatric ARDS, Arnold et al recently conducted a survey of 10 PICUs across the United States, in an attempt to clarify the current role of HFOV and examine possible correlations between HFOV and better outcome.27 From those 10 centers a total of 290 patients were identified who were treated with HFOV over an 18-month period. Patients were further subdivided according to the presence of pre-existing lung disease and their acute response to HFOV (patients were designated “acute failures” if they were on HFOV less than a total of 3 h). Patients with congenital heart disease were analyzed separately. Both patients with and without pre-existing lung disease had improved oxygenation index during the initi-

### Table 2. Ranked Outcomes Versus Pattern of Ventilator Use

<table>
<thead>
<tr>
<th></th>
<th>HFOV</th>
<th>CV to HFOV</th>
<th>CV</th>
<th>HFOV to CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival without severe lung disease (%)</td>
<td>83</td>
<td>21</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>Survival with severe lung disease (%)</td>
<td>11</td>
<td>37</td>
<td>30</td>
<td>18</td>
</tr>
<tr>
<td>Death (%)</td>
<td>6</td>
<td>42</td>
<td>40</td>
<td>82</td>
</tr>
</tbody>
</table>

HFOV = high-frequency oscillatory ventilation  
CV = conventional ventilation  
Severe lung disease was defined as the requirement for supplemental oxygen with an $F_{IO_2}$ of > 0.3 at 30 days. The overall relationship between ranked outcome and pattern of ventilator use was highly significant ($p$ < 0.001).

(Adapted from Reference 23.)
ation of HFOV (Fig. 5). Interestingly, the following variables were found to correlate with risk of mortality in that group of patients: immunocompromise, sepsis syndrome, oxygenation index prior to institution of HFOV, oxygenation index at 12 and 24 hours after HFOV initiation, and time on conventional ventilation prior to initiation of HFOV.

Summary of High-Frequency Oscillatory Ventilation

The PICU clinician is thus left with a quandary. Though the data on lung-protective strategy would lead one to believe that this is a mainstay of ARDS support, a review of the HFOV data would lead one to believe that early initiation of HFOV is of marked benefit. Like so many other areas of medicine, the art of ARDS support must also play a role. It would appear that use of a lung-protective strategy to support oxygen delivery would be a logical first step. However, if oxygenation is not being supported in a patient on low-V$_T$ mechanical ventilation (combined with useful adjuvants outlined below), early initiation of HFOV would appear to be a viable clinical option.

Adjuncts to Mechanical Ventilation for Acute Respiratory Distress Syndrome

Though many advances have been made in the mechanical ventilation management of children with ARDS and acute lung injury, strides have also been made in the arena of adjunct therapy. The use of agents with specific phys-
iologic goals, such as nitric oxide, has been studied in a wide variety of adults and children with ARDS.

Nitric Oxide

Nitric oxide is an endogenous vasodilator that has been studied in a wide variety of human diseases in which pulmonary hypertension is a major component. Certainly in persistent pulmonary hypertension of the newborn, inhaled nitric oxide (INO) therapy is an effective tool and has reduced the need for extracorporeal membrane oxygenation (ECMO) therapy. Figure 6 summarizes the rationale for the use of INO in ARDS, in which pulmonary hypertension can be a major component.

Several adult trials of INO have been performed. Ros-saint et al performed one of the earliest studies of INO in adults and children with ARDS. Ten consecutive adult patients with severe respiratory failure were treated with 2 concentrations of INO for 40 min. INO therapy led to a decrease in pulmonary artery pressure and an increase in \( P_{aO_2}/F_{IO_2} \) ratio in the majority of patients. Although the trial was designed as a brief therapy of INO, some patients were continued on the therapy for a prolonged period, and some patients demonstrated prolonged improvement in oxygenation variables. However, survival rates among the INO patients were similar to historical controls.

Likewise, a large randomized trial, published in 1998, comparing INO to placebo in adult patients demonstrated improved oxygenation in ARDS patients but failed to show a difference in mortality between the 2 groups.

The first studies of INO for pediatric ARDS appeared in the early 1990s. Abman et al reported 17 consecutive patients (10 of whom had ARDS) who were treated with low-dose INO. Treatment with INO led to improved oxygenation in the majority of patients. INO acutely improved oxygenation in 15 of 17 patients: mean arterial oxygen tension increased from 58 ± 13 mm Hg (baseline) to 86 ± 25 mm Hg after 30 min (p < 0.01). INO lowered mean pulmonary artery pressure (42 ± 6 mm Hg at baseline vs 31 ± 6 mm Hg; p < 0.01) and intrapulmonary shunt (39% ± 7% vs 32% ± 7%; p < 0.01) without changing systemic arterial pressure or pulmonary capillary wedge pressure. Of interest is the fact that oxygenation appeared to improve most in the subset of pediatric respiratory failure patients with ARDS (Fig. 7). However, no differences in mortality could be demonstrated when comparing treated patients to historical controls.

A randomized, placebo-controlled trial of INO was published by Dobyns et al in 1999. They randomized children to either INO or routine mechanical ventilation for 72 hours. During the first 12 hours, oxygenation index was better in the INO-treated patients (Fig. 8). That effect, however, was short lived, and a post-hoc analysis showed long-term improvement in oxygenation index only in those patients with either evidence of profound disruption of oxygenation at presentation (oxygenation index > 25) or with a diagnosis that included immunocompromise.

Many clinical variables can contribute to the improved oxygenation seen in several of the above studies. For instance, the use of vasoactive drugs can improve compromised right ventricular output and thus improve pulmonary blood flow and ventilation-perfusion mismatch. Likewise, ventilator management to improve \( P_{aCO_2} \) may cloud the interpretation of oxygenation improvement. An interesting report by Baldauf et al, published in 2001, set out to define a tool for evaluating the efficacy of INO therapy. During an interim analysis of their trial of INO for pediatric ARDS, Baldauf et al reported on 19 children who met the ARDS definition of the consensus conference and who had oxygenation indexes of > 12. Data were collected during the first 72 hours of INO therapy, and an escalating dose of INO was used (5 ppm for 30 min, 10 ppm for 30 min, and 25 ppm for 30 min). Patients were continued on the INO dose that appeared to improve oxygenation the most. If oxygenation improved (as measured by a ≥ 15% improvement in \( P_{aO_2}/F_{IO_2} \) ratio), a note was recorded per a predetermined model as to whether the therapy was due to INO, or not due to INO, or it was not clear whether the change was due to INO (Fig. 9). Thus the authors set out to identify with a post-hoc tool whether INO or some other therapy was responsible for the improved oxygenation.

From the 19 patients a total of 119 data points were available for analysis. Fifty of the data points (42%) failed to show an improvement in \( P_{aO_2}/F_{IO_2} \) ratio of ≥ 15%, and those patients were deemed nonresponders to INO. In 32 instances (27%), the increase in \( P_{aO_2}/F_{IO_2} \) ratio was attributed to INO. In 35 instances (29%), the improvement in \( P_{aO_2}/F_{IO_2} \) ratio was determined to be either nonspecific or due to other factors. Twelve of the 19 patients survived.

These authors concluded that about a quarter of the time...
an improvement in oxygenation was attributable to INO. Though this study supports the limited role of INO in pediatric ARDS, it also adds a valuable research tool to help sift out differences in the presence of multiple variables and allows a more precise definition of the role of NO.

Summary of Nitric Oxide

Though INO has a solid role in the therapy of several pediatric diseases, its use for ARDS remains unclear. The data would suggest that INO improves short-term oxygenation in pediatric ARDS patients, but that little change is seen in long-term oxygenation indices. Thus INO would appear to remain a short-term therapy, best used to improve oxygenation as other therapeutic avenues (ie, HFOV, ECMO, prone position) are considered in the support of these critically ill children.

Surfactant

Much like the use of INO for persistent pulmonary hypertension of the newborn, the use of surfactant for ARDS was initially inspired by its success in the respiratory distress syndrome of premature infants.36,37 Though the pathophysiology of ARDS is quite different than the primary surfactant deficiency of respiratory distress syndrome, some pathophysiologic properties of ARDS may lend themselves to treatment with surfactant. Gregory et al showed that surfactant composition is deranged in ARDS patients and the degree of alteration in phospholipid and protein composition correlates with the severity of clinical derangement. Gregory’s group was the first to publish on the use of surfactant in adult ARDS patients.38,39 Likewise, Hallman et al demonstrated that surfactant is functionally and quantitatively deranged in ARDS patients.40

The first large randomized trial of surfactant use in ARDS was published by Anzueto et al, in 1996.41 They randomized 725 patients with ARDS secondary to sepsis to either placebo (saline) or surfactant via aerosolization continuously for up to 5 days. The primary outcome variable was 30-day mortality, and the secondary outcome was oxygenation indices. No differences in outcome or oxygenation were found between the 2 groups (Fig. 10). However, no detailed description was provided of the method of mechanical ventilation, and the authors pointed out that pre-
vious studies have demonstrated that only 4% of aerosolized surfactant may reach the alveolus.

The use of surfactant for pediatric hypoxic respiratory failure was studied by Willson et al and published in 1999. They randomized children from 8 centers to receive either conventional therapy or surfactant instilled via the endotracheal tube (placebo was deemed unwarranted). The group that received surfactant had a rapid and sustained oxygenation improvement, as measured by the oxygenation index (Fig. 11). Patients in the surfactant group also had significantly less time on mechanical ventilation and shorter ICU length of stay. There were 3 deaths in the surfactant group and 2 in the control group, with an overall mortality rate of 11%. The study did not, however, control for other therapies such as HFOV or ECMO, although the use of those therapies was evenly distributed between the 2 groups. The authors concluded that surfactant therapy appears to improve oxygenation acutely and lead to more rapid weaning from mechanical ventilation.

A recent, smaller study published in 2002 would seem to support Willson’s conclusions. Hermon et al reported on a group of 19 children who received surfactant for ARDS. The study, though retrospective and nonrandomized, found an impressive improvement in oxygenation after the first dose of surfactant (oxygenation index improved from a median of 14 to 7). However, the patient population was quite young (mean age 9 mo) and mortality was relatively high (53%).

**Summary of Surfactant**

To draw conclusions regarding the use of surfactant for pediatric ARDS is difficult. Though Willson’s study does point to a dramatic improvement in oxygenation index with the use of surfactant, the study population contained both ARDS and non-ARDS causes of respiratory failure. Also, no difference in mortality was demonstrated. Thus we are again left with a therapy that has a sound footing in pathophysiology but lacks a strong, randomized trial in pure pediatric ARDS. Much like INO, surfactant appears to be a useful adjuvant to meticulous ICU care in selected patients. The exact selection criteria for patients who would benefit from this therapy remain to be seen.
Prone Positioning

The use of prone positioning for ARDS patients was first advocated by Bryan in 1974. The exact mechanism underlying the improved oxygenation seen in ARDS patients placed in the prone position has yet to be elucidated. However, Gattinoni et al have shed some light on potential mechanisms by demonstrating that ARDS patients have inhomogeneous distribution of alveolar collapse and that patients in the prone position appear to have more recruitment of atelectatic dorsal lung regions. Other potential explanations include decrease in abdominal compression of the thorax and/or optimizing mobilization and removal of secretions.

The literature on ARDS is filled with case reports describing the successful use of prone positioning with hypoxemic ARDS patients. Jolliet et al reported 19 consecutive patients with ARDS and severe hypoxemia ($P_{aO_2}/F_{IO_2} < 150 \text{ mm Hg}$) who were turned to the prone position for 2 hours and, if oxygenation improved, were kept in the prone position for 12 hours total. Fifty-seven percent (11/19) of these adult patients were considered responders, as demonstrated by an improvement in the $P_{aO_2}/F_{IO_2}$ ratio of 20 mm Hg! That improvement was the most dramatic at 1 hour but was further improved over the 12-hour therapy and persisted when the patient was returned supine (Fig. 12). Like other studies reviewed above, this report is a bit difficult to evaluate, as there was no randomization and several other therapies were used in selected patients (eg, INO). However, a 96% response rate is dramatic and certainly serves as a nidus for further investigation.

Like many other facets of ARDS therapy, the pediatric critical care clinician is left to analyze multiple adult studies and relish the few pediatric studies of a particular treatment. Two small reports of the use of prone positioning in children have been published but rendered different results as far as improvement in oxygenation.

Kornecki et al, from Toronto, recently published a randomized trial of prone positioning in children diagnosed with ARF. Patients were considered eligible for the study if they had bilateral infiltrates on chest radiograph and had oxygenation impairment (based on an oxygenation index of $\geq 12$ and $F_{IO_2}$ of 0.50 for $> 12$ hours). Once entered in the study, patients were randomized to either a prone-supine sequence or a supine-prone sequence, in a crossover design. Though the ventilator management was not strictly controlled, the authors used a lung-protective ventilation strategy that was similarly used by all PICU attendings.
Summary of Prone Positioning

Based on revolutionary work that demonstrated differing areas of alveolar collapse in dependent lung regions in ARDS patients, the use of prone positioning appears to make sound clinical sense. Likewise, though none of the prone positioning reports are perfect, the addition of a treatment that improves oxygenation as the body attempts to heal itself just makes sense. We may never be able to show a significant change in mortality from one therapy alone; thus we are left with examining each new therapy with a specific pathophysiologic role in mind. In the case of prone positioning, the data would support its use in selected children with ARDS.

Extracorporeal Membrane Oxygenation

The use of ECMO to support oxygen delivery while allowing lung healing has been advocated in a variety of diseases, including neonatal persistent pulmonary hypertension and pediatric ARF. The use of ECMO in adult patients remains controversial, although some centers have reported improved survival in the sickest of patients.

In the study of pediatric ECMO, most investigations present a mixed bag of respiratory failure patients that contain subgroups of patients with classic ARDS. Despite these limitations, ECMO has become much more of a mainstay of therapy for children than for adults. Outside the spectrum of “pure” ARDS, case reports have demonstrated successful use of ECMO in diverse diseases, including septic shock and severe burns.

At the University of Pittsburgh, Morton et al conducted a retrospective review of 28 patients who were placed on ECMO for respiratory failure, 8 of whom met the classic definition of ARDS. The overall mortality rate was 54% and 4 of the 8 ARDS patients survived. No clear pre-ECMO predictors of death could be identified in either...
ARDS or non-ARDS patients. There were a variety of bleeding complications in survivors and nonsurvivors. Interestingly, recovery of lung function by ECMO day 7 appeared to correlate with a good outcome. Morton et al concluded that, although there was no identified control group, ECMO appears to be an effective therapy for the most extreme cases of pediatric ARDS, with patients who have a high risk of dying with conventional therapy.

Though no randomized, controlled trials of ECMO have been performed in pediatric patients with ARDS and/or ARF, in 1996 the Pediatric Critical Care Study group published one of the largest retrospective studies examining the role of ECMO in ARF. In this cohort analysis, the use of ECMO with patients suffering severe ARF was associated with lower mortality among the sickest patients (predicted mortality 50–75%). The patients with the highest chance of dying from their diseases had the most dramatic improvement in outcomes. Interestingly, the use of HFOV was not associated with significantly better outcome in these patients. Though this was a retrospective, noncontrolled trial (in reality a prospective, controlled study would probably be impossible to perform) and did include many diagnoses in addition to ARDS, it does point to a profound improvement in survival in the sickest children who were treated with ECMO.

### Summary of Extracorporeal Membrane Oxygenation

In a recent review, Robert Bartlett from the University of Michigan, one of the founding fathers of ECMO therapy, concluded that “ECMO is a safe and effective means to keep patients alive during severe respiratory failure that would otherwise be fatal.” Though the use of ECMO has without a doubt saved some of the sickest children with ARDS, with the complications of ECMO therapy being so

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**Table 3. Cardiovascular and Gas-Exchange Variables**

<table>
<thead>
<tr>
<th></th>
<th>Supine Position*</th>
<th>Prone Position*</th>
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</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>78 ± 16</td>
<td>82 ± 16</td>
</tr>
<tr>
<td>CI (L/min/m²)</td>
<td>3.8 ± 0.9</td>
<td>4.2 ± 0.6†</td>
</tr>
<tr>
<td>ITBVI (mL/m²)</td>
<td>1,008 ± 187</td>
<td>1,036 ± 180</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>75 ± 10</td>
<td>81 ± 11†</td>
</tr>
<tr>
<td>CVP (mm Hg)</td>
<td>16 ± 5</td>
<td>15 ± 5</td>
</tr>
<tr>
<td>SVRI (dyn/s/cm⁻⁵/m²)</td>
<td>1,308 ± 363</td>
<td>1,273 ± 254</td>
</tr>
<tr>
<td>PₐO₂/F(IO)₂ (mm Hg)</td>
<td>194 ± 66</td>
<td>269 ± 68†</td>
</tr>
<tr>
<td>PₐCO₂ (mm Hg)</td>
<td>45 ± 6</td>
<td>47 ± 6</td>
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<tr>
<td>DO₂I (mL/m²/min)</td>
<td>558 ± 122</td>
<td>620 ± 74†</td>
</tr>
<tr>
<td>Hemoglobin (g/L)</td>
<td>109 ± 9</td>
<td>110 ± 9</td>
</tr>
<tr>
<td>pH*</td>
<td>7.42 ± 0.05</td>
<td>7.40 ± 0.07</td>
</tr>
</tbody>
</table>

*p Tested on a randomized basis
†p < 0.05 versus supine position, t test for dependent samples
HR = heart rate
CI = cardiac index
ITBVI = intrathoracic blood volume index
MAP = mean arterial pressure
CVP = central venous pressure
SVRI = systemic vascular resistance index
P(IO)₂ = fraction of inspired oxygen
DO₂I = oxygen delivery index

(Adapted from Reference 54.)
potentially devastating (ie, massive central nervous system bleeding) the quest for improving conventional therapy continues in earnest.

**Prognosis and Predictors of Outcome in Pediatric Acute Respiratory Distress Syndrome**

**Overall Prognosis**

Though each of the above outlined therapies target a particular therapeutic challenge in ARDS, in the end all the new therapies are ultimately designed with 2 major goals in mind: to preserve and/or restore oxygen delivery in ARDS patients and to decrease mortality. Data on outcomes in ARDS, though once again largely based on adult data, would lead one to conclude that these goals are being achieved.

A review of ARDS registries from 5 adult ICUs revealed that overall mortality in ARDS had decreased significantly between 1983 and 1993. The largest decrease in mortality was found in patients with sepsis-induced ARDS, among whom mortality declined from 67% in 1990 to 40% in 1993. The overall ARDS mortality rate also declined over the 10 years studied, to a low of 36% in 1993, although after adjusting for age, ARDS risk, and gender, the crude mortality rate was largely unchanged. Still the authors concluded that meticulous ICU care and newer ARDS therapies appear to have improved outcomes.

The data on outcomes in pediatric ARDS are more difficult to interpret. No large pediatric review of mortality from ARDS has been published since the mid-1990s. In 1991 Timmons et al reviewed 3 years of experience with ARDS patients and reported an overall mortality rate of 75%. They also identified several clinical variables that predicted worse outcome, including a higher oxygenation index and mean airway pressure.

A review, published in 1993, of 60 children with ARDS indicated an overall mortality of 62%, comparable to previous reports. These authors drew conclusions similar to those of Timmons et al: an alveolar-arterial oxygen difference > 420 mm Hg was highly predictive of a poor outcome.

Sarnaik et al reported on a group of children who were diagnosed with acute severe respiratory failure and who received HF ventilation. In this rather homogenous group of patients (very few of whom met the definition of ARDS) the mortality rate was 42%, and ability to improve oxygenation in the first 6 hours of HF ventilation was strongly predictive of a better outcome.

Likewise, a 1999 study from Israel reported an overall mortality rate of 61% in children with ARDS from a variety of causes. Like so many other groups, Paret et al found worse oxygenation indices in children who did not survive ARDS.

Certain groups of children still appear to have an even more dreadful mortality rate from ARDS. Specifically, immunocompromised children and those who have received bone marrow transplants have only a 15–20% survival of ARF.

Many factors make interpretation of these data difficult. First, since the adaptation of adult-proven strategies such as lung-protective ventilation, no large epidemiologic studies on pediatric ARDS have been published. Second, many of the above-outlined trials lump ARDS patients in with other forms of respiratory failure, thus making it difficult to comment on ARDS outcomes. However, with improvements in both mechanical ventilation and adjuvant therapy, we are beginning to make an impact on this devastating disease.

**Prognostic Indicators**

Though the mortality rate from ARDS appears to be slowly improving, the clinician is still left searching for prognostic indicators to guide clinical decision making and to provide realistic expectations for families.

Several studies suggest that profound hypoxemia and the need for high ventilatory support predict a worse outcome, but not every study has found that to be the case. Indeed, patients with profound depression of oxygenation indices can recover and go on to enjoy relatively normal lung function. Likewise, the presence of pneumothoraces and air leaks do not always indicate a worse prognosis. What appears to be true across all studies is that patients with multi-organ failure and those whose oxygenation fails to improve after 6 days appear to have the worst prognosis.

A unique approach to prognostication was undertaken by Shorr et al and published in 2002. They examined D-dimer levels (a protein that is produced by the breakdown of blood clots) and demonstrated that these levels correlated with circulating levels of pro-inflammatory cytokines and with mortality. Though these authors did not specifically look at ARDS, the concept of ARDS as an inflammatory disease would lend itself to this type of prognostication tool and should be investigated in a larger series of patients.

**Long-Term Consequences of Acute Respiratory Distress Syndrome**

Though the quest for therapies to improve pediatric ARDS outcomes and for accurate prognosticators continues, the good news remains that survivors of pediatric ARDS appear to have little in the way of pulmonary sequelae. In a small review of 12 years of experience with children who survived ARDS, Ben-Abraham et al found that almost all of the located survivors (unfortunately only
7 of the 28 total patients) had normal pulmonary function test results and exercise capacity.70

Adult patients do not seem to fare as well. Recent follow-up studies found long-term abnormalities in pulmonary function and decreased quality of life.71–73

Summary

ARDS remains a fascinating but devastating disease. From a wide variety of insults, the patient’s immune system appears to be primed for attack. Unfortunately, in the case of ARDS, the lungs appear to be the target of the immune system’s wrath. The normal integrity of the capillary-alveolar membrane is compromised and alveolar damage ensues. Profound changes in lung compliance and ventilation-perfusion mismatch lead to hypoxemia; the resultant end-organ damage appears to be responsible for the ultimate death of many patients.

In 2002 the mainstay of care for children with ARDS remains meticulous, team-based ICU care. Though we search for immunomodulators and new therapies to help treat the root causes of ARDS, careful attention to oxygen delivery and avoidance of harmful ventilator settings remain the key to good ARDS care. The use of low VT, titration of PEEP for lung recruitment, early consideration of HFOV, and adjuvant therapies such as INO and surfactant appear to be a sound, scientifically based approach to the care of these challenging patients.

Yet, even with improvements in the care of ARDS patients, the search continues. Can we identify sooner those children who will go on to develop ARDS? Likewise can we intervene earlier so that the cascade of hypoxemia and end-organ damage is squelched? Are there new modes of ventilation that will improve oxygen delivery in pediatric ARDS patients while minimizing ventilator-induced damage? With the mortality from this disease unacceptably high, our search continues with a 110% effort!

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Discussion

Wiswell: I have a question about lung-protective strategies. You mentioned the strategy of respiratory acidosis or “permissive hypercapnia.” To date I have not really been impressed with either the pediatric or adult literature that, in and of itself, permissive hypercapnia is beneficial. The majority of articles demonstrate either no benefit or worse outcomes. Nonetheless, there are still a lot of proponents of permissive hypercapnia among both adult and pediatric clinicians who practice it.

I’m also intrigued by surfactant therapies. Probably the study by Anzueto et al didn’t work because they had only sepsis patients. Moreover, the surfactant was given in a nebulized form, and the estimates are that patients received less than 5% of what was administered. Gregory et al did a trial with the surfactant Survanta, and at least one of the treatment groups did well. They would need copious amounts of surfactant, but did reasonably well. There are some ongoing trials with 2 synthetic surfactants that are in the developmental stage. Both of those surfactants contain peptides. The German surfactant Venticute contains recombinant surfactant protein C. There is some reasonably good preliminary data regarding Venticute for ARDS. Additionally, I have worked with Surfaxin (also known as KL₄ surfactant) in one adult ARDS trial. We performed bronchopulmonary surfactant lavage via bronchoscopy in that trial and had some success. So I think we’re still searching for the best way to administer the surfactants in various populations.

Lastly, you referred to nitric oxide trials. I think all of us in this group, as clinicians and therapists, love to see the oxygenation improve when a patient is given inhaled nitric oxide. However, oxygenation itself is not a hard outcome. Hard outcomes in ARDS patients are mortality and morbidity, and, perhaps, duration of ventilation, duration of hospitalization, and incidence of chronic lung disease. Hard outcomes are what have to be improved in the final bottom line in order to show whether a particular therapy is good.

REFERENCES


Anderson: I intentionally avoided discussing permissive hypercapnia because I think the jury is still out and I didn’t want to go into it until we have better data. I see permissive hypercapnia as a byproduct of the lung-protective strategy. I think it makes sense from a nuts-and-bolts clinical standpoint to titrate the PEEP as best you can to recruit alveoli, whether you’re looking at chest radiograph or lung expansion or inflection point, and use as small a tidal volume as you can get.
away with to avoid large lung pressure fluctuations.

**Rotta:** You mentioned using PEEP to recruit lung, and I want to disagree with that, because I don’t think that you can apply PEEP to recruit the lung, since PEEP is an *expiratory* maneuver. Recruitment happens during *inspiration*, with a sustained inflation or other recruitment maneuver, and PEEP is applied to prevent lung from derecruiting during exhalation. We need to be careful in talking about using PEEP to recruit the lung.

Also I want to second what Dr Wiswell said about needing to uncouple our desire to make the lung look normal by physiologic variables such as oxygenation, because those variables do not necessarily have any direct influence on final outcome. For instance, in the ARDS network trial the group receiving lower tidal volume had lower mortality, yet those patients had a trend toward a lower PdO2/FIO2 ratio than the conventional tidal volume group.

You also commented on prone positioning and nitric oxide, stating that nitric oxide is useful for oxygenation in the first 24 hours. However, nitric oxide has no impact on mortality or any other clinically important outcome. The same is true for prone positioning. Although I know prone positioning is an endearing strategy—one that we all want to believe works—the data show that it does not decrease mortality. I view these adjuncts as cosmetic methods of making a variable such as oxygenation look better for a short period of time—a variable that we have now shown does not really affect important outcomes. I would like to know what you think of that.

**REFERENCES**


**Anderson:** I agree with your definition of recruitment. I think a better term for the use of PEEP would be “prevention of de-recruitment.” Perhaps that’s the double negative that may be more appropriate. I also agree on your second point: if you look at the outcomes in a lot of these trials, you see that it’s difficult to piece together. No one has found a magic bullet. As we try in the real world to put this all together, no one is just going to treat a kid with prone positioning. We’re going to try to bring all these different therapies to bear.

So I have to dissect out what a particular therapy does. What does it do to oxygenation, for instance? And then, overall, can we improve outcome as we start to add these therapies together? That’s my perhaps too simplistic way of thinking of it. You’re right that there’s been no magic bullet that shows a great change in mortality. But I think that’s the way it is in looking at individual studies, gleaning what data I can, and then trying to come up with the best individualized care for my patient.

**Cheifetz:** I agree with Dr Rotta’s comment about the need to adequately open the lungs with a careful consideration of sustained inflation and volume recruitment maneuvers. You mentioned the need to “get the lung open,” but you did not provide details about how you propose to do that. There is a reasonable quantity of data from the adult population regarding lung recruitment, but pediatric data are lacking. Do you have any suggestions? Also, specifically related to the oscillator as a lung recruitment device, how would you recommend accomplishing lung recruitment?

**Anderson:** That’s a great question. There’s more data from adults than kids—by a lung full, if you will. I addressed the therapies that have a lot of adult data and a smattering of pediatric data, but I couldn’t find enough good data regarding pediatric lung recruitment to even comment on it. There’s a huge void in the pediatrics literature regarding acute hypoxic respiratory failure, and specifically ARDS. That’s why I didn’t go into it.

**Black:** Do you have any comments on using pressure-controlled versus volume-controlled ventilation?

**Anderson:** I come from a place where your hands would be chopped off if you put somebody on pressure-controlled ventilation. Perhaps it’s Pavlovian in thinking that. I don’t know of good studies comparing those 2 control modes. I don’t think those studies have been done. In my institution, we’re fans of volume-control, and I didn’t discuss pressure-control because we don’t use it.

**Black:** I really like pressure control because you’ve got much greater control over the inspiratory time and the ratio of inspiratory time to expiratory time. If you want sustained inflation, it’s a kinder, gentler way to get sustained inflation than with volume control, but I know that there’s very strong feelings in both camps.

**Anderson:** Which are probably influenced more by emotion than data.

**Cheifetz:** I believe the biggest difference between volume-control and pressure-control is not the volume limit or the pressure limit: it is the inspiratory flow pattern and whether it is a constant flow pattern or a variable, decelerating flow pattern.
REFERENCE

Donn: I would like to register a caveat that we shouldn’t make the same mistake with pediatric ARDS that we did with ECMO. That is, we’re dealing with a population with very diverse disease and pathophysiologic states. It very well may be that in a study large enough to stratify appropriately for the underlying pathophysiology, the results may be very different with the different strategies that are being applied.

Rotta: I have a question about acidosis. You mentioned that one of the aspects of lung-protective ventilation is that we tolerate acidosis, and I wonder what is the basis for that. Dr Kavanagh in Toronto has published some interesting data suggesting lung-protective effects from acidosis in experimental lung injury.1,2 On the other hand, the ARDS Network showed that a reduced-tidal-volume strategy is possible without acidemia,3 so I wonder where are the data that show that we should tolerate acidosis, particularly since now we have a strategy that can largely uncouple oxygenation from ventilation—specifically, high-frequency oscillatory ventilation, which can provide optimal oxygenation without having to accept subnormal carbon dioxide elimination.

REFERENCES

Anderson: I think that’s a great argument for the use of high frequency ventilation. I again go back to the initial question about respiratory acidosis; I see it more as a byproduct of accepting lower tidal volumes to prevent volume-induced alveolar trauma, and I don’t see a lot of harm in the respiratory acidosis process. I see it as more of a byproduct of a therapy that seems to be beneficial.