Pediatric Critical Care

Current Controversies

Christopher W. Mastropietro
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Editors

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Foreword

Guided by controversy to deliver "a little of a lot of therapies" to the critically ill child

In the period surrounding the origin of our specialty of pediatric critical care medicine, life was simpler. We often had an approach that could be characterized with the phrase "pour it like you don't own it!" With time, however, our zeal to cure has tempered, on and off, often as the result of controversies that were created by our approach. This has led to eras across which a given therapy has been the subject of a veritable roller-coaster ride. For example, regarding fluids, I vividly remember periods in time where one attending physician would say that "a full patient is a stable patient," while another attending later in my career said, "make them pee dust." Indeed, we are now in an era of very judicious fluid administration. Similar controversies have evolved surrounding many of our so-called standard interventions such as corticosteroids administration in septic shock, optimal oxygen use in the critically ill, nutritional assessment and delivery, sedation practices, timing of the institution of ECMO in acute lung injury, and the application of hypothermia in acute brain injury, among others. This textbook, *Pediatric Critical Care: Current Controversies,* is thus timely if not overdue. Drs. Mastropietro and Valentine have assembled an outstanding group of experts in our field including Drs. Paul Checchia, Ira Cheifetz, Kanwaljeet Anand, Nilesh Mehta, David Askenazi, Gail Annich, Leticia Castillo, Joseph Carcillo, Kasum Menon, Hector Wong, Ericka Fink, Chani Traube, and Thomas Nakagawa, among many others, to address a number of key controversies that have challenged, if not plagued, our field for decades. This textbook also features a clinical case embedded within each chapter to highlight situations where many of these controversies are most daunting—adding a special and practical component for the reader. The textbook offers a great deal to caregivers in our field from trainees to senior faculty, both for bedside care and to spearhead and direct future investigations. Often I have found that the solution to optimal care in the PICU is one where we bring "a little of a lot of therapies" to critically ill infants and children. Get the right dose

of the optimal therapies to tackle the big problems that we face while limiting toxicity and other unwanted side effects, some of which we do not even (yet) recognize. I believe that this textbook will help us to achieve that important goal.

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Preface

Controversy as a Cornerstone of Pediatric Critical Care

Controversy is as much a part of pediatric critical care medicine as physiology, pharmacology, and microbiology. Controversy surrounding the diagnosis and management of critically ill children can be seen throughout the medical literature, as well as in plenaries and debates at professional national and international meetings, and at the bedside of many of our patients, where physicians within the same institutions can have difficulty agreeing on one strategy or another. Though these controversies are the source of frustration for many of us, they also motivate us to attempt to answer the questions and settle the debates and, in doing so, move our specialty forward.

For this textbook, we have enlisted experts in the field of pediatric critical care medicine to scour the medical literature and, along with their own individual experiences and expertise, present a comprehensive assessment of many of the controversial scenarios that we face in our daily practice. The chapters of the textbook have been organized by sections based on the organ systems on which the controversies are focused. For each chapter, the authors have been tasked to focus more on what we know rather than what we do not know, an approach that should prove more helpful to the readers and their patients. Through case scenarios, data from the most important and most recent published studies, and a wealth of personal experiences, the authors of these chapters have provided excellent resources filled with knowledge and guidance for current and future members of our field, including not only physicians but advanced practice providers, bedside nurses, respiratory therapists, and others who comprise contemporary multidisciplinary pediatric ICU teams.

Flaws can be detected in any research study, no matter the quality of the methods or the stature of the journal. Moreover, in many cases, our perception of flaws within the current literature is often enhanced or minimized, depending on our inherent biases. I would argue that, despite their flaws, value can be found in most of the published works that encompass our current ever-expanding body of literature. With this notion in mind, we hope that, as readers progress through this textbook, they will appreciate the valuable contributions that have been made to our field thus far and be inspired to build upon the foundation that have been provided by the authors as we continue to evolve as a specialty and vocation.

Indianapolis, IN, USA — Christopher W. Mastropietro, MD, FCCM
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Part I

Respiratory Controversies

1 Ventilator Management for Pediatric Acute Respiratory Distress Syndrome

Travis P. Vesel and Ira M. Cheifetz

Clinical Case

A 2-year-old child presents to the emergency department (ED) with poor feeding, fussiness, and tachypnea. His mother reports that he is otherwise healthy, but yesterday he started coughing and developed a fever. The child has been breathing faster than normal over the past 12 hours and has had poor oral intake. In the ED, vital signs include temperature 39.0 C, heart rate 150, respiratory rate 55, blood pressure 90/55, and oxygen saturation 82% on room air. The child is awake but somewhat somnolent. On physical examination, he has nasal flaring, supraclavicular and subcostal retractions, and mild wheezing and rhonchi on auscultation.

- What is the likely diagnosis?
- Does this child meet the definition of pediatric ARDS (PARDS)? If not, what additional data are required to make this diagnosis?
- What is the severity of the child's illness?

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Pathogenesis of Acute Respiratory Distress Syndrome

The clinical presentation of PARDS includes dyspnea, tachypnea, decreased lung compliance, pulmonary edema, and hypoxemia. Acute respiratory distress syndrome (ARDS) is characterized by two major modes of pathogenesis: direct lung injury and indirect lung injury [1]. In pediatric patients, the most common causes of direct lung injury are pneumonia, aspiration, and near drowning, with sepsis as the most common cause of indirect lung injury [2].

The three phases of ARDS are exudative, proliferative, and fibrotic. The exudative phase of lung injury is dominated by direct or indirect lung injury causing an increase in permeability of the alveolar-capillary barrier, with an influx of protein-rich edema fluid, neutrophils, macrophages, erythrocytes, and cytokines into the airspaces causing further damage to the alveolar and bronchial epithelial cells, as well as deactivation of surfactant. This pathophysiologic cascade results in intrapulmonary shunt physiology and arterial hypoxemia.

The flat type I pneumocytes are most sensitive to injury during the acute phase. During the proliferative phase, the cuboidal type II pneumocytes proliferate and differentiate into type I pneumocytes, re-epithelializing the denuded alveolar epithelium to repair the damaged lung segments. Although many patients recover, some

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survivors progress to a chronic fibrosing alveolitis, characterized clinically by chronic hypoxemia, increased alveolar dead space, and decreased pulmonary compliance.

Definition of Pediatric ARDS

In 2015, members of the Pediatric Acute Lung Injury Consensus Conference (PALICC) developed the first reported pediatric-specific definition of ARDS (Fig. 1.1) [3]. Earlier definitions of acute respiratory distress syndrome include the American European Consensus Conference [4] and Berlin [5] definitions and do not include pediatric-specific criteria. The pediatric definition created by PALICC sought to include the unique pathophysiology of PARDS and include consideration of the developmental factors that may influence lung pathology in children. It is important to note the term "acute lung injury" (ALI) was eliminated from the stratification scheme in the 2015 PALICC definition.

The disease severity of PARDS is initially stratified based on noninvasive mechanical ventilation or invasive mechanical ventilation. Considering the increased use of noninvasive mechanical ventilation (i.e., CPAP or BiPAP), the PALICC definition includes patients supported in this manner; however, these patients are not stratified as mild/moderate/severe. In patients supported with invasive mechanical ventilation, disease severity is stratified using oxygenation index (OI) and oxygen saturation index (OSI). Considering pediatric patients are less likely to have arterial catheters as compared to adult patients, diagnostic criteria and disease severity stratification were expanded to include saturation by pulse oximetry. Previous definitions of ARDS relied on PaO_2 by arterial blood gas to make the diagnosis of ARDS. By expanding this definition,

Age	Exclude patients with peri-natal related lung disease			
Timing	Within 7 days of known clinical insult			
Origin of Edema	Respiratory failure not fully explained by cardiac failure or fluid overload			
Chest Imaging	Chest imaging findings of new infiltrate(s) consistent with acute pulmonary parenchymal disease			
Oxygenation	**Non Invasive mechanical ventilation**	**Invasive mechanical ventilation**		
	PARDS (No severity stratification)	**Mild**	**Moderate**	**Severe**
	Full face-mask bi-level ventilation or CPAP ≥5 cm H_20[2] PF ratio ≤ 300 SF ratio ≤ 264[1]	4 ≤ OI < 8 5 ≤ OSI < 7.5[1]	8 ≤ OI < 16 7.5 ≤ OSI < 12.3[1]	OI ≥ 16 OSI ≥ 12.3[1]
	Special Populations			
Cyanotic Heart Disease	Standard Criteria above for age, timing, origin of edema and chest imaging with an acute deterioration in oxygenation not explained by underlying cardiac disease. [3]			
Chronic Lung Disease	Standard Criteria above for age, timing and origin of edema with chest imaging consistent with new infiltrate and acute deterioration in oxygenation from baseline which meet oxygenation criteria above.[3]			
Left Ventricular dysfunction	Standard Criteria for age, timing, and origin of edema with chest imaging changes consistent with new infiltrate and acute deterioration in oxygenation which meet criteria above not explained by left ventricular dysfunction.			

Fig. 1.1 2015 PALICC pediatric acute respiratory distress syndrome (PARDS) definition. [1]Use PaO_2-based metric when available. However, if PaO_2 is not available, wean FiO_2 to maintain $SpO_2 \leq 97\%$ to calculate oxygen saturation index or SpO_2:FiO_2 ratio. [2]For non-intubated patients. [3]Stratification of disease severity by oxygen index or oxygen saturation index should not be used for children with chronic lung disease supported with invasive mechanical ventilation at baseline or children with cyanotic congenital heart disease [3]. (Used with permission)

more patients can be diagnosed with PARDS for treatment and research study purposes.

Other diagnostic criteria similar to previous definitions include chest imaging findings of new infiltrates consistent with acute pulmonary parenchymal disease. The definition was expanded to include unilateral radiographic findings, although this has been debated whether underlying disease pathology in PARDS can cause unilateral lung disease [3]. Timing of onset of PARDS symptoms of hypoxemia and radiographic changes must occur within 7 days of known clinical insult and is used to distinguish from existing chronic lung disease.

Although excluded from previous definitions of ARDS, the 2015 PALICC definition sought to include patients with chronic lung disease (with acute exacerbation), cyanotic congenital heart disease, and left ventricular dysfunction (left atrial hypertension). Diagnosis of PARDS and disease severity is difficult to define in children with chronic lung disease as some of these children are supported with mechanical ventilation and/or supplemental oxygen at baseline. They may also have radiographic findings that meet ARDS criteria at their clinical baseline. Similarly, patients with cyanotic congenital heart disease have low oxygen saturations by definition with a wide spectrum of baseline saturations. Patients with left ventricular dysfunction may develop pulmonary edema with less severe lung injury, considering an elevated baseline left atrial pressure.

It is recommended that all of these at risk populations be considered for diagnosis of PARDS when there is an acute clinical insult, a new finding or change in chest imaging consistent with parenchymal lung disease, and an acute deterioration in oxygenation not explained by changes in cardiac disease. It is important to include these patient groups in the definition of PARDS to allow for earlier diagnosis and therapeutic intervention and to improve the ability to include these patient populations in future research. Limitations to stratification in these patient populations of disease severity based on OI and OSI must be taken into consideration due to the variable, and below normal, baseline.

Clinical Case (Continued)

The child is started on 2 liters per minute (lpm) nasal cannula in the ED with improvement in oxygen saturations to the low 90% range as well as improvement in work of breathing. He is admitted to a pediatric unit but has worsening oxygen saturations over the next 12 h despite increasing oxygen flow. A rapid response is called by the bedside nurse, and the team arrives to find the patient on 4 lpm nasal cannula of 100% oxygen, significant respiratory distress, and oxygen saturation 78%. He is placed on a non-rebreather mask and is transferred to the PICU where he is intubated and started on a conventional ventilator.

- What are the options to improve hypoxemia in this child?
- Are there other less invasive respiratory support options available?
- What ventilator management strategies would you consider in this situation?

Noninvasive Respiratory Support

Although this chapter is focused on current controversies in invasive ventilator management for PARDS, it is important to mention noninvasive respiratory support. Noninvasive respiratory support has had increased use over the last decade, potentially preventing some of the adverse effects caused by invasive mechanical ventilation. These support modalities include high-flow nasal cannula and noninvasive mechanical ventilation devices, including nasal and full-face continuous positive airway pressure (CPAP) and bi-level positive airway pressure (BiPAP). As with invasive mechanical ventilation, the benefits of these noninvasive modalities include delivery of high-oxygen concentration to the alveoli and decreased energy expenditure of the respiratory muscles with the added benefit of preserving natural

airway clearance mechanisms. CPAP helps maintain airway and alveolar patency, thereby preventing and/or improving atelectasis, a significant cause of shunt physiology and arterial hypoxemia. Additionally, adding inspiratory pressure with BiPAP helps increase tidal volume delivery in lungs with low compliance, improving alveolar ventilation and reducing $PaCO_2$ [6].

For most patients, noninvasive support devices are well tolerated, reduce the need for sedation, and possibly prevent intubation and mechanical ventilation, generally in patients with more mild disease. Currently, there are only a few studies to support the use of noninvasive respiratory support in children. In one study of 50 children with acute hypoxemic respiratory failure, predominantly secondary to bronchiolitis, supported with BiPAP or standard treatment (face mask oxygen), the patients supported with BiPAP showed a significantly decreased rate of intubation (28%) over those receiving standard therapy (60%, $p = 0.045$) [7]. This study showed noninvasive ventilation improved hypoxemia, tachycardia, and tachypnea as well as prevented some patients from endotracheal intubation and invasive mechanical ventilation. However, another study comparing noninvasive positive-pressure ventilation to inhaled oxygen post-extubation in children 28 days to 3 years of age showed no difference in re-intubation rates (9.1% vs 11.3%, $p > 0.05$) [8]. These studies did not include selection criteria or stratification by ARDS criteria and highlight the need for further studies in the benefits and potential adverse events related to the use of noninvasive respiratory support in the PARDS population.

In light of the current lack of data in patients with PARDS, noninvasive positive-pressure ventilation may be a safe alternative for pediatric patients with mild PARDS and can be considered to prevent intubation in some patients. It could be debated that noninvasive ventilation should only be considered in patients with less severe disease and not used in patients with moderate to severe lung disease. The clinician must understand potential risks associated with these modalities, including the risk of providing inadequate and untimely respiratory support with subsequent cardiopulmonary deterioration in patients with more severe disease. As noninvasive ventilation is trialed, careful and rapid assessment of the patient's response to therapy is necessary. Patients who will respond to therapy will likely show improvement in respiratory distress and oxygenation within the first 30–60 minutes. Clinical vigilance is required to determine if a patient is adequately supported with noninvasive ventilation and whether invasive mechanical ventilation should be pursued.

Lung-Protective Strategies

In the modern era of mechanical ventilation, much attention has been focused on what has been coined "lung-protective strategies" to prevent ventilator-induced lung injury (VILI). The major focus of these strategies is reduction of mechanical stresses on the alveoli, mainly overdistension (volutrauma), cyclic opening and closing of alveoli (atelectrauma), and excessive plateau pressure (barotrauma). Bedside goal-directed strategies, including tidal volume 5–8 ml/kg, positive end-expiratory pressures (PEEP) 10–15 cm H_2O, inspiratory plateau pressure < 28 cm H_2O [9], permissive hypercapnia (pH > 7.25 without a specific target $PaCO_2$), and permissive hypoxemia (SpO_2 > 88%, PaO_2 55–80), are the mainstay of lung-protective ventilator management strategies.

Tidal Volume Delivery: Volutrauma

Prior to the early 2000s, the general approach to mechanical ventilation targeted tidal volumes of 10–15 ml/kg, normal $PaCO_2$, and normal oxygen saturations. It should be noted that the normal resting tidal volume in humans is generally 6–8 ml/kg. In 2000, a landmark study by the ARDS Network showed a significant decrease in mortality in adult ARDS patients with targeted tidal volumes of 6 ml/kg (31%) as compared to "traditional" tidal volumes of 12 ml/kg (39.8%, $p = 0.007$) [10]. The results of this large adult study provided the basis for a significant shift in

the mechanical ventilation management strategies of ARDS patients. In practice, to achieve low tidal volumes and lower inspiratory pressures, a deviation from the goals of normal $PaCO_2$ and PaO_2 (SpO_2) was developed and coined permissive hypercapnia and permissive hypoxemia, respectively.

Although no pediatric study has confirmed a mortality benefit to low tidal volume ventilation in PARDS, pediatric critical care clinicians, in general, have been keen to adopt this strategy for its potential benefit. However, in contrast to the outlined adult findings, it must be noted that observational pediatric studies have shown a relationship between higher tidal volumes and lower mortality [11] or no relationship between tidal volume and mortality [12, 13]. Although they did not find a relationship with mortality, Khemani and colleagues showed higher tidal volumes were associated with increased ventilator-free days. It is important to note these pediatric studies were performed in the era of "lower than traditional" targeted tidal volumes (i.e., <10 ml/kg); thus, a comparison group to the "traditional" ARDS Network tidal volume group of >12 ml/kg is not available. Considering the limitations of observational studies, it is likely these findings represent a heterogeneous severity of disease, with higher tidal volumes seen in patients with better lung compliance (less severe lung injury) with the use of pressure-control ventilation mode. Additionally, in patients with more severe lung injury, physicians likely targeted lower plateau pressures to avoid barotrauma, resulting in lower tidal volumes.

Predicted body weight as compared to actual body weight is recommended when targeting a specific tidal volume as lung capacity is more closely related to height than weight [14]. Targeting predicted body weight may decrease the risk of over distension and volutrauma in obese patients.

The current recommendation for tidal volume management for PARDS, as described by PALICC, is to target tidal volumes of 5–8 ml/kg predicted body weight and as low as 3–6 ml/kg in patients with poor respiratory system compliance [9]. This recommendation is based largely on the findings of the initial adult studies, which have guided the clinical practice of ARDS with lower tidal volume goals. The studies in pediatrics that show lower mortality related to higher tidal volumes have suggested further study is likely warranted to assess a causal relationship between tidal volume and outcome in those with PARDS.

PEEP Titration: Atelectrauma

During normal respiration, the vocal cords close at the end of expiration to maintain a low level of positive pressure in the airways and alveoli to prevent atelectasis. In ARDS, the functional residual capacity of the damaged alveoli decreases, causing atelectasis unless higher mean airway pressure is applied. The use of higher positive end-expiratory pressure (PEEP) may help to avoid repetitive collapse-opening-collapse injury (atelectrauma).

Determining the optimal PEEP at the bedside can to be a difficult task, with methods including incremental increases (decreases) in PEEP while monitoring lung compliance (estimated using tidal volumes, drive pressure, and pressure/volume loops) and radiographic findings. During PEEP adjustment, especially at higher pressures, cardiopulmonary interactions and hemodynamic monitoring must be considered as elevated PEEP (i.e., intrathoracic pressure) may adversely affect central venous return and right ventricular afterload, therefore decreasing cardiac output.

It should be noted that atelectrauma has only been shown in experimental studies [15]. In the era of targeted low tidal volume, three adult trials in ARDS patients evaluating low PEEP vs. higher PEEP showed no significant difference in mortality [16–18]; however, two systematic reviews and meta-analyses suggested a small survival benefit of higher PEEP in patients with severe ARDS [19, 20]. Interesting to the pediatric critical care provider, a pediatric multicenter, retrospective analysis of 1134 patients with PARDS showed that 26% of pediatric patients were managed with lower PEEP than suggested by the ARDSnet protocol based on FiO_2. The investigators found an

increased mortality in that group as compared to the patients in which PEEP was within the protocol (OR 2.05, 95% CI 1.32, 3.17) [21].

PALICC guidelines suggest maintaining elevated levels of PEEP (10–15 cm H_2O) with consideration of higher titration in severe ARDS with attention to limiting the plateau pressure [9]. Considering no pediatric PEEP titration protocol has been studied prospectively, controversy remains as to whether the ARDSnet adult PEEP/FiO_2 titration chart is optimal for both adult and pediatric patients with ARDS.

Plateau Pressure and Drive Pressure (ΔP): Barotrauma

Plateau pressure refers to the equilibrated static pressure at the end of inspiration during an inspiratory hold, which is a result of the tidal volume delivered above PEEP without influence of airways resistance (flow). In pressure control mode of mechanical ventilation, peak inspiratory pressure (PIP) is controlled by the clinician, and ΔP (drive pressure) = PIP − PEEP. The drive pressure is influenced by: (1) airways resistance, (2) chest wall elastance, and (3) alveolar compliance, whereas the plateau pressure reflects the compliance of the alveoli. The tidal volume is then dependent on the compliance of the lung, with worsening lung compliance resulting in lower tidal volumes at the same inspiratory/plateau pressure.

Elevated peak airway pressures may cause trauma simply by pressure injury to the lung parenchyma. Another mechanism suggested for barotrauma is linked to the heterogeneous nature of ARDS, with some alveolar units more affected than others, resulting in different compliance of different lung segments. This may lead to low tidal volumes in poorly compliant lung segments and overdistension in more compliant (and potentially healthier) lung segments. This concept supports the use of pressure control ventilation modes in patients with PARDS, decreasing the risk of over distension of healthier lung segments, although the debate of volume control vs pressure control is more complex than this single point.

Pediatric observational studies have shown both an association between high inspiratory pressures and increased mortality [11, 12] and a lack of association between inspiratory pressure and mortality [13]. None of these studies were randomized or powered to determine the relationship between inspiratory pressure and mortality. A recent adult study in ARDS patients showed the drive pressure to be most predictive of mortality [22]. Whether there is a relationship between peak inspiratory, plateau, and/or drive pressures and mortality in PARDS is yet to be determined.

Based on the available data and clinical expertise, the PALICC recommendation is to maintain plateau pressures <28 cm H_2O, with consideration to increased pressure (28–32 cm H_2O) in patients with increased chest wall elastance (i.e., decreased chest wall compliance), such as those with obesity, chest wall edema, or severely increased abdominal pressure [9]. This recommendation may be considered controversial to some clinicians who argue that a higher plateau pressure (30–32 cm H_2O) in those without decreased chest wall compliance may be safe. Further studies are needed to delineate a "safe" plateau pressure in those with PARDS with the shared goal to decrease secondary lung injury caused by barotrauma.

Clinical Case (Continued)

The patient has been in the PICU for 72 h and continues to have worsening hypoxemia and progressive bilateral infiltrates on chest radiograph. His viral panel is positive for influenza. Despite attempts at lung-protective ventilator strategies including increased PEEP, plateau pressure < 28 cm H_2O, and tidal volume 5–8 ml/kg ideal body weight, his oxygen saturations are consistently ~80–85%. He is on the conventional ventilator in pressure control mode with FiO_2 0.80, PEEP 14 cm