Pediatric Acute Respiratory Distress Syndrome

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The data available to guide clinical management of acute lung injury and acute respiratory distress syndrome are much more limited for infants and children than for adult patients. This paper reviews the available medical data and the pertinent physiology on the management of pediatric patients with acute lung injury. With the collaboration of multicenter investigation networks, definitive pediatric data may be on the horizon to better guide our clinical practice. *Key words: pediatric; acute respiratory distress syndrome; ARDS; acute lung injury; ALI; mechanical ventilation; gas exchange; lung protection; oxygenation; ventilation; extracorporeal life support; ECMO; PEEP; tidal volume; high-frequency ventilation; nitric oxide; surfactant.* [Respir Care 2011;56(10):1589–1599.

Introduction

Although representing a small percentage of the total number of pediatric intensive care unit (PICU) admissions, acute respiratory distress syndrome (ARDS) is one of the most challenging patient populations for a clinician to manage. Even more challenging to the pediatric practitioner is the lack of definitive data to guide clinical management. As data are more readily available in the adult population, one must ask whether children are really different than adults in regard to treatment strategies for acute lung injury (ALI) and ARDS? The answer to this question could be debated for quite some time and really depends on the

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individual patient, the etiology of the lung disease, underlying comorbidities, and patient age and weight.

As a starting point, it is important to note that the definitions of ALI and ARDS for infants (older than one month of life), children, and adolescents are essentially identical to those for adults.[1-3] However, there are intrinsic differences between pediatric patients and adults, which often can affect management strategies. Infants and young children, as compared to older children, adolescents, and adults, have more compliant chest walls, higher sedation requirements, lower hematocrit (which may affect global oxygen delivery), higher baseline airways resistance, and lower functional residual capacity. Additionally, the still developing and growing lung may be at greater risk for ventilator-induced lung injury at a lower airway pressure than the developed lung of an adult.

Although one may debate how, or even whether, adult data are applicable to children,[4] the answer is somewhat arbitrary without knowing the specific clinical details. Clearly, a 14-year-old adolescent with ARDS resembles an adult patient in terms of anatomy, physiology, and pathophysiology much more closely than an 8-month-old infant. Additionally, adult data are more likely to be applicable to a previously healthy child with viral-induced ARDS than a child with underlying complex congenital heart disease.

Epidemiology of Pediatric ALI and ARDS

The first step in discussing pediatric ALI and ARDS requires an understanding of the epidemiology of this important clinical entity. The Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) network described the incidence of ALI and ARDS.[5,6] Of note, the focus of this report was to describe the characteristics of those patients eligible for a mechanical ventilation weaning study and, thus, it likely underestimated the true incidence of ALI/ARDS in the total PICU population. Of the total 6,403 admissions, 1,096 (17.1%) required mechanical ventilation for more than 24 hours, and 395 (6.2%) were eligible for the weaning study.[6] Of the 303 (4.7%) enrolled patients, only 23 had ARDS, representing 7.6% of the eligible patients and 0.4% of the total population screened. Although that report likely underestimates the true incidence of pediatric ARDS, it met its primary goal of describing why definitive clinical trials for pediatric ALI/ARDS have been very limited.

Santschi et al, in collaboration with the PALISI Network and the European Society of Pediatric and Neonatal Intensive Care,[7] reported the incidence of the broader clinical entity of pediatric ALI (ie, not just ARDS) in a more global population. This larger-scale study included 59 PICUs in 12 North American and European countries. Of 3,823 pediatric patients screened, 414 (10.8%) were diagnosed with ALI by the clinical care teams at the individual centers. Of interest, only 165 (4.3%) of the total screened met pre-established inclusion/exclusion criteria for a clinical trial: a number that closely matches the data from the PALISI Network.[2]

Erickson et al[2] described the Australia/New Zealand experience with pediatric ALI in a prospective 12-month observational study. Overall, there were 117 cases of ALI in the total PICU population of 5,252 children, which is an incidence of only 2.95 per 100,000 population $<$ 16 years of age. ALI accounted for 2.2% of all PICU admissions during that one-year period.

Overall, the risk factors and pathophysiology of ALI/ARDS are similar for children and adults.[8] In a comprehensive description of pediatric ALI/ARDS,[9] the primary diagnoses were pneumonia (35%), aspiration (15%), sepsis (13%), near-drowning (9%), concomitant cardiac disease (7%), and other clinical entities (21%). Infectious causes, including sepsis and pneumonia, represented approximately half of all clinical disorders associated with ALI.

Although the overall incidence of pediatric ALI is low,[2,5-7] the mortality in this population remains high, ranging from 22% to 35%.[2,9] Erickson[2] reported that mortality from ALI/ARDS accounted for 30% of all PICU deaths. The highest mortality rates are with near-drowning (54%), associated cardiac disease (39%), and sepsis (31%).[9] Lower mortality rates are associated with pneumonia (11%) and aspiration (12%).[9] Using reported population estimates, between 500 and 2,000 children die from ALI/ARDS in the United States annually. The exact mortality rate is difficult to determine, as ALI/ARDS is not a reportable disorder. It should be noted that the reported mortality from pediatric ALI/ARDS has been as low as 8% in some studies.[10] However, one must be cautious in generalizing mortality data from randomized controlled trials, as such clinical investigations have strict inclusion/exclusion criteria that are likely to eliminate patients with more severe lung injury and/or important high-risk comorbidities, such as bone marrow transplantation.

Important pre-admission mortality risk factors include pre-existing comorbidities and substantial immunosuppression.[2] Higher ventilation requirements and the development of multiple-organ system failure are associated with a higher mortality rate.[2] The literature differs on whether patient age is a factor in predicting mortality. Erickson et al found higher mortality with older age,[2] whereas Flori et al found no age-mortality relationship.[9] Other predictors of outcome for pediatric ALI/ARDS include multi-organ system dysfunction/failure, severity of illness, and degree of impairment in oxygenation.[9,11-13]

It is also important to mention some recent work in attempting to identify infants and children with ALI/ARDS earlier in their presentation, often prior to obtaining arterial blood gas samples.[14-16] These studies have favorably compared the S_{pO_2}/F_{IO_2} ratio and the P_{aO_2}/F_{IO_2} ratio to

formulate a useful noninvasive diagnostic tool for helping to define ALI/ARDS.

Where Are the Pediatric Data?

A search of the PubMed database (on July 1, 2011) yielded 25,829 entries related to ALI and/or ARDS. However, only 1,495 articles remained when this search was limited to pediatric patients. Although that is still a substantial number of publications, only a very small number of them describe multicenter randomized controlled clinical trials.

As described in the previous section, data from the PALISI Network[5-7] have helped to explain the lack of definitive pediatric ALI/ARDS studies. Based on the small number of patients in the pediatric ALI descriptive reports,[6,7] one can conclude that a study of pediatric ALI/ARDS would require the cooperation of multiple centers, most likely within a larger network such as PALISI,[5-7,17,18] the Collaborative Pediatric Critical Care Research Network,[19-22] or the Australian and New Zealand Intensive Care Society Clinical Trials Group.[2,23,24] The funding and institutional cooperation that such a study would require are quite substantial.

Once an appropriate number of international centers is identified, clear and concise ventilator-management protocols must be accepted by those involved in the study. Khemani et al[25] described potential difficulties with any pediatric ALI/ARDS study by characterizing mechanical ventilation practices for intubated children in 16 North American PICUs. The substantial variability in ventilation strategies they described would have clear implications when choosing PICUs for a clinical investigation. In that report the vast majority of the infants and children were ventilated with PEEP of 5 cm H_2O, and few infants or children were ventilated with PEEP settings outside of the 4–8 cm H_2O range.

Many adult ALI/ARDS studies were designed with mortality as an end point. However, when considering a primary end point for a pediatric ALI/ARDS investigation, debate occurs as to the optimal end point, since a mortality difference is an unrealistic goal for most such studies. If severely immunosupressed patients (eg, bone marrow transplant patients) and other high-risk patients are excluded, mortality for a pediatric ALI/ARDS clinical trial would be estimated at 8–15%. Given that low mortality rate, it would require approximately 2,000 pediatric subjects per study group to detect a moderate (25%) decrease in mortality.[26] An even greater number of patients would be required to detect smaller, but still clinically important, improvements in mortality. This is obviously not feasible because of the low occurrence of pediatric ALI/ARDS.

Khemani and Newth described the hurdles involved in pediatric ALI/ARDS clinical trials and made suggestions for the future.[27] Specific concerns included heterogeneous management strategies, a lack of explicit ventilation protocols for pediatric patients, an unpredictable relationship between lung injury severity and outcome, and the reliance on potentially biased surrogate outcome measures such as ventilator-free days. Given the hurdles in studying pediatric ALI/ARDS, clinicians involved with the care of critically ill infants and children are left with extrapolation of data from the adult population, reliance on the limited available pediatric data, careful assessment of applicable principles of physiology and pathophysiology, and/or reliance on clinical experience.

Clinical Management Strategies

Clinical management strategies for ALI/ARDS are targeted at improving mortality and morbidity, hastening recovery with shorter duration of ventilation, and optimizing long-term pulmonary and neurologic function. Although mechanical ventilation is often life-saving, decreased lung compliance and elevated airway pressure can lead to ventilator-induced lung injury from volutrauma (ie, alveolar overdistention), atelectrauma (ie, repeated alveolar collapse and re-expansion), and oxygen toxicity. The overall management approach to the adult patient with ALI/ARDS focuses on lung-protective ventilation with low tidal volume (V_T)[28-33] and moderate to high PEEP.[34-37] Although this approach has become the standard of care for adult ALI/ARDS, definitive data for infants and children are lacking.

Tidal Volume

Despite the generally accepted V_T of 6 mL/kg (based on ideal body weight) to improve survival in adult ALI/ARDS patients,[28] the reported mean V_T for pediatric ALI in various studies include 8.3 mL/kg by Santshci et al,[7] 8.0 mL/kg by Erickson et al,[2] and 8.1 mL/kg by Albuali et al.[38] It is important to note that these pediatric V_T are reported per actual body weight. So, given the incidence of pediatric obesity, we should speculate that the V_T per ideal body weight was significantly greater.

It should be noted that although most standard textbooks include ideal body weight calculations only for older children, adolescents, and adults, several Internet programs provide interactive calculators to determine the ideal body weight for pediatric patients as young as one year of age. Required inputs are sex, age, and height/length. Alternatively, one may estimate the ideal body weight for a child by using the available sex and age growth charts (eg, http://www.cdc.gov/growthcharts/clinical_charts.htm). On the appropriate chart, graph the patient's height/length. Once the height/length percentile is known based on sex

and age, simply determine the predicted weight that corresponds to that percentile.

It is unclear why not all pediatric clinicians are routinely limiting V_T delivery to 6 mL/kg ideal body weight for infants and children with ALI/ARDS. Various possibilities exist. Some pediatric practitioners may simply not believe that the adult-based V_T data are applicable to infants and children. Other providers may believe in limiting V_T to 6 mL/kg, but the extrapolation to "real life" bedside practice may be lacking. While another possibility is that pediatric practitioners may believe a delivered V_T of 6 mL/kg is appropriate, but the V_T set on the ventilator is intentionally increased to compensate for the V_T lost due to the distensibility of the ventilator circuit.

For older children and adults it is reasonable to measure V_T at the expiratory valve of the ventilator, since the volume of gas lost due to circuit distensibility is minimal when expressed as a percent of the total V_T delivered. However, for infants and smaller children, a substantial proportion of the delivered V_T may be lost due to circuit distensibility. Cannon et al[39] found that for neonatal circuits the expiratory V_T measured at the endotracheal tube was on average only 56% of that measured at the expiratory valve. Somewhat improved correlation was found with pediatric circuits: the average measured V_T at the endotracheal tube was 73% of that measured at the ventilator. Similar findings have been reported by Castle et al,[40] Chow et al,[41] and Heulitt et al.[42]

Thus, when determining the actual delivered V_T for smaller pediatric patients, the use of a pneumotachometer placed at the endotracheal tube would seem to be the optimal approach. Most newer-generation ventilators include software that is supposed to account for the circuit compliance in calculating the actual delivered V_T,[42] but those algorithms have not been systematically studied in the "real life" clinical situation.

PEEP

As noted above, Khemani et al[25] reported relatively low PEEP settings for pediatric ALI/ARDS patients. Explanations for this finding may include a general "PEEP phobia," the frequent conversion to high-frequency oscillatory ventilation (HFOV) as an alternative to a "higher" PEEP strategy, and/or an inaccurate representation of actual management, given the small number of centers ($n = 16$) in the study.

Several large-scale adult PEEP trials have found no survival benefit with more aggressive PEEP strategies. Brower et al,[34] in the ARDS Network's ALVEOLI trial, found no mortality difference with a more aggressive PEEP strategy despite improved arterial oxygenation and improved pulmonary compliance. It is important to note that the "lower" PEEP group in that study was not a "low" PEEP approach, but rather an "adequate" PEEP approach. A follow-up study in adults with ALI/ARDS, Meade et al[35] also found no survival benefit from a high-PEEP strategy with recruitment maneuvers, although oxygenation improved. Mercat et al[36] also found no mortality difference, but did find improved lung function, shorter duration of ventilation, and lower incidence of multi-organ failure with a more aggressive PEEP strategy.

Thus, one is left explaining the findings from the various PEEP studies in the adult population. It is likely that individual patients respond differently to different PEEP levels, and the difference might be even greater for infants and children, given the heterogeneity of the pediatric population. Patients with recruitable lung may benefit from a more aggressive PEEP strategy. In that subset of patients, increased PEEP might improve pulmonary compliance and, thus, the ability to provide higher PEEP without significantly elevating the peak or plateau pressure. On the other hand, in patients without recruitable lung, higher PEEP would not translate to improved pulmonary compliance, so the peak and plateau pressures would be expected to increase with higher PEEP.

Thus, it seems reasonable to speculate that in patients with recruitable lung a more aggressive PEEP strategy might improve outcomes, whereas in patients with nonrecruitable lung a more aggressive PEEP strategy might worsen outcomes. Thus, in a heterogeneous patient population the published studies[31-33] would be expected to show a neutral mortality effect from higher PEEP, because the contrary effects in the 2 subgroups (recruitable vs nonrecruitable lung) would cancel each other (Fig. 1).[43]

One may then propose a PEEP management algorithm as shown in Figure 2. The bedside clinician could determine lung recruitability by assessing whether pulmonary compliance, oxygenation, and/or dead space substantially improves with increased PEEP. If so, a more aggressive PEEP strategy should be considered. If not, then a less aggressive PEEP strategy would seem more reasonable.

Of interest, when Briel et al[37] extracted data from the Brower,[34] Meade[35] and Mercat[36] studies, it became apparent that a higher PEEP approach benefited those patients who met the standard accepted criteria for ARDS—a group that may be speculated to have more recruitable lung. Briel et al concluded that higher PEEP may be associated with shorter duration of ventilation and lower hospital mortality in adults with ARDS. In contrast, this benefit was not seen in non-ARDS patients. The applicability of these findings to pediatric patients is worth careful consideration.

Although the data for adult patients are quite helpful, the pediatric critical care clinician is again left wondering about the best approach for infants and children with ALI/ARDS. Are the adult PEEP data applicable to infants and children due to their differences in chest-wall compliance, cardiac reserve, and generally higher sedation requirements

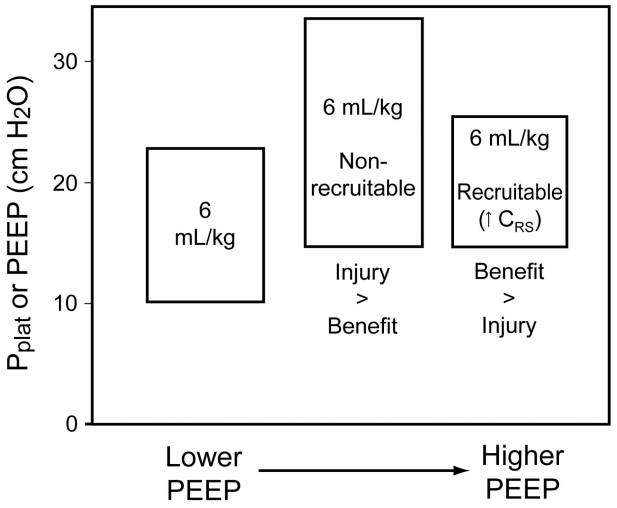

Fig. 1. Potential effects of PEEP increase. If the potential for alveolar recruitment is low, increasing the PEEP increases the plateau pressure (P_{plat}) to an unsafe level, and the risk of over-distention probably outweighs any benefit from alveolar recruitment. If the potential for alveolar recruitment is high, increasing the PEEP results in little increase in P_{plat}, and the potential benefit of increased PEEP probably outweighs the risk from the small P_{plat} increase. (From Reference 43, with permission.)

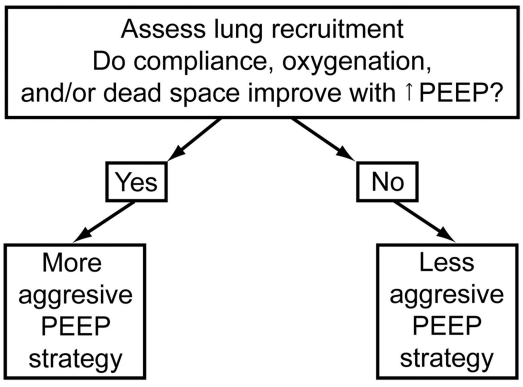

Fig. 2. PEEP titration based on lung recruitability.

needed to tolerate mechanical ventilation at increased mean peak airway pressure? Unfortunately, answers to this question as well as definitive data on PEEP management for pediatric ARDS simply do not exist. Practitioners must carefully consider the pathophysiology of an individual patient before determining the applicability of the available data from adult ARDS to infants and children.

High-Frequency Oscillatory Ventilation

A common management strategy for pediatric ALI/ARDS is HFOV. It should be noted that only one randomized controlled trial has compared HFOV to conventional ventilation in pediatric patients, but the control group received a high-V_T approach, as the study was reported in 1994.[44] More recently, Sud et al,[45] in a meta-analysis that included both pediatric and adult studies, concluded that HFOV "might improve survival and is unlikely to cause harm." Unfortunately, that may be the best available summary on HFOV in pediatric or adult ALI/ARDS for some time to come. Despite the lack of a definitive, randomized controlled trial in pediatric patients demonstrating an advantage of HFOV over a lung-protective (ie, low-V_T) conventional ventilation strategy, the use of HFOV for infants and children has become commonplace.[46-48]

It remains uncertain whether we will obtain definitive data on HFOV versus lung-protective conventional ventilation in pediatric ALI/ARDS. With the current widespread use of HFOV, it seems unlikely that such a clinical study will be performed, because equipoise may be lacking, especially in centers that routinely employ HFOV. Without those, generally larger, centers there may be an inadequate sample size available within a reasonable time frame and within funding constraints. In the meantime, the available data support at least equivalency between HFOV and lung-protective conventional ventilation. One may speculate that HFOV would be found superior if studied in a sufficiently powered, randomized controlled trial, because it takes the concept of low-V_T ventilation to the extreme.

Exogenous Surfactant

Although exogenous surfactant administration is the standard of care for infants with neonatal respiratory distress syndrome,[49-53] its use for pediatric ALI remains uncertain. The preliminary results[54-56] of surfactant administration for pediatric ALI were promising, but more recent studies have been disappointing.[17,57,58] Many had hoped that the Calfactant Therapy for Direct Acute Respiratory Distress Syndrome and Direct Acute Lung Injury in Children (CARDS) trial, which involved 30 international centers, would provide definitive guidance for the surfactant management of pediatric patients with direct lung injury; however, the study was recently closed for futility.[59]

At this point the clinician is left with his or her own interpretation of the data by Willson et al.[17,54,59] Calfactant improved oxygenation and significantly decreased mortality in a heterogeneous group of pediatric patients with ALI.[17] However, there were no significant differences in the duration of ventilation, intensive care unit stay, or hospital stay. Additionally, the placebo group contained a higher proportion of high-risk, immunosuppressed patients and, thus, might be expected to have a higher mortality rate. At this point the administration of exogenous surfactant for a pediatric patient with ALI/ARDS must be left to the discretion of the bedside clinician. But it is important to note that if a clinician administers surfactant based on the data by Willson et al,[17] then it should be done early in

the course of lung injury, generally within 48 hours of ALI/ARDS onset.

Inhaled Pulmonary Vasodilators

For almost 2 decades, inhaled nitric oxide (INO) has played an essential role in the management of persistent pulmonary hypertension of the newborn. However, its use for pediatric ALI/ARDS remains controversial. Despite both pediatric and adult studies finding clear oxygenation improvement with INO,[60-63] no outcome improvements were found.[62,64,65] Many researchers have hypothesized that INO should benefit patients with ALI, by improving oxygenation and thus allowing lower ventilator settings, which decreases the risk of ventilator-induced lung injury. Unfortunately, this hypothesis has never proven to be correct.

In a meta-analysis of 14 randomized controlled trials, which included 1,303 patients, INO had no statistically significant effect on mortality, duration of ventilation, ventilator-free days, ICU stay, or hospital stay.[64,65] Afshari et al concluded that INO cannot be recommended for patients with acute hypoxemic respiratory failure, because INO transiently improves oxygenation but does not decrease mortality.[64,65] Based on the currently available data, this conclusion seems applicable to children with ALI/ARDS in the absence of clinically important pulmonary hypertension. A possible exception to this recommendation are patients with congenital heart disease and passive pulmonary blood flow (eg, after Fontan or Glenn procedure).

Another pulmonary vasodilator that has received attention recently is aerosolized prostacyclin. Similar to INO, aerosolized prostacyclin improves oxygenation in children with ALI.[66] Unfortunately, clinical outcome data are lacking.

Non-respiratory Management Strategies

Beyond the respiratory management of the pediatric ALI/ARDS patient, the clinician must consider fluid management, glucose titration, and transfusion criteria. The care of the pediatric ALI/ARDS patient clearly goes beyond pulmonary support.

Diuretics are frequently administered to pediatric ALI/ARDS patients to manage fluid status. Although no survival difference was found between conservative and liberal fluid-management strategies in adult ALI/ARDS, a conservative fluid approach increased the number of ventilator-free days and ICU-free days, without more adverse effects.[67]

Although definitive fluid-management data do not currently exist for pediatric ALI/ARDS patients, a general approach to the infant or child with ALI is to similarly use diuretics with a conservative fluid-management strategy in mind. The PALISI Network[5,6,18] is currently considering such a study. Key issues for a clinical fluid-management investigation include the optimal fluid targets (eg, in/out fluid balance, central venous pressure, and daily weight). In preliminary work, the PALISI Network found[18] that cumulative fluid balance in pediatric ICU patients with ALI did not appear to have clinical utility.

The key to success of such a ALI/ARDS fluid-management study will be clear agreement among the investigators on the liberal and conservative management fluid algorithms, the types of invasive monitoring lines, fluid titration end points, and outcome measures. Until pediatric data become available, it seems reasonable to extrapolate the ARDS Network fluid management concept to pediatric ALI/ARDS patients and use a fluid-conservative approach. Unfortunately, the ARDS Network algorithms[67] are not applicable to most infants and children.

Glucose/insulin-management strategies remain very controversial, and recommendations have fluctuated over the past several years.[68-72] Despite multiple studies, it remains uncertain whether strict glycemic control improves outcomes for ALI/ARDS patients. This uncertainty is even greater in the pediatric population, especially infants, as the neurologic risk of hypoglycemia may greatly outweigh any potential benefit of tight glycemic control.[68] The PALISI Network is about to embark on a glucose-control study in critically ill pediatric patients. Hopefully, a definitive answer is on the horizon.

Although the data on transfusion criteria for critically ill children are more clear than those on glucose/insulin management, their applicability to ALI/ARDS may be questioned. Lacroix et al[73] found that in stable, critically ill children a hemoglobin threshold of 7 g/dL for red-cell transfusion can decrease the transfusion requirement without increasing adverse effects. However, a conservative approach to transfusion thresholds for pediatric ARDS has not been studied in combination with permissive hypoxemia,[74] which is gaining acceptance. Furthermore, it must be noted that profound hypoxia was a study exclusion in the Lacroix study.[73]

Extracorporeal Membrane Oxygenation

Extracorporeal life support, most often in the form of extracorporeal membrane oxygenation (ECMO), can be life-saving for infants and children with refractory hypoxemia due to ARDS. The currently reported overall survival rate for ECMO for pediatric ARDS is 54%.[75] However, recent publications have reported survival rates over 70% in relation to ECMO for pediatric and adult patients with H1N1-influenza-induced ARDS.[76-78]

Much has been learned from the over 45,000 patients in the Extracorporeal Life Support Organization registry.[75]

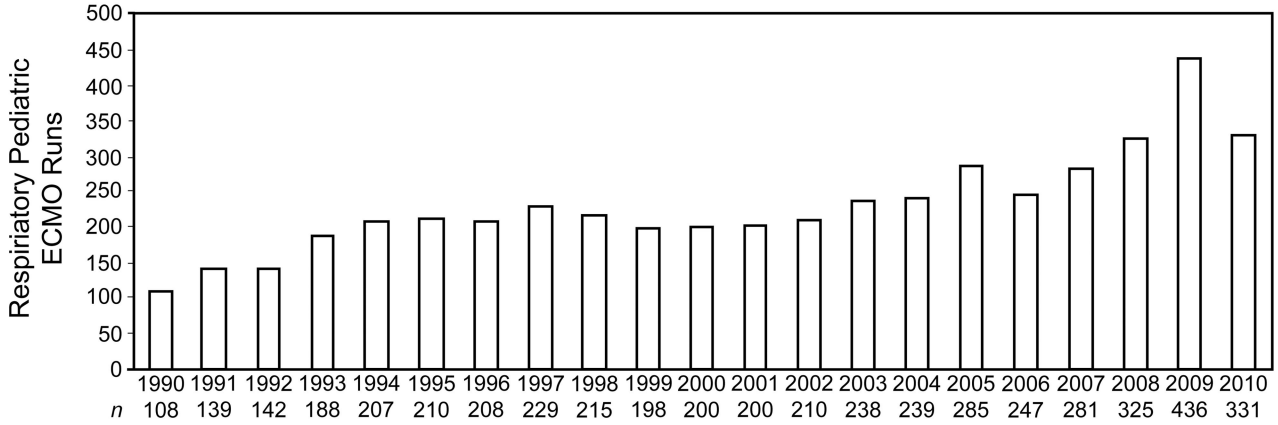

Fig. 3. Recent trends in the utilization of extracorporeal membrane oxygenation (ECMO) for refractory pediatric respiratory failure. (Adapted from Reference 75, with permission.)

Over the past decade, the technological advances in extracorporeal life support rival any other in the management of ARDS. The most important of these advances include the introduction of centrifugal pumps, hollow-fiber oxygenators, and improved double-lumen venous cannulas. Centrifugal pumps and hollow-fiber oxygenators allow for smaller priming volume and shorter pump setup time. The Avalon double-lumen cannula (Avalon Laboratories, Rancho Dominguez, California) decreases the degree of recirculation, improves the possibility of single-site cannulation in venovenous ECMO, and improves the possibility of ambulation and physical rehabilitation in patients on ECMO.[79,80]

The typical pediatric ECMO patient is changing. Traditionally, ECMO criteria included less than 7–10 days of substantial ventilator support prior to cannulation. However, recent data indicate similar survival with pre-ECMO duration of ventilation up to 14 days.[81] Also of note is increasing ECMO use in patients with comorbidities.[81]

The recent increased use of ECMO in pediatric patients with ARDS[75] is likely to continue (Fig. 3). With simplification of ECMO technology we may no longer need 1:1 nurse/ECMO-specialist-to-patient ratio, which would improve resource allocation.[78] ECMO should no longer be considered a therapy of desperation, but instead part of our standard armamentarium for severe ARDS.[79]

The decision to initiate ECMO in a patient with severe lung injury is difficult because we have limited data available to make a risk/benefit assessment, and the published data do not always reflect current clinical practice. Unfortunately, there are no data to guide the timing of ECMO cannulation in a patient with refractory hypoxemia, and such data are unlikely to become available in the foreseeable future. Thus, the bedside clinical care team must make a careful risk/benefit assessment for each individual patient.

Management Algorithm

Until definitive randomized controlled trial data become available, it seems reasonable to ventilate infants and children with ALI/ARDS with a V_T of 6 mL/kg predicted body weight. This recommendation is supported by retrospective pediatric data from Albuali et al,[38] which indicated 40% lower mortality in pediatric ALI/ARDS patients with lower V_T.

Additional recommendations based on a composite of pediatric and adult data include maintaining the plateau pressure less than 30 cm H_2O. Because many pediatric patients are still ventilated with uncuffed endotracheal tubes, measuring the plateau pressure is not always possible. Thus, it would seem reasonable to take an even more conservative approach and maintain the *peak* airway pressure less than 30 cm H_2O.

Unfortunately, definitive data do not exist to guide PEEP management for the pediatric ALI/ARDS patient. One must, therefore, balance the cardiorespiratory effects of higher PEEP by determining the optimal relationship between increased pulmonary compliance, reduced dead-space ventilation, and acceptable hemodynamics, while maintaining adequate, but not maximal, oxygenation.[74] It must be remembered that optimal oxygen delivery may not occur at the point of maximal arterial oxygen content, because this may correspond to excessive mean intrathoracic pressure and, thus, lower cardiac output. The key for optimal global oxygen delivery is determining the best possible balance between cardiac output (as clinically determined, given the lack of available cardiac output monitors for infants and small children) and arterial oxygen content. It must be stressed that close cardiorespiratory monitoring is essential when titrating PEEP, especially in younger pediatric patients and those with underlying cardiac structural anomalies and/or dysfunction.

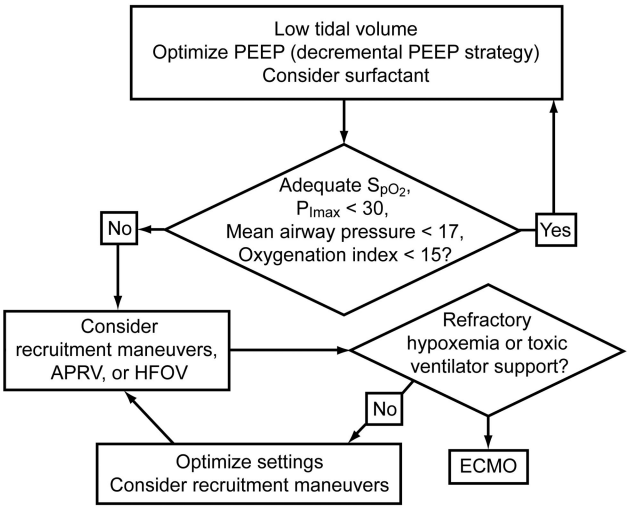

Fig. 4. Proposed algorithm for pediatric acute lung injury and acute respiratory distress syndrome. P_{Imax} = maximum inspiratory pressure. APRV = airway pressure-release ventilation. HFOV = high-frequency oscillatory ventilation. ECMO = extracorporeal membrane oxygenation.

In terms of determining appropriate gas-exchange goals, it should be stressed that oxygenation and ventilation should have "adequate" rather than "optimal" targets. Permissive hypercapnia and permissive hypoxemia should be employed when clinically indicated, to minimize exposure to toxic ventilatory support.[74,82-86] The target P_{aO_2}, S_{pO_2}, and P_{aCO_2} are likely to differ between patients and within an individual patient over time, based on the degree of ventilatory support the patient requires (ie, risk of ventilator-induced lung injury).

In summary, Figure 4 shows a general suggested approach to the management of pediatric ALI/ARDS. Initial management should include low-V_T ventilation, optimization of PEEP (preferably utilizing a decremental titration strategy), and consideration of exogenous surfactant. If "adequate" oxygenation and ventilation can be obtained with a peak inspiratory pressure less than 30 cm H_2O, a mean airway pressure less than 17 cm H_2O, and an oxygenation index less than 15, then a suggested approach is to continue with periodic optimization of the delivered V_T and PEEP, along with close cardiorespiratory monitoring. If those ventilation goals cannot be met, consider recruitment maneuvers and/or transitioning to HFOV or airway pressure-release ventilation.

In general, INO should not be included in the general management of the pediatric ARDS patient; however, INO should be considered if substantial pulmonary hypertension exists, and as a potential bridge to ECMO, to maintain oxygenation and clinical stability while preparing for ECMO cannulation. If hypoxemia can be appropriately managed without "toxic" ventilatory support, then optimization of ventilatory settings should continue with frequent reassessment.

If refractory hypoxemia or "toxic" ventilatory support persists/develops, consider the appropriate timing for ECMO. As previously stated, the bedside clinical care team must make a careful risk/benefit assessment for each individual patient.

From a non-respiratory perspective, it seems reasonable to use diuretics to strive for a conservative fluid-management approach, keeping in mind that the appropriate target for "dry lungs" in pediatric patients remains unknown. Persistent hyperglycemia should probably be avoided; however, data are lacking to support the need for strict glycemic control. Hypoglycemia should be avoided as much as possible, especially in younger patients. Transfusion thresholds remain at the discretion of the bedside clinician while attempting to balance a lower hematocrit (ie, avoid transfusions) while providing adequate (but not necessarily supranormal) global oxygen delivery. Striving for a supranormal oxygen delivery is more likely to lead to increased toxicity from the interventions than to improve outcome.[74] No data support the need for supranormal oxygen delivery. The key point is to avoid oxygen debt at the cellular level of the organs and tissues throughout the body. Serial monitoring of blood gases and serum lactate levels are generally required. The use of cerebral oximetry (as a surrogate to mixed venous oxygen saturation monitoring) should be considered.

Summary and Thoughts for the Future

Unfortunately, definitive pediatric data are lacking to guide clinical ALI/ARDS management. So pediatric critical care clinicians must extrapolate data from other populations (ie, neonates and adults), rely on their own and their colleagues' clinical experience, and apply the pertinent physiology and pathophysiology with each individual patient. When applying the available data, one must also carefully consider the numerous uncontrolled variables in the individual "real life" critical care setting, including the knowledge and experience of the respiratory therapists, physicians, nurse practitioners, bedside nurses, ECMO specialists, pharmacists, and other personnel.

At the conclusion of this paper, the reader should be left with the view that additional prospective, randomized controlled trials for pediatric ALI and ARDS are clearly needed. One should remain hopeful that more definitive pediatric data are forthcoming, especially with the cooperative efforts and recent growth of the various pediatric clinical research networks. Hopefully, more definitive data to guide pediatric critical care clinicians in their management of infants and children with ALI and ARDS are on the horizon.

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