Pediatric Acute Respiratory Distress Syndrome

A Clinical Guide

Steven L. Shein
Alexandre T. Rotta
Editors

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To my parents, Jeff and Diane, and brother, David, thank you for all of your support growing up. To my countless teachers, mentors, co-residents, co-fellows, and all the rest at CWRU, RBC, and CHP, thanks for teaching me and being in the trenches with me. To my wife, Monica, and my children, Jack and Emily, thank you for your love, your support, your patience, your understanding, your hugs, and your laughter. And to all of the parents and families who have permitted me to care for their critically ill loved one, thank you for the privilege of doing so.

Steven L. Shein

To my parents, Enio and Newra, for their contagious love for medicine. To my brother, Francisco, for setting the bar so high. To my mentor, Ashok, for showing me the way. To my teachers, Brad and David, for all the knowledge. To my wife, Kristy, and my daughters, Ashlynn and Valentina, for their encouragement, support, sacrifices, patience, and unconditional love.

Alexandre T. Rotta

Preface

In 1967, Ashbaugh and colleagues described a group of predominantly adult patients with various underlying conditions who developed a peculiar form of respiratory failure. Regardless of the inciting etiology, these patients shared a common rapid progression to respiratory failure with hypoxemia, diffuse infiltrates on chest radiographs, decreased lung compliance, and decreased functional residual capacity, requiring the application of positive end-expiratory pressure (PEEP) to improve oxygenation. This condition, which we now know as the acute respiratory distress syndrome (ARDS), was based on somewhat vague diagnostic criteria and was not specific enough to exclude other medical conditions with similar manifestations.

Our understanding of ARDS has increased greatly during the past five decades. ARDS definitions and diagnostic criteria have also evolved over time, including the Murray Lung Injury Score (1988), the American-European Consensus Conference Definition (1994), and the Berlin Definition (2012) put forth jointly by the European Society of Intensive Care Medicine (ESICM) and the Society of Critical Care Medicine (SCCM). Each of these definitions represented a step forward in delineating this important diagnosis, yet the applicability of these adult-centric definitions had significant limitations for children since they did not consider ARDS factors germane to the pediatric patient.

The lack of a pediatric-specific ARDS definition, coupled with a rapidly growing body of literature on children with acute hypoxemic respiratory failure, led an expert panel to assemble the Pediatric Acute Lung Injury Consensus Conference (PALICC, 2015) and put forth the first definition of pediatric ARDS (PARDS). This definition represented a major step forward for those involved in PARDS diagnosis, treatment, and research. It provided the framework that would allow for comparisons across multiple institutions, helped define the actual worldwide prevalence of this condition, and clarified the role of various treatment modalities and their impact on outcomes.

This textbook will provide a comprehensive review of the available and emerging science related to PARDS, discuss state-of-the-art treatment modalities and strategies, and reflect on clinical outcomes for this important condition. The various chapters were written by established experts in the field of PARDS, many of whom participated in the original PALICC effort.

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We are grateful for the diligent work and dedication of our contributors, without whom this book would have never amounted to more than an idea. We are also thankful to Sheik Mohideen, Andy Kwan, and the entire team at Springer Nature for keeping us on track and for their expert assistance.

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The History of ARDS and the Need for a Pediatric Definition

1

Howard Eigen

The history of acute respiratory distress syndrome (ARDS) is long, complex, and very interesting. It is one of the few conditions first named in children, in this case neonates with infant respiratory distress syndrome (IRDS), also known as hyaline membrane disease. The term was then applied to adults with acute respiratory failure exhibiting clinical and pathophysiological features closely resembling those of the neonatal counterpart. It is likely that the clinical entity we now know as ARDS has existed for centuries, yet its recognition as an organized syndrome did not occur until just over half a century ago.

The initial description of pulmonary hyaline membranes is generally attributed to Hochheim [1], who, in 1903, described 2 neonatal cases at autopsy and attributed the presence of alveolar membranes to the aspiration of amniotic sac contents. They were first described in the English-language literature in 1925 by Johnson [2], who regarded hyaline membranes as a form of neonatal pneumonia. The studies of Farber in the 1930s attributed pulmonary hyaline membranes to the peripheralization by respiratory activity of aspirated amniotic sac contents – particularly vernix – into the distal airways of the lung [3, 4]. This concept of IRDS remained predominant until the mid-1950s.

In 1959, James [5] contributed new observations of the clinical features of IRDS because of the then novel practice of caring for these infants, unclothed in clear-walled incubators, which allowed for the observation of the patient struggling through several hours of rapid and labored breathing with deep sternal and intercostal retractions alternating with periods of apnea. This is similar to how the understanding of ARDS evolved: the rudiments of the pathology and the clinical course were each identified separately, without a full understanding of the links between them.

Perhaps the earliest published description of ARDS came in 1821 when Laennec characterized anasarca of the lungs and pulmonary edema without heart failure in his book "Treatise on Diseases of the Chest." The concept of ARDS as an unnamed clinical entity certainly was known early in World War I. A military medical textbook published in 1915 and used by Canadian armed forces during World War I contains a graphic description of ARDS in relation to a poison gas attack: "Edema of the lungs, with general asphyxia. Livid cyanosis with great dyspnea is the outstanding clinical feature. A yellow serous fluid fills the air passages in such quantities that it may drip from the mouth of the living patient when the stretcher is tilted head downwards. Death in this stage may occur at any time from the first to the fourth or fifth day." [6] Concomitantly, physicians

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in World War I established the relationship between trauma and a sudden and severe respiratory failure ultimately leading to death, then termed "posttraumatic pulmonary massive collapse." [7]

A 1946 publication by Brewer and colleagues [8] described the "wet lung" in the following manner: "In handling this large number of casualties it was found in the forward hospitals in particular, that those cases with dry lungs gave us very little trouble. On the other hand, those showing a wet pulmonary tree were difficult to resuscitate from shock." By the close of World War II, the syndrome of "wet lung" had been characterized further, in which life-threatening respiratory distress complicated the progressive recovery from hemorrhagic and traumatic shock incurred during combat.

During the Vietnam War, as the survival rate following circulatory collapse on the battlefield improved, the syndrome was frequently identified, but under various names. Thus, "wet lung," "shock lung," "transfusion lung," or "Da Nang lung" became synonyms for severe acute respiratory failure that followed successful resuscitation from circulatory collapse. The sequence was similar in all of those named syndromes: severe nonthoracic injury, blood loss, and hypotension acquired during combat, successful resuscitation on the battlefield, and prompt evacuation to a medical facility for further management. In a few days, there followed progressive respiratory distress and failure. Although only a small fraction of those who reached the hospital developed "shock lung," in those who did, the pattern of evolution was consistent: insidious onset of rapid shallow breathing, crackles, refractory cyanosis, radiographic appearance of enlarging interstitial and alveolar infiltrates with the entire lung eventually enveloped in a diffuse haze, and a chest radiographic "white out." Administration of high oxygen concentrations and assisted ventilation became less and less effective, followed by death resulting from respiratory insufficiency often complicated by circulatory collapse.

In 1967, Ashbaugh and colleagues [9] published a more detailed, systematic, and cohesive description of the syndrome based on the clinical course of 12 patients with acute respiratory failure that did not respond to usual methods of respiratory support. These patients had tachypnea, hypoxemia, and loss of lung compliance following a variety of insults, exhibiting clinical and pathological characteristics thought to be "remarkably similar to the infantile respiratory distress syndrome" [9]. In a follow-up publication in 1971, Petty and Ashbaugh [10] used the term *adult* respiratory distress syndrome, presumably not to exclude children from the diagnosis, but in an attempt to distinguish it from the well-established IRDS. In fact, one of the patients described in the original cohort was an 11-year-old with the ARDS clinical syndrome, and 4 others were teenagers (18- and 19-year-olds) that would have been routinely cared for by pediatric intensivists in the current era.

The incidence and recognition of the adult respiratory distress syndrome increased dramatically after 1967, coinciding with the height of the Vietnam War. With the advent of better treatments in the field and rapid staged evacuations, more casualties survived to reach higher-level care and had time to develop ARDS, or before 1967, one of its synonyms (Box 1.1). Given the magnitude of the disease in morbidity, mortality, and cost, a clear, widely accepted, and clinically useful ARDS definition was needed.

Over the next couple of decades, ARDS continued to be an important cause of morbidity and death. Nevertheless, the heterogeneous nature of

Box 1.1 ARDS Historical Synonyms

- Congestive atelectasis
- Wet lung
- Hemorrhage lung
- Shock lung
- Pump lung
- Trauma lung
- Transfusion lung
- White lung
- Da Nang lung
- Adult hyaline membrane disease
- Adult respiratory distress syndrome

Table 1.1 The American-European Consensus Conference definition of ARDS

	Timing	Oxygenation	Chest radiograph	Pulmonary artery wedge pressure
ALI criteria	Acute onset	$PaO_2 \leq 300$ mm Hg (regardless of PEEP level)	Bilateral infiltrates seen on frontal chest radiograph	≤18 mm Hg when measured or no evidence of left atrial hypertension
ARDS criteria	Acute onset	$PaO_2 \leq 300$ mm Hg (regardless of PEEP level)	Bilateral infiltrates seen on frontal chest radiograph	≤18 mm Hg when measured or no evidence of left atrial hypertension

PEEP positive end-expiratory pressure, *ALI* acute lung injury, *ARDS* acute respiratory distress syndrome

ARDS created great difficulty in determining its true incidence and outcomes, especially in the absence of a clear definition. As an example, the published ARDS mortality rate varied between 10% and 90%, and its reported incidence differed vastly between European countries and the United States [11]. This was due to, at least in part, the lack of an agreed upon definition among various countries, or even among different studies within the same country. In an attempt to bring clarity and uniformity to the definition of ARDS, a series of meetings were held under the auspices of the American Thoracic Society and the European Society of Intensive Care Medicine in 1992. The American-European Consensus Conference on ARDS (the AECC) was convened with the charge of not only defining ARDS, but also to bring light to the issue of incidence, focus on the emerging understanding of pathophysiologic mechanisms, and establish guidelines for the conduct and coordination of clinical studies. The AECC published its position paper in 1995, but the formal definition was not easily arrived at, as some participants suggested that the definition of ARDS should be different for research, epidemiology, and individual patient care. Early on, it was decided that there should be a return to the term "acute" (rather than "adult") respiratory distress syndrome in recognition of the fact that ARDS is not limited to adults. Unfortunately, the AECC also introduced the term acute lung injury (ALI) to the definition, in an effort to characterize the less severe end of the ARDS spectrum. Later on, this simply caused confusion as the cutoff points for ARDS and ALI became a topic for debate. More recently, ALI has been dropped from general usage and termed "mild ARDS."

The AECC defined ARDS as the acute onset of hypoxemia (arterial partial pressure of oxygen to fraction of inspired oxygen ratio [PaO_2/FIO_2] ≤200 mm Hg) with bilateral infiltrates on a frontal chest radiograph, with no evidence of left atrial hypertension (Table 1.1). The AECC did not consider the type or intensity of respiratory support to be a requirement in defining ALI or ARDS because resources for ventilator therapy and physician practice patterns vary considerably. Also, there are many cases in which mechanical ventilation is intentionally withheld because of patient request or a determination that aggressive support is futile. In general, it is best to keep disease definitions independent of the therapy used to treat them. Definitions of any disease states suffer at the margins, usually at the lower end of the severity spectrum.

Nearly 2 decades later, the Berlin Conference was organized to clear up multiple issues regarding the reliability and validity of the AECC definition. The ARDS conceptual model proposed by the Berlin Conference stated that ARDS is a type of acute diffuse, inflammatory lung injury that leads to increased pulmonary vascular permeability, increased lung weight, and loss of aerated lung tissue. The clinical hallmarks are hypoxemia and bilateral radiographic opacities. These are associated with increased venous admixture, increased physiological dead space, and decreased lung compliance. The morphological hallmark of the acute phase is diffuse alveolar damage (i.e., edema, inflammation, hyaline membrane, or hemorrhage). The Berlin Conference proposed three disease severity categories and tested outcomes of these categories against a validation dataset of previous cases (Table 1.2). Using the Berlin definition, patients

Table 1.2 The Berlin definition of ARDS

Acute respiratory distress syndrome	
Timing	Within 1 week of a known clinical insult or new worsening respiratory symptoms
Chest imaging[a]	Bilateral opacities – not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload Need objective assessment (e.g., echocardiography) to exclude hydrostatic edema in no risk factor present
Oxygenation[b] Mild Moderate Severe	200 mm hg < PaO_2/FiO_2 ≤ 300 mm hg with PEEP or CPAP ≥5 cm H_2O[c] 100 mm hg < PaO_2/FiO_2 ≤ 200 mm hg with PEEP or CPAP ≥5 cm H_2O PaO_2/FiO_2 ≤ 100 mm hg with PEEP or CPAP ≥5 cm H_2O

CPAP continuous positive airway pressure, *FiO_2* fraction of inspired oxygen, *PaO_2* partial pressure of arterial oxygen, *PEEP* positive end-expiratory pressure
[a]Chest radiograph or computed tomography scan
[b]If altitude higher than 1000 m, the correction factor should be calculated as [PaO_2/FiO_2 × (barometric pressure/760)]
[c]This may be delivered noninvasively in the mild ARDS group

with mild, moderate, or severe ARDS exhibited incremental mortality (27%, 32%, and 45%, respectively), as well as increased median duration of mechanical ventilation in survivors [12]. Compared with the AECC definition, the final Berlin definition had better predictive validity for mortality and was rapidly accepted worldwide for its overall superiority.

Both the AECC and Berlin definitions of ARDS were created without specific consideration to ARDS that occurs in children. If a case were to be made for a separate pediatric definition, it must have been made on the basis that the current definition for adults does not properly characterize the disease in children. Unlike in adults with ARDS, the Berlin definition severity stratification fails to show an incremental mortality between children with mild and moderate ARDS at 6, 12, or 24 hours from diagnosis [13]. Any new template proposed for PARDS should be carefully drawn so as to properly characterize the syndrome and show what elements are unique to the disease in children.

In 2015, Pediatric Acute Lung Injury Consensus Conference (PALICC) published the much needed and long overdue first pediatric-specific definition of ARDS [14]. In addition, it put forth consensus recommendations regarding therapies for pediatric acute respiratory distress syndrome (PARDS), defined a subset of patients considered to be "at risk" for PARDS, addressed PARDS in specific populations (i.e., cyanotic heart disease, chronic lung disease, left ventricular dysfunction), and delineated priorities for future research. The definitions and recommendations were developed over the span of 2 years by 27 experts in the field of PARDS representing 21 academic institutions from 8 countries in 3 continents. The PALICC experts evaluated clinical issues on 9 topics related to PARDS and developed and voted on 151 recommendations. Strong agreement (meaning that all experts rated the recommendation 7 or higher on a scale of 1–9) was reached in 132 recommendations.

The PARDS definition was a central component of the PALICC report [14]. Like the Berlin definition, PALICC determined that the onset of PARDS must occur within 7 days of a known clinical insult and the respiratory failure must not be fully explained by cardiac failure or fluid overload. Significant changes from the Berlin definition included abandoning the PaO_2/FiO_2 ratio in the grading of PARDS severity (mild, moderate, and severe) in favor of the oxygenation index (OI) or the oxygen saturation index (OSI). Using the OI or the OSI allows for a more precise appreciation of the role of mechanical ventilation support on oxygenation and severity of illness classification. The presence of bilateral pulmonary infiltrates is no longer a requirement in the PALICC definition, since there is no evidence that pediatric patients with unilateral pulmonary involvement have different clinical courses and outcomes than those with bilateral disease. PALICC deliberately chose not to specify age criteria for PARDS, but it should be understood that the definition is intended to cover the demographics generally cared for by pediatric intensivists and excludes neonates with perinatal-

related lung disease (e.g., meconium aspiration, hyaline membrane disease, alveolar capillary dysplasia). Chapter 2 covers the PALICC definition in detail.

ARDS has had a longer history than many would think. Our understanding of this important syndrome was built through thoughtful and astute clinical observations with the ultimate goal of making therapy more effective and improving patients' lives. It is clear that the disease in children is distinct from that in adults, so although ARDS definitions have evolved over time, the recent development of a pediatric-specific definition has been widely welcomed by the critical care community. This much needed thoughtful and relevant new PARDS definition provides a unifying language for those caring for critically ill children or advancing the field through research.

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2 Pediatric Acute Respiratory Distress Syndrome: Definition and Epidemiology

Fernando Beltramo and Robinder G. Khemani

Introduction

In 1821, Laennec described in his "Treatise on Diseases of the Chest" probably the first published description of ARDS. Laennec described the gross pathology of the heart and lungs as idiopathic anasarca of the lungs – pulmonary edema without heart failure. By the 1950s, pulmonary edema had become a medical entity; however, no distinction was made at that time between cardiac and noncardiac causes. For a period of time, ARDS went by the name of inciting injuries (shock lung, posttraumatic lung, Da Nang lung, etc.). It was not until 1967, in a landmark article published in Lancet, that the term acute respiratory distress syndrome (ARDS) was mentioned [1]. Ashbaugh and colleagues described a syndrome of tachypnea, hypoxia, and decreased pulmonary compliance in a series of 11 adults and one child with respiratory failure. The pathologic features included interstitial and intra-alveolar edema and hemorrhage, as well as hyaline membrane formation.

Like other clinical syndromes, ARDS lacks a definitive gold standard for diagnosis. Histopathology is impractical for real-time clinical applications, no definitive biomarker is present in all cases, and there is a spectrum of the degree of injury. While elements of the pathobiology continue to be established, in vitro and in vivo models have improved the fundamental understanding of the pathobiology of ARDS. As such, our diagnostic criteria have sought to identify clinical signs and symptoms reflective of this pathobiology related to the diffuse albeit nonhomogeneous nature of the injury at both the alveolar epithelial and endothelial surface, inflammation, loss of functional residual capacity and impairment in pulmonary compliance, hypoxemia, and elevations in alveolar dead space.

In 1994, the American European Consensus Conference (AECC) defined ARDS as a syndrome of inflammation and increased permeability in the lungs that is associated with a constellation of clinical, radiologic, and physiologic abnormalities that cannot be explained by, but may coexist with, left atrial or pulmonary capillary hypertension [2]. For years, pediatric practitioners used the AECC definition of ARDS for clinical care, research, and prognostication.

While this definition was used for nearly 30 years, there were several limitations of the AECC definition of ARDS related to the influence of ventilator settings on hypoxemia, the timing of disease, use of noninvasive ventilation, defining a spectrum of hypoxemia severity in ARDS, and how to specifi-

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S. L. Shein, A. T. Rotta (eds.), *Pediatric Acute Respiratory Distress Syndrome*,
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cally handle left ventricular dysfunction. These limitations were addressed by the Berlin definition in 2012. While some of these issues are common between adults and children with ARDS, pediatric-specific considerations were not included in either Berlin or AECC definitions [3, 4]. Although there are similarities in the pathophysiology of ARDS in adults and children, pediatric-specific practice patterns, comorbidities, and differences in outcome necessitated a pediatric-specific definition [5].

In 2015, the Pediatric Acute Lung Injury Consensus Conference (PALICC) published specific definitions for pediatric ARDS (PARDS) (Table 2.1) and those gauged to be at risk for PARDS (Table 2.2), as well as recommendations regarding management and suggested priorities for future research [6]. PALICC was a two-year process that consisted of 27 experts from eight countries on three continents. The group was tasked with determining whether the Berlin crite-

Table 2.1 PARDS definition

<table>
<tr><td rowspan="5">Age: Exclude patients with perinatal-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</td><td colspan="3">Oxygenation</td></tr>
<tr><td colspan="3">Noninvasive mechanical ventilation: Full-face mask bi-level ventilation or CPAP ≥ 5 cm H_2O[b] with PF ratio ≤300 or SF ratio ≤ 264[a]</td></tr>
<tr><td colspan="3">Invasive mechanical ventilation</td></tr>
<tr><td>Mild</td><td>Moderate</td><td>Severe</td></tr>
<tr><td>4 ≤ OI < 8
5 ≤ OSI < 7.5[a]</td><td>8 ≤ OI < 16
7.5 ≤ OSI < 12.3[a]</td><td>OI ≥ 16
OSI ≥ 12.3[a]</td></tr>
<tr><td colspan="4">Cyanotic heart disease: Standard criteria with an acute deterioration in oxygenation not explained by underlying cardiac disease
Chronic lung disease: Standard criteria with chest imaging consistent with new infiltrate and acute deterioration in oxygenation from baseline
Left ventricular dysfunction: Standard criteria with chest imaging changes and acute deterioration in oxygenation not fully explained by left ventricular dysfunction</td></tr>
</table>

OI = oxygenation index = (FiO_2 × mean airway pressure × 100)/PaO_2
OSI = oxygen saturation index = (FiO_2 × mean airway pressure × 100)/SpO_2
[a]Use PaO_2-based metric when available. If PaO_2 not available, wean FiO2 to maintain SpO2 ≤ 97% to calculate OSI or SF ratio
[b]For non-intubated patients treated with supplemental oxygen or nasal modes of noninvasive ventilation, see Table 2.2 for at-risk criteria

Table 2.2 At risk of PARDS definition

<table>
<tr><td rowspan="4">Age: Exclude patients with perinatal-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</td><td>Oxygenation</td></tr>
<tr><td>Nasal mask CPAP or BiPAP
FiO_2 ≥ 40% to attain SpO_2 88–97%</td></tr>
<tr><td>Oxygen via mask, nasal cannula, or high flow
SpO_2 88–97% with oxygen supplementation at minimum flow[b]:
<1 year: 2 L/min
1–5 years: 4 L/min
5–10 years: 6 L/min
>10 years: 8 L/min</td></tr>
<tr><td>Invasive mechanical ventilation
Oxygen supplementation to maintain SpO_2 ≥ 88% but OI < 4 or OSI < 5[a]</td></tr>
</table>

[a]If PaO_2 not available, wean FiO_2 to maintain SpO_2 ≤ 97% to calculate OSI
[b]Given lack of available data, for patients on an oxygen blender, flow for at-risk calculation = FiO2 × flow rate (L/min) (e.g., 6 L/min flow at 0.35 FiO2 = 2.1 L/min)

ria for ARDS, created by adult practitioners and validated with data from adult patients with ARDS, was applicable in children. The Berlin definition of ARDS was seen as an iterative improvement, and although there is value in having a single definition applicable to all ages of patients, pediatric-specific shortcomings of the Berlin definition were identified in relation to (1) whether age or stage of lung development affects the definition of ARDS, (2) the importance and reliability of radiographic criteria, (3) respiratory criteria for severity of disease and risk stratification, (4) the increasing use of noninvasive respiratory support and noninvasive monitoring for acute hypoxemic respiratory failure, and (5) the ability to diagnose ARDS in patients with pediatric pulmonary and cardiac comorbidities. Aspects of the Berlin definition related to (6) timing of disease and (7) coexistence of cardiac disease and ARDS with methods to define left ventricular dysfunction were likely to be similar across a spectrum of age, with some pediatric-specific modification.

Definition of Pediatric ARDS (PARDS) by the Pediatric Acute Lung Injury Consensus Conference

The Berlin and PALICC definitions of ARDS are similar in regard to the development of signs and symptoms within 7 days of a clinical insult and the development of pulmonary edema that is not fully explained by cardiac failure of fluid overload. Unlike the Berlin definition, the PALICC definition does not require bilateral infiltrates on chest radiograph, incorporates pulse oximetry metrics when PaO_2 is not available, introduces the use of oxygenation index (OI) and oxygenation saturation index (OSI) to stratify severity groups instead of PaO_2/FiO_2 (PF ratio) with minimum positive end-expiratory pressure (PEEP), and creates specific criteria to define PARDS in children with chronic lung disease and cyanotic heart disease. In addition, no upper limit of age is defined for PALICC criteria, although children with perinatal-related lung injuries are excluded. Moreover, PALICC had pediatric-specific criteria to define PARDS and at risk for PARDS in infants and children on noninvasive ventilation.

Rationale for Age Criteria

PALICC specifically excludes children with perinatal-related lung disease from the PARDS definition, although there is no upper limit for age. Although the pathobiology of acute lung injury caused by perinatal events such as aspiration of meconium or group B Streptococcus may be similar to the diffuse inflammatory and injury mechanisms of PARDS, the unique pathophysiology related to persistent fetal circulation, changes in perinatal pulmonary vascular resistance, and the processes of care by neonatologists as compared with pediatric intensivists made it important to consider this group of patients separately. In response to this, a similar consensus conference was convened to create a neonatal definition of ARDS, which has many similarities to the PALICC definition [7].

The PALICC definition has no upper limit of age, because there was no clear break point in the incidence or mortality of ARDS, sepsis, or pneumonia between adolescents and young adults [8–12]. Furthermore, there is no clear break point at which critically ill patients are no longer cared for by pediatric intensivists. Increasingly, there are patients in their twenties cared for by pediatric practitioners, and many adolescents are cared for in adult institutions. As such, there is no clear age cut point at which a patient with ARDS should be considered “pediatric” versus “adult.” In order to reduce confusion and improve recognition of ARDS, PALICC recommended health care providers caring for adolescents and young adults should use the definition of ARDS with which he or she is most familiar.

Timing and Triggers

Acute onset has been included in definitions of ARDS to differentiate ARDS from existing chronic lung disease. In the AECC definition, acute onset was mandated but timing was not

specified; in the Berlin definition ARDS onset was mandated to be within 1 week of a known clinical insult or new or worsening respiratory symptoms [2, 4]. Review of both the pediatric and adult literature identified key similarities in the timing of ARDS after an inciting event such as sepsis, trauma, or aspiration, with most of patients developing symptoms within the first 24 hours and almost all within 7 days [13–19].

Some subgroups of patients develop ARDS very quickly. For example, transfusion-related acute lung injury (TRALI) is defined as ARDS that develops within 6 hours of a transfusion [20, 21]. Similarly, neurogenic pulmonary edema develops rapidly following intracranial insult, typically from traumatic brain injury or subarachnoid hemorrhage [22]. Likewise, ARDS usually develops promptly in the setting of pediatric drowning-related lung injury [23].

Coexistence of ARDS with Left Ventricular Failure/Dysfunction

The issue of left ventricular (LV) dysfunction/failure is specifically addressed by both the AECC criteria and the Berlin criteria. The goal is to differentiate hydrostatic causes of pulmonary edema from ARDS. In the original AECC criteria, the presence of left atrial hypertension (pulmonary capillary wedge pressure > 18 mm Hg or clinical evidence of left atrial hypertension) was an exclusion criterion for ARDS. Berlin revised this to allow ARDS to coexist with left ventricular dysfunction, as long as there are clear risk factors for ARDS. If not, objective assessment to exclude cardiac failure (echocardiography) should be performed. PALICC concluded that these phenomena are similar in children. Varying degrees of left ventricular dysfunction are frequently reported in children with ARDS and may be associated with increased mortality [24, 25]. Furthermore, echocardiography is widely used in pediatrics to quantify ventricular function and is a good predictor of cardiac symptoms and outcomes in children with left ventricular failure [26].

Radiographic Findings in PARDS

Both AECC and Berlin definitions of ARDS require the presence of bilateral pulmonary infiltrates on chest radiograph. The primary argument to include bilateral infiltrates in the definition of ARDS is to allow for discrimination between localized processes such as lobar pneumonia and the diffuse inflammatory processes seen in both lungs with ARDS. However, PALICC removed the requirement for bilateral infiltrates, instead requiring patients had evidence of pulmonary parenchymal disease. The main arguments for the removal of bilateral infiltrates surrounded (1) the lack of sensitivity of chest radiographs to detect all pulmonary parenchymal inflammation and edema, (2) that opacification on chest imaging often lags behind hypoxemia, and (3) that the presence of bilateral infiltrates on chest radiograph does not seem to impart additional risk for poor outcome not otherwise captured with the degree of hypoxemia. PALICC elected not to eliminate radiology altogether from the definition to help differentiate other causes of acute hypoxemic respiratory failure, which do not share the pathophysiology of ARDS (i.e., asthma without coexisting pneumonia). However, because there is some evidence to suggest that the presence of bilateral infiltrates may have prognostic relevance in certain subgroups of patients, radiographic data should be included in the design of research studies for enrollment stratification or subgroup analyses based on the presence or absence of bilateral infiltrates.

Respiratory Criteria for Disease Severity

Unlike the Berlin definition, PALICC allows for the use of pulse oximetry criteria when an arterial PaO_2 is not available and recommends the use of oxygenation index (or oxygen saturation index) instead of PF ratio for those on invasive mechanical ventilation.

PALICC argued that pulse oximetry criteria are crucial to define ARDS in children because arterial

lines are not used in all ventilated children. Increasingly, arterial blood gases or arterial line monitoring are reserved for patients with hemodynamic instability or severe hypoxemia. Requiring arterial blood sampling would lead to a significant underrecognition of children with PARDS and make the definition subject to selection bias based on provider preference in obtaining an ABG. Investigators have highlighted that even after stratifying for similar degrees of hypoxemia, mechanically ventilated children with ABGs are sicker, have higher severity of illness, and are on more vasopressor support [27]. Furthermore, several studies have validated that SpO_2-based criteria have a strong clear predictable relationship with PaO_2-based criteria, validating both SpO_2/FiO_2 ratio and the oxygen saturation index. However, it is important to remember that theses metrics require that the SpO_2 be ≤97% since the oxyhemoglobin dissociation curve is nearly flat when SpO_2 is >97% [25, 28–32].

OI Versus PF Ratio

The Berlin definition for ARDS accounts for differences in ventilator management by requiring a minimal PEEP of 5 cm H_2O or CPAP of 5 cm H_2O for noninvasively ventilated adults. A minimum PEEP of 10 cm H_2O was considered to define severe ARDS, but this requirement was removed from the definition because it did not discriminate increased risk of mortality as compared with a PEEP of 5 cm H_2O. It is important to note that most patients included in the validation of the Berlin criteria were enrolled in ARDSNet studies, and oftentimes PEEP management was protocolized with a PEEP/FiO_2 table, with over 50% of patients having a baseline PEEP >10 cm H_2O [3, 4, 33, 34]. Pediatric intensivists generally use less PEEP than their adult colleagues [25, 28, 35], are more variable in how PEEP is applied as a function of hypoxemia, and less frequently escalate PEEP above 10 cm H_2O [35, 36]. This may be important because observational data suggests that failure to escalate PEEP as hypoxemia worsens is independently associated with mortality in PARDS [37].

While some investigators recommend assessing PF ratio on standard ventilator settings (i.e., PEEP of 10 cm H_2O) [38], PALICC determined that requiring specific ventilator manipulations may impair recognition of PARDS by clinicians. Instead, PALICC elected to use oxygenation index (OI = [FiO_2 × mean airway pressure × 100] ÷ PaO_2) to account for the degree of ventilator support. Cut points were derived and validated using existing datasets and the risk of death nearly doubled for each successive cut point: OI < 4 (at risk for PARDS), 4–8 (mild PARDS), 8–16 (moderate PARDS), and > 16 (severe PARDS) with a relatively equal distribution of patients within the mild, moderate, and severe groups. Like the Berlin definition, PALICC developed PARDS severity groups to facilitate common definitions for future research and therapies targeting children with different degrees of lung injury. Given clear differences in mortality and outcome based upon disease severity, as well as potential differences in pathophysiology, risk-benefit profiles may differ based upon disease severity [39, 40].

Pulse Oximetry Versus PaO_2

Fewer arterial blood gases are obtained in pediatric ICUs, and the use of noninvasive respiratory support has resulted in increasing number of patients with lung injury that are cared for outside of ICUs [35, 41–43]. Therefore, it was imperative to create a definition for PARDS that did not rely upon the subjective decision to obtain an ABG [44]. Given the strong linear relationship between oxygen saturation index [OSI = (FiO_2 × mean airway pressure × 100)/SpO_2] and OI when the SpO_2 is ≤97%, PALICC established OSI cut points to correspond with the OI cut points proposed earlier [31]. The SF ratio also has a strong relationship with PF ratio [31, 32, 45], particularly for those on invasive mechanical ventilation. It is unclear how well SF ratio performs in relation to PF ratio for children receiving noninvasive ventilation, given difficulties in calculating delivered FiO_2 and the potential effect of modification based upon the degree

of ventilator support. For this reason, PALICC did not recommend applying SF ratios for non-intubated patients (or those not on full-face mask noninvasive ventilation) to grade severity, but rather created guidelines based on combinations of SpO_2 and minimal delivered oxygen to establish who is at risk for PARDS. Unfortunately, conventional methods of estimating the fraction of delivered oxygen (FdO_2) for those on nasal modes on NIV may over- or underestimate FiO_2 depending on the rate of flow delivered to the patient, the patient's minute ventilation, and whether the flow is warmed or humidified. The published guidelines for the calculation of FiO_2 by the American Association of Respiratory Care (AARC) suggest that nasal cannula do not provide a FiO_2 greater than 40% [46–49].

PALICC recommended that patients who are on full-face mask modes of noninvasive ventilation with a minimum CPAP of 5 cm H_2O who have PF ratios ≤300 or SF ratios ≤264 be considered to have PARDS. Patients who are on full-face mask CPAP or BiPAP but do not fulfill all the criteria for PARDS should be considered at risk for PARDS. To apply SpO_2 criteria to diagnose PARDS, oxygen therapy must be titrated to achieve an SpO_2 between 88 and 97%.

Defining PARDS in Children with Existing Lung or Cardiac Disease

A number of exclusion criteria related to gestational age, preexisting chronic lung disease, cyanotic congenital heart disease, and coexisting left ventricular failure/dysfunction have been applied in variable ways in previous PARDS investigations. PALICC sought to standardize criteria in these subpopulations to facilitate future research and clinical care because these preexisting comorbidities do not exclude the potential for these patients to develop PARDS, and these comorbidities represent important at-risk patient populations.

The most important factor in the diagnosis of PARDS in patients with preexisting lung disease is the acute deterioration in oxygenation in response to a known clinical trigger. This is important because at baseline these children may have evidence of pulmonary parenchymal disease on chest imaging and may be on invasive or noninvasive mechanical ventilation. Hence, PALICC recommends that patients with preexisting chronic lung disease who are treated with supplemental oxygen, noninvasive ventilation, or invasive ventilation via tracheostomy should be considered to have PARDS if they have acute changes that meet standard PARDS criteria (acute onset, a known clinical insult, chest imaging supporting new-onset pulmonary parenchymal disease) and have an acute deterioration in oxygenation from baseline which meets oxygenation criteria for PARDS.

Patients with cyanotic congenital heart disease have not been addressed in either the AECC or the Berlin criteria. In general, the presence of cyanotic congenital heart disease has been considered an exclusion criterion for the diagnosis of ARDS in children. This is understandable as intracardiac mixing or right-to-left shunting of blood affects the PF ratio and other indices of oxygenation. However, it is clear that PARDS can occur in children with cyanotic congenital heart disease [50]. Hence, worsening hypoxemia with pulmonary parenchymal disease on chest radiograph in the absence of changes in the underlying cardiac disease may be consistent with a diagnosis of PARDS.

The diagnosis of ARDS in these children requires individual providers to exclude new changes in intracardiac shunt/mixing or worsening left ventricular dysfunction as the cause of worsening hypoxemia. Unfortunately, there are limited objective criteria to exclude new changes in intracardiac shunt. Echocardiography has limitations, although it may be useful in excluding selected cardiac causes of acute deterioration in oxygenation (e.g., systemic-pulmonary shunt thrombosis or narrowing, increasing right ventricular outflow tract obstruction, increasing pulmonary hypertension). More invasive modalities such as cardiac catheterization, CT angiography, and magnetic resonance imaging (MRI), while useful in defining intracardiac shunts, pose significant risks in children with ARDS. Hence,

PALICC chose a pragmatic approach, stating patients with cyanotic congenital heart disease are considered to have PARDS if they fulfill standard criteria (acute onset, a known clinical insult, chest imaging supporting new-onset pulmonary parenchymal disease) and have an acute deterioration in oxygenation not explained by the underlying cardiac disease.

Incidence and Epidemiology

Using the AECC definition, the incidence of ARDS in US, European, Australian, and New Zealand children is estimated at 2.0–12.8 per 100,000 person·years [19, 24, 38, 44, 51]. A series of observational studies in the 1990s and 2000s found that ARDS occurs in 3–6% of PICU patients and between 5 and 8% of mechanically ventilated PICU patients. ARDS mortality in children appears to be lower than in adults (18–27% vs 27–45%) [8, 14, 52–54], although, there are some populations in which adult and pediatric ARDS mortality appears similar (35%) [9, 15, 25, 38, 55]. A recent systematic review and meta-analysis [65] has found that the overall pooled mortality (including the control arm of RCTs and observational studies) for PARDS was 24% (95% CI 19–31) and has been improving over time.

Most pediatric studies report an increased incidence of ARDS in males versus females, but males do not seem to have increased mortality from ARDS [9, 14, 24, 25, 35, 52–54, 57, 58]. Preexisting comorbidities are common among PARDS patients (12–74%) and may be associated with higher mortality [9, 16, 24, 35, 38, 53, 54, 56]. Immunodeficiency is a common preexisting condition, and most studies show increased mortality among immunodeficient patients who develop PARDS [9, 14, 24, 53, 54, 57, 58]. PARDS triggers may contribute to differences in outcome between children and adults or even among children, but pneumonia, sepsis, aspiration, and trauma account for 63–92% of ARDS in both adults and children [8, 9, 14, 24, 25, 35, 38, 54]. Likewise, there may be differences in the rates of pulmonary and extrapulmonary sepsis between children and adults, but the lack of uniformity in the reporting of pulmonary and extrapulmonary etiologies and mortality in ARDS patients makes direct comparison difficult [59, 60]. The PALICC definition is likely to identify many more patients with PARDS, which will likely change both the incidence and mortality rates.

Validation of the PALICC Guidelines in Recent Publications

Parvathaneni et al. [61] compared the PALICC, AECC, and Berlin definitions among children admitted to a single multidisciplinary PICU in the United States. They found that the PALICC criteria nearly doubled the number of patients diagnosed with PARDS, largely because of the pulse oximetry–based criteria in PALICC. Nearly all patients who met Berlin or AECC criteria also met PALICC criteria. The overall mortality for those who met Berlin or AECC criteria was approximately 30% compared to 22% for those who met PALICC criteria. Approximately 40% of the patients who only met PALICC criteria had mild PARDS and 11% were on NIV, but 20% had severe PARDS, with 31% mortality. Furthermore, for patients in whom both PALICC and Berlin criteria were met, PALICC identified ARDS approximately 12 hours earlier. Interestingly, it appeared as if those with severe PARDS had substantially higher mortality than those with mild to moderate PARDS, with minimal mortality difference between those with mild or moderate PARDS.

Yehya et al. [62] conducted a prospective study looking at variables associated with mortality and ventilator-free days at 28 days among PARDS patients at a single tertiary/quaternary ICU in the United States. This cohort was restricted to children who met criteria with an arterial blood gas (PF ratio for AECC and Berlin, OI for PALICC) and similarly identified that nearly all patients who met AECC or Berlin criteria also met PALICC criteria. They found that neither Berlin PaO_2/FiO_2 nor PALICC OI categories at onset of PARDS could discriminate mortality. However, 24 hours after PARDS onset,

there was a stepwise increase in mortality as severity increased (with both PALICC and Berlin groupings).

Rowan et al. [63] investigated whether PALICC criteria discriminated mortality in hematopoietic stem cell transplant (HSCT) recipients requiring invasive mechanical ventilation in multiple PICUs in the United States. Using intubated HSCT patients without PARDS as the reference population, there was no difference in the OR of mortality between HSCT patients with no PARDS versus mild PARDS (OR 1.1, 95% CI, 0.3–4.2; $p = 0.84$) and no PARDS versus moderate PARDS (OR = 1.8, 95% CI, 0.6–5.5; $p = 0.31$) group. The severe PARDS group had a significantly higher risk of mortality with an OR of 6.1 (95% CI, 2.1–17.8; $p < 0.001$). The nonsurvivors were more likely to have multiple consecutive days at moderate to severe PARDS ($p < 0.001$). Most (70%) of the patients met PARDS criteria by day 1 of mechanical ventilation and 89% met criteria by day 3. The moderate and severe PARDS patients had longer PICU length of stay and longer course of mechanical ventilation.

Wong et al. [64] evaluated the PALICC criteria in a multicenter study in Asia. They found that the PALICC criteria for stratification into mild, moderate, and severe groups were associated with a stepwise decrease in ventilator-free days and a stepwise increase in short-term and intermediate-term mortality. The overall mortality in this study was 30.3%, which is comparable with overall PARDS mortality reported in other studies in Asia, although different than what is reported in the United States and Europe.

The Pediatric Acute Respiratory Distress syndrome Incidence and Epidemiology (PARDIE) study [66] prospectively evaluated PALICC criteria in approximately 170 international intensive care units, representing 27 countries. PARDIE found that using the PALICC definition, PARDS occurs in approximately 3% of children admitted to the PICU, or 6% of those on mechanical ventilation. The incidence of "at risk for PARDS" is undoubtedly higher, and a substantial number of these children (32% in one single-center study of children with bronchiolitis) will subsequently be diagnosed with PARDS. In PARDIE, mortality was similar (approximately 15%) for those who have noninvasive ventilation, mild, or moderate PARDS, with significant higher mortality (>30%) for those with severe PARDS. A delayed measure of PARDS severity (6 hours after PARDS onset) appears to better stratify mortality risk than initial PARDS severity. The PALICC definition identified approximately 40% more children as having PARDS and diagnosed PARDS a median 12.8 hours sooner than the Berlin definition within the first 3 days. PALICC definitions by use of oxygenation index or oxygenation saturation index measurements seem to stratify mortality better than the Berlin PF-based severity groups. Bilateral opacifications were identified in 75% of PARDS patients at the time of PALICC PARDS diagnosis, and 87% of patients had bilateral infiltrates within 3 days of PARDS diagnosis.

Where Do We Go from Here?

The PALICC definition was meant to be a starting point to unite the PARDS community in establishing a pediatric-specific definition to be used for clinical care and research. Further external validation of this definition is crucial, which should continue to be a focus of investigation. Based on the validation studies conducted to date, it is clear that the PALICC definition is capturing patients who have met previous definitions of ARDS (oftentimes earlier than previous definitions), plus another subset of patients. A substantial proportion of these patients simply do not meet historical criteria because of changes in clinical practice with regard to the use of arterial catheters. Interestingly, the reported incidence of PARDS with the PALICC definition is comparable to historical studies using AECC definition, prior to practice changes related to pulse oximetry and arterial blood gases. Hence, it is possible that the PALICC definition has now just better aligned to our evolution in clinical practice and has not fundamentally changed the epidemiology of the disease.

The elimination of bilateral infiltrates in the PALICC definition is among the most controversial changes and is a departure from both adult and neonatal ARDS definitions. Diffuse inflam-

mation is a crucial element in the pathobiology of ARDS, and bilateral lung opacifications have historically been used as a clinical sign to characterize this inflammation. Given limitations in the ability for routine chest radiographs to consistently characterize this inflammation, the PALICC definition chose to eliminate the requirement with the argument that this inflammation be adequately captured by other elements of the definition (such as hypoxemia). The PARDIE study has highlighted that nearly all patients who meet PALICC criteria are gauged to have bilateral infiltrates within 3 days of PARDS diagnosis and that the absence of bilateral infiltrates is not associated with outcome when controlling for other factors. It also confirmed high levels of disagreement on the interpretation of bilateral infiltrates. The importance of chest imaging in the diagnosis of PARDS should continue to be a focus of PARDS research and should continually be reevaluated if more specific methods for chest imaging are incorporated into routine clinical practice. When constructing a definition, it is crucial that the diagnostic criteria can be applied in all environments likely to treat the disease and is not practitioner dependent.

Like the Berlin definition, PALICC retained disease severity stratifications to help target prognosis and therapy. Interestingly, the data from Asia seem to support stepwise increases in mortality as a function of initial PARDS severity groups, while other data highlight major mortality differences between severe PARDS and all other PARDS patients. However, ventilator-free days and length of ventilation among survivors appear better calibrated with PARDS severity groupings. This may be the more important metric, as it is often difficult to understand how often children with PARDS die *from* PARDS (i.e., hypoxemia) or *with* PARDS (i.e., shock, neurologic injury). Additionally, it is clear that these severity groupings have different prognostic relevance at PARDS diagnosis compared to 6–48 hours after PARDS diagnosis. In fact, none of the ARDS definitions have mandated a delayed measure of ARDS severity, which may have important implications to gauge response to therapy, persistence of disease, and prognosis. These of course have to be balanced with the importance of early identification of patients who are likely to benefit from PARDS-specific therapies. Furthermore, these trajectories are also very clearly influenced by factors such as genetics, comorbidities, degree of inflammation, and therapies [67–69], which are not captured in the PARDS definition. As our diagnostic capabilities expand, it will be important to frequently reevaluate whether we can use other diagnostic tests, which better reflect the pathobiology of PARDS in our definitions.

Conclusion

In conclusion, there are unique elements to the pathobiology of PARDS, which mandate a pediatric-specific definition. The PALICC group has created a pediatric-specific definition for ARDS, which was initially based on consensus opinion from established investigators in PARDS, with some validation using data from existing PARDS studies. Recent studies have provided some validation of this definition in a variety of international critical care settings. Furthermore, pediatric-specific evidence for therapeutic approaches are lacking in many important areas, but using the PALICC definition as a framework to better evaluate the risk-benefit profiles of individual therapies is important for both future investigations and clinical care of children with PARDS.

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Pathobiology of Pediatric Acute Respiratory Distress Syndrome

3

Lincoln S. Smith

Introduction

"Wet lung," "Da Nang lung," and "shock lung" were some of the many terms used to name conditions affecting patients who died from severe hypoxia and pulmonary edema in the 1940s–1960s [1]. In 1967, Ashbaugh and colleagues published a case series of twelve patients who died from severe acute hypoxemic respiratory failure, poor lung compliance, with diffuse alveolar infiltrates on chest X-ray, and although the cohort comprised a child and 4 teenagers, they first coined the term "acute respiratory distress syndrome in adults" and subsequently the "adult respiratory distress syndrome." [2–4]

The clinical definition of acute respiratory distress syndrome has now been revised multiple times and currently includes adult (Berlin) and pediatric (Pediatric Acute Lung Injury Consensus Conference (PALICC)) definitions [5–7]. The initial case series of patients with ARDS described by Ashbaugh had common clinical signs and symptoms, but all of the patients died, and autopsy findings unified the description of the syndrome. Clinical definitions should be relatively easy to apply and have high sensitivity and specificity. The removal of the requirement for bilateral infiltrates on chest X-ray continues to be a controversial element of the PALICC definition of ARDS, because it is not clear whether the pathologic sine qua non of ARDS – diffuse alveolar damage – necessitates evidence of bilateral infiltrates on chest X-rays. Most of the pathobiology of ARDS discussed in this chapter have been determined through the combination of careful human research combined with relevant animal models. Many of the processes described here cannot yet be easily determined by clinicians but are important to understand the disease process and inform future research.

Clinical Pathophysiology

ARDS is a restrictive lung disease (reduced respiratory system compliance) due to pulmonary edema, atelectasis, surfactant dysfunction, and chest wall restriction (chest wall edema, ascites, peritonitis, etc.). Hypoxemia results from pulmonary edema, loss of functional residual capacity (FRC), and especially when closing capacity (CC) increases above FRC causing heterogeneous intrapulmonary shunt (V/Q = 0) and V/Q ratios <1. Regions with increased physiologic dead space (ventilation but reduced to no perfusion or V/Q ratios >1) are also common in ARDS from mechanisms related to endothelial injury and coagulation,

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impaired cardiac output or pulmonary perfusion, and regional overdistension.

Chest imaging often shows evidence of patchy, asymmetric to diffuse infiltrates. In patients for whom the syndrome does not resolve, persistent hypoxemia and low lung compliance persists, but alveolar dead space worsens. In these patients, chest imaging begins to show linear opacities, formation of bullae, and development of pneumothoraces.

Pathobiology

The primary pathologic description of ARDS is a diffuse disruption of the alveolar epithelial-endothelial barrier (diffuse alveolar damage) resulting in noncardiogenic pulmonary edema. Disruption of alveolar fluid clearance and surfactant, inflammation, apoptosis, and coagulopathy are pathobiological mechanisms associated with worse lung injury [8]. Etiologies associated with ARDS can be divided into direct (alveolar epithelial) and indirect (endothelial) injuries (Table 3.1). There are three conceptual phases of ARDS (acute, fibroproliferative, and resolution), which overlap temporally, but nonetheless provide important clinical and research frameworks of pathobiological relevance [9–11].

Significant overlap exists between the regulation of normal postnatal lung growth and development and clearance of alveolar fluid, apoptosis, innate immunity, early inflammatory responses to mechanical ventilation, as well as repair mechanisms in the lungs [12, 13]. The design and interpretation of existing and future studies investigating mechanisms of lung injury and repair should include consideration of the possibility that there are age-dependent differences.

Table 3.1 ARDS risk factors

Direct	Indirect
Pulmonary infections	Sepsis
Inhalations	Multiple trauma
Pulmonary contusions	Blood transfusion
Aspiration	Severe burns
Mechanical ventilation	Pancreatitis
	Major surgery
	Ischemia-reperfusion injury

Exudative Phase: Acute Alveolitis

This phase is characterized by disruption of the alveolar epithelial-endothelial barrier by injury to alveolar epithelial cells, pulmonary capillary endothelial cells, or both. The large surface area and thin structure of the alveolar unit – consisting of the unique structure of alveolar epithelial and pulmonary capillary endothelial cells sharing a common basement membrane – is efficient for gas exchange but makes it susceptible to injury. The pathobiologic processes of this phase are the rapid accumulation of a proteinaceous fluid (exudate) and infiltration of activated leukocytes into the alveolar airspace, reduced production and/or inactivation of surfactant, coagulopathy, activation of apoptotic pathways, and initiation of fibrosis [8, 14, 15].

Direct Epithelial Injuries

Early pathologic descriptions of diffuse alveolar damage (DAD) suggested a predominance of alveolar epithelial cell injury [16]. Injury to alveolar epithelial cells results in loss of surfactant production, decreased alveolar fluid clearance, and exposure of the shared pulmonary epithelial-endothelial basement membrane, further activating inflammatory and coagulation cascades.

Infectious pathogens and aspiration are the most common causes of direct alveolar epithelial injuries [17–19]. Pathogens may cause alveolar cell necrosis, apoptosis, or pyroptosis [20–22]. Alveolar epithelial cell necrosis and pyroptosis cause uncontrolled release of damage-associated molecular patterns (DAMPs) as well as pro-inflammatory cytokines [23–26].

Mechanical ventilation is the life-saving support for patients with ARDS. The earliest observations of patients with ARDS suggested that adding positive end-expiratory pressure (PEEP) improved survival, and limiting tidal volume remains the single most significant improvement to the care of these patients [27, 28]. However, the converse is also true in that mechanical

ventilation may also worsen lung injury [29]. Ventilator-associated lung injury (VALI) describes the potential contribution of mechanical ventilation to patients with existing lung injury, whereas ventilator-induced lung injury (VILI) is used to describe injury directly caused by mechanical forces. Since many carefully designed laboratory studies have established multiple mechanisms by which the mechanical forces imposed on the respiratory system causes injuries in the lungs, VILI will be used throughout the rest of this chapter. Ventilator-induced lung injury may occur by shear stretch (volutrauma), repeated opening and closing of atelectatic lung (atelectrauma), production of pro-inflammatory cytokines via mechanotransduction (biotrauma), and oxidative stress [30, 31]. Barotrauma is a term that continues to be used to describe lung injury resulting in air leaks (pneumothorax, pneumomediastinum, etc.) as well as lung injury associated with high airway pressure. However, barotrauma is likely somewhat of a misnomer as an elegant study by Dreyfuss and colleagues showed that pressure, in the absence of high absolute lung volume, did not cause lung injury [32].

The apparent discrepancy between volutrauma and barotrauma in the ARDS patient with significant amounts of derecruited lung and high airway pressures can be reconciled by recognizing that, in heterogeneous lung disease, the energy of each tidal volume is delivered to only [33, 34]. Amato's work showing that "driving pressure" was the variable that most stratified risk is consistent with the concept that mechanical power is the sum of the forces needed to recruit atelectatic and stretch inflated regions, divided by the time in which those forces are applied [35–37]. PEEP and prone positioning have potential to recruit atelectatic regions (preventing atelectrauma) and thereby reduce the fraction of tidal stretch delivered to individual lung regions by increasing the total amount of inflated lung [38, 39]. This is the most likely physiologic rationale for studies that have shown improved outcomes in adult and pediatric patients with ARDS treated with higher PEEP [40, 41]. However, if additional PEEP does not recruit atelectatic regions, then the remaining lung regions will rest at higher levels of inflation at end inspiration, and the fractional tidal stretch will be increased – worsening volutrauma [42]. Although high-frequency oscillatory ventilation (HFOV) has potential to provide improved recruitment with a constant high mean airway pressure and avoid volutrauma by delivering ultralow, subphysiologic dead space tidal volumes, the potential to cause VILI with the oscillator should now be apparent. The frequency of HFOV is inversely related to convective tidal volume, and the time in which that tidal volume is delivered is very short, making the potential for the power delivered to regions of inflated lung to be high [37, 43–45].

There are many benefits to having patients breathe spontaneously while treated with mechanical ventilation, but high amounts of power, causing worse direct injury to the lung, may be difficult to discern during spontaneous breathing [46]. In order to reduce the power delivered to the lung, there was early recognition that hypercapnia should be permitted [47]. Although data suggest that hypercapnia may even be therapeutic, patient dyspnea from respiratory acidosis remained a substantial barrier to effective implementation of "lung-protective ventilation" in many academic centers [47, 48]. Significant negative inspiratory forces generated at a high rate by the dyspneic patient with lung injury are likely to contribute to "VILI" [46, 49]. Treatment of ARDS patients with neuromuscular blockade has been shown to reduce biomarkers of alveolar epithelial and endothelial injury as well as reduce mortality [50–52]. There remains much controversy surrounding the use of extracorporeal life support for the treatment of patients with ARDS, but it is likely the only way to truly "rest" the lungs [53–59]. The nuances of "rest settings" are beyond the scope of this chapter.

Indirect Lung Injury

Indirect lung injury refers to injury to or activation of the vascular endothelium. Sepsis is the commonest cause of indirect lung injury (Table 3.1) [17, 18]. However, injury to the pulmonary endothelium may also be a direct injury. The effect of mechanical stretch is often considered within the

scope of injury to the alveolar epithelium, but a large body of data suggests that VILI includes the pulmonary endothelium [60]. Mechanical, chemical, and cellular injuries to the pulmonary endothelium cause alveolar barrier dysfunction, activate inflammatory and coagulation cascades, change pulmonary vascular resistance, and lead to multiorgan dysfunction [61, 62]. Elevated pulmonary vascular resistance and thrombosis of pulmonary capillary beds can increase alveolar dead space. Biomarkers of endothelial activation and injury have been widely studied, and several have been associated with outcomes in children and adults with ARDS [8, 62–64]. An animal model of endothelial injury suggests that age-dependent differences in endothelial permeability are due to differential regulation of adherens junctions between endothelial cells [65].

Angiopoietin 1 (Ang-1) and angiopoietin 2 (Ang-2) are important endothelial growth factors that function in opposition via Tie2 receptors on endothelial cells [66, 67]. Ang-1 is a Tie2 agonist and is highly important to normal, quiescent, endothelial barrier function via cytoskeletal reorganization and increased VE-cadherin at inter-endothelial junctions. Ang-1 stimulation increases endothelial barrier function and thereby reduces tissue edema in multiple infectious and inflammatory models [66, 67]. Ang-2 competitively inhibits Ang-1-Tie2 binding and is released by endothelial cells during inflammatory states. Ang-2 neutralization and antibody clustering has reduced mortality and organ failure in laboratory models of severe infections [66]. The ratio of Ang-2/Ang-1 in plasma has been associated with mortality in adults with ARDS and high dead space fractions, and plasma Ang-2 was associated with mortality in critically ill adults and children with ARDS [68–70].

The endothelial surface layer (ESL) is a glycocalyx comprised of an apical extracellular matrix of glycoproteins, proteoglycans, and glycosaminoglycans (GAGs) creating an organized carpet-like layer between the endothelial cell membrane and the capillary lumen [71, 72]. Advances in understanding the dynamic structure and function of the glycocalyx were limited by tissue fixation techniques until intravital microscopy techniques allowed visualization in living animals [73, 74]. The glycocalyx contributes to fluid and molecular permeability of the endothelial barrier, transduces vascular shear stress, and regulates leukocyte-endothelial adhesion and platelet activation [73, 74]. The pulmonary glycocalyx appears to be significantly thicker (1.5 μm vs 0.5 μm) as compared with some vascular beds but may occupy less of the lumen as compared with the heart or kidney [75–78].

Glycocalyx fragments are found in adult patients with septic shock, and mounting evidence supports that disruption of the glycocalyx is an important mediator of the pathophysiology of sepsis [73, 79]. Heparan sulfate is one of the GAGs in the glycocalyx and contributes to the regulation of endothelial barrier dysfunction, mechanotransduction of shear stress-induced vasoreactivity, and leukocyte adhesion [74]. In a murine model of sepsis, pulmonary endothelial cells released activated heparinase, cleaving heparan sulfate, thinning the ESL, and exposing endothelial adhesion molecules for neutrophils [76]. Elevated plasma levels of heparan sulfate has also been shown in adult patients with lung injury from sepsis and pancreatitis, but not from bacterial pneumonia [80]. In a sepsis model of lung injury, mice treated with intraperitoneal lipopolysaccharide (LPS) showed disruption of the 3-dimensional glycocalyx structure, increased plasma levels of glycocalyx components (syndecan-1) and thrombomdulin, increased permeability of pulmonary capillaries, and activated neutrophils binding and traversing pulmonary endothelial cells [78]. However, not all studies of disruption of the glycocalyx are consistent with changes in vascular permeability. In an experimental rat model of nontraumatic hemorrhagic shock, endothelial degradation and shedding of glycocalyx occurred without evidence of increased vascular barrier permeability [81].

Neutrophil reactive oxygen species, supplemental oxygen, and altered endothelial nitric oxide signaling may contribute to elevated pulmonary vascular resistance. Pulmonary endothelial angiotensin-converting enzyme (ACE) and ACE2 genetic polymorphisms and activity correlate with mortality in children and adults with ARDS [8, 82]. ACE and ACE2 are another mech-

anism by which pulmonary endothelial biology, pulmonary vascular resistance, inflammation, apoptosis, and coagulation may intersect in the pathobiology of ARDS [83].

Alveolar Fluid Clearance

Injuries to the alveolar epithelial-endothelial barrier results in increased permeability and disruption of alveolar fluid clearance (AFC), leading to pulmonary edema. Accumulation of pulmonary edema fluid reduces respiratory system compliance and impairs gas exchange (ventilation/perfusion mismatch and shunt). The integrity of the alveolar epithelial-endothelial barrier requires maintenance of a thin layer of alveolar wall liquid (AWL) coating the alveolar epithelium. The AWL is necessary for the dispersion of surfactant and is dependent on regulated flow of water, proteins, and small solutes across postcapillary venules into the alveolar airspace [84]. Excess alveolar fluid is removed by sodium-dependent transport by type II alveolar epithelial cells [85].

Activation of the pulmonary endothelium results in increased permeability by both para- and transcellular pathways [86]. The endothelial glycocalyx is highly hydrated and regulates large molecular permeability into it, making the "Starling principle" an inadequate explanation of the forces regulating flow of fluid across endothelial barriers [77, 87–89]. Furthermore, the dynamic structure of the glycocalyx makes modeling flow across the barrier even more complex [88]. Injury to the pulmonary endothelial glycocalyx is likely to be an important mechanism of increased alveolar permeability, and restoration of the glycocalyx is associated with resolution of pulmonary edema [78].

The rate of AFC has been associated with mortality in adult patients with ARDS [90]. Epithelial sodium channels (ENaC), the cystic fibrosis transmembrane conductance regulator (CFTR), Na^+-K^+-ATPase, and aquaporins (cell membrane water channels) are involved in the clearance of fluid from the distal airspaces into the interstitium of the lung. Salt and water transport is regulated by catecholamines, glucocorticoids, mineralocorticoids, thyroid hormone, growth factors (epidermal growth factor (EGF), transforming growth factor alpha (TGFα), keratinocyte growth factor (KGF), or fibroblast growth factor 7 (FGF-7)), fibroblast growth factor 10 (FGF-10), nuclear factor kappa-B (NFκB), serine proteases, and Fas/FasL, although therapies targeting AFC have not improved outcomes in adults with ARDS [85, 91–93]. Regulation of postnatal lung development may be a protective factor in children with ARDS, in part through preservation of AFC [13]. Age-dependent differences in alveolar epithelial-endothelial barrier function have been shown in mice treated with intraperitoneal lipopolysaccharide [65].

Male gender has been associated with lower alveolar fluid clearance in adult patients with ARDS, whereas premenopausal women are more likely to have high alveolar fluid clearance. These findings are supported by animal data showing that progesterone and estrogen increased expression and function of the epithelial sodium channel [90, 94]. Beta-adrenergic agonists upregulate alveolar fluid clearance in human lungs [95]. However, two randomized placebo-controlled trials of treatment with intravenous salbutamol did not show a reduction in ventilator-free days or mortality in adults with ARDS [96, 97]. Animal studies of KGF therapy for acute lung injury have suggested that pre- but not postinjury treatment is protective [98]. A double-blind, randomized, placebo-controlled trial of KGF for adults with ARDS did not show improvement in oxygenation metrics, ventilator-free days were fewer, and 28-day mortality was increased [99].

Children have not been included in studies of alveolar fluid clearance in patients with ARDS, and nothing is known about the rate of alveolar fluid clearance in children with ARDS as compared with adults. However, KGF is an important mediator of postnatal lung morphogenesis. Therefore, throughout childhood the lung may be "pretreated" with KGF before any insult occurs.

Surfactant

Surfactant creates variable surface tension at the air-liquid interface of the alveoli and contributes to innate immunity [100, 101]. Surfactant proteins B (SP-B) and C (SP-C) are hydrophobic and

lower the surface tension of the alveolar wall liquid. The surfactant proteins A (SP-A) and D (SP-D) are collectins and contribute to innate immune responses to microbial pathogens. All four of the surfactant proteins have immunomodulatory effects and affect pulmonary fibrosis and lung remodeling [102, 103].

Adults with ARDS have low levels of SP-A, SP-B, and SP-D in bronchoalveolar lavage (BAL) fluid, and increased serum levels of these proteins in children and adults are associated with severity of lung injury [104–108]. There are lower levels and changes in the overall composition of phospholipids present in BAL fluid of patients with ARDS [109]. Reactive oxygen species from high concentrations of supplemental oxygen and activated neutrophils in the alveolar spaces of patients with ARDS may cause surfactant dysfunction [110, 111]. Finally, patients with genetic polymorphisms that result in lower levels of SP-B have a higher risk of developing ARDS, or have more severe lung injury when they become ill [112–114]. Similar findings are also seen with SP-A and SP-D with regard to development of ARDS for adults with pneumonia [115].

Several clinical trials and small case series suggested a benefit of exogenous surfactant in adults and children, but an international randomized controlled study of children with direct lung injury treated with calfactant was closed due to futility [116]. Although routine use of exogenous surfactant is not currently recommended for children with PARDS, the central role of surfactant in the pathogenesis of ARDS seems to warrant future studies [117, 118]. Secretory phospholipase A2 (sPLA2) is an enzyme with pro-inflammatory function as well as a catabolist of surfactant, and a multicenter study has been planned to investigate the role of sPLA2 in neonates and infants with lung injury [119].

Leukocytes and Inflammation

Macrophages reside in the quiescent alveolar airspace and are sentinels against pathogens [120]. Alveolar macrophages express pathogen-associated molecular pattern (PAMP) and DAMP receptors, providing early signals to the presence of pathogens and tissue injury [121]. Stimulated macrophages may also induce pyroptosis via an autocrine pathway involving the pro-inflammatory cytokine interleukin 1β (IL-1β) [122, 123]. Release of mitochondrial DNA via pyroptosis potently upregulates inflammation [25, 122]. Infiltration of activated neutrophils into the alveolar airspace is a pathologic hallmark of ARDS, but transformed alveolar and recruited macrophages, epithelial cells, and T cells also mediate the host's innate immune inflammatory response to pathogens and lung injury [9, 26, 121, 124, 125]. In a cohort of adults with ARDS due to pneumonia, a high ratio of Treg lymphocytes to all CD4+ cells in bronchoalveolar lavage fluid collected in the first 24 h of ICU admission was associated with increased 30-day mortality [126]. Treg and T helper (Th)17 cell development and function are regulated by transforming growth factor β1 (TGF-β1), likely exerting an opposite function in immune responses, and Treg cells can be "converted" to Th17 cells [127]. In another case-control study of adults, the ratio of Th17 to Treg cells in blood collected within the first 24 h after diagnosis of ARDS was higher as compared with controls and associated with severity of ARDS and mortality [127].

Severe systemic inflammation (high levels of circulating cytokines and chemokines) activates the alveolar endothelium and circulating leukocytes resulting in "indirect" lung injury. In addition to alveolar fluid accumulation, the cell surface adhesion molecules expressed on activated alveolar endothelial cells regulate neutrophil rolling, binding, activation, and migration into the alveolar space by both para- and transcellular mechanisms [8, 128, 129].

Apoptosis

Apoptosis is a controlled, energy-dependent mechanism of programmed cell death that occurs by ligand-triggered "extrinsic" or stress-induced "intrinsic" pathways [130]. Increased alveolar epithelial cell apoptosis is associated with severity of lung injury and mortality in adults with

ARDS [131, 132]. Nuclear factor kappa-B (NFκB)-dependent innate immune signaling via Toll-like receptors results in apoptotic signaling [133, 134]. Studies also suggest that Fas ligand, transforming growth factor beta (TGF-β), and lipopolysaccharide mediate inflammation, alveolar fluid clearance, and apoptosis of epithelial and endothelial cells in the lungs [92, 135–144].

Apoptosis is important for normal postnatal lung development [145–147]. Intersections between postnatal lung morphogenesis, inflammation, alveolar fluid clearance, and apoptosis may affect the outcome of children with lung injury [13, 148]. Fas has been shown to mediate apoptosis in normal lung development, and Fas/FasL may protect against hyperoxic lung injury in newborn mice [149, 150]. Fibroblast growth factor 10 (FGF-10) regulates postnatal lung morphogenesis and appears to reduce DNA damage and apoptosis of alveolar epithelial cells treated with cyclic mechanical stretch [151]. However, other animal studies suggest that mechanical ventilation during infancy may increase apoptosis in the lungs of newborns, thereby disrupting normal postnatal lung development [152]. Age-dependent mechanisms of apoptosis in the lungs of patients with ARDS remain an opportunity for future research.

Coagulation

Endothelial function, inflammation, and coagulation are inextricably linked [153, 154]. The intact glycocalyx is essential for normal intravascular anticoagulant function, and disruption of the glycocalyx has been associated with platelet activation and disseminated intravascular coagulation in sepsis [73, 155]. Activation and/or injury to the endothelium results in expression of tissue factor (TF) and von Willebrand factor (vWF) antigen, and vWF has been associated with mortality in pediatric and adult ARDS patients [156, 157]. Plasminogen activator inhibitor-1 (PAI-1) has also been associated with severity of illness and mortality in adult and pediatric patients with ARDS [8, 158, 159]. Coagulopathy and fibrinolysis are not isolated to the vascular space in the lungs of patients with ARDS, as activated protein C, thrombomodulin, and TF activity have been found in the alveolar compartment and associated with alveolar epithelial cell function [8, 158, 160].

Fibrosis and Repair

The acute pro-inflammatory response is essential to recover from direct lung injury, but prolonged inflammation in the lungs can be pathologic and lead to pulmonary fibrosis [11, 161]. Coordination of a balanced pro- and anti-inflammatory response that results in appropriate resolution of inflammation once the inciting injury has resolved requires soluble mediators, cellular immunity, and likely stem cells [162]. Catabasis is the restoration of normal organ function after an inflammatory injury [163]. Unfortunately, experimental models to investigate pulmonary fibrosis and repair have proven more challenging than ARDS models of the acute phase [164]. Since patients often present to the ICU hours to days after the initial injury has occurred, therapeutic interventions that affect the fibroproliferative phase to result in an effective "gas exchange apparatus" seems prudent [165]. Effective repair requires restoration of the air-lung and blood-lung interfaces, as well as the interstitium [166].

Coordinated activity of type II alveolar epithelial cells, macrophages, neutrophils, T cells, dendritic cells, mesenchymal stem cells, and fibroblasts is necessary for normal repair of the injured lung [86, 163, 164, 167]. Type II alveolar epithelial cells and resident mesenchymal stem cells proliferate and differentiate into type I alveolar epithelial cells, restoring the alveolar epithelium [86, 167]. The hyperplastic type II cells then undergo apoptosis to restore the normal cellular architecture of the alveolar epithelium [168]. Murine models of lung injury suggest that epithelial cell proliferation requires neutrophils and Treg cells [169, 170]. Restoration of the endothelium and glycocalyx are also necessary to clear alveolar edema and restore the normal AWL. Restoration of epithelial sodium channels (ENaC) is critical to restoring the AWL, and regulation of ENaC expression

appears to be tightly linked to stem-cell-mediated reepithelialization [164, 171].

Neutrophil apoptosis is important for resolution of lung inflammation [132, 163, 172, 173]. However, studies have shown that the presence of neutrophils in the airspace is important to early fibrosis and normal repair mechanisms, suggesting that the timing of neutrophil apoptosis ideally occurs well after resolution of the inciting injury [174–176]. Resolution of inflammation and clearance of neutrophils is coordinated by Treg cells and macrophage subpopulations [121, 177–179]. Although cell-cell interactions play important roles in the resolution of inflammation, soluble mediators (IL-10, granzyme B, and lipid mediators) are also required [163, 180–182]. Studies of macrophage subpopulations suggest that they are important to both the induction and repair phases of ARDS [121, 179]. IL-10-mediated resolution of inflammation in the lung appears to require T cells and macrophages, whereas IL-4 reprograms macrophages in the absence of Treg cells [178, 183].

Remodeling the lung interstitium requires clearance of interstitial edema and remodeling of fibrin deposition [164]. Matrix metalloproteinases (MMPs) are secreted by neutrophils and appear to play an important role in the remodeling of the alveolar epithelium and extracellular matrix (ECM). [174, 184] Studies have shown that the wingless-related integration site (Wnt) signaling via β-catenin also regulates MMPs and is important early in lung injury as well as remodeling the extracellular ECM and signaling stem cells [185]. Intense research is ongoing to understand mechanisms and therapeutic targets in the ECM [162].

Stem cells derived from adult mesenchyme have limited potential to differentiate but have immunomodulatory effects. Mesenchymal stem (stromal) cells (MSCs) have been widely studied, can be expanded and cryopreserved for future use, and have an established safety for treatment of several diseases [186]. In experimental models of acute lung injury, MSCs appear to modulate inflammation, augment tissue repair, enhance pathogen clearance, and reduce severity of injury, pulmonary dysfunction, and death [186, 187]. Many of these effects occur without engraftment, but rather by paracrine effects [188]. A fixed pool of MSCs in postnatal lungs that are depleted with age may be a mechanism for age-dependent differences in outcomes of patients with ARDS.

Summary

ARDS has multiple etiologies, and the complex pathways of alveolar fluid clearance, inflammation, coagulation, apoptosis, fibrosis, and repair are regulated as a complex biological network. As definitions of ARDS in adults and children continue to evolve, knowledge of pathobiologic mechanisms will allow improvements in specificity of subtypes of the syndrome. Furthermore, overlap between regulation of postnatal lung morphogenesis and the pathobiology of ARDS suggests that the response to and outcome from a given lung injury will differ across the spectrum of age.

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4 Risk Factors and Etiologies of Pediatric Acute Respiratory Distress Syndrome

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In the original description of what Ashbaugh and colleagues described as "the acute respiratory distress syndrome in adults" in 1967, special attention was paid to the inciting illness or injury (e.g., severe trauma, viral infection, acute pancreatitis) and possible contributing factors (e.g., hypotension, acidosis, fluid overload) [1]. Interestingly, of the 12 patients that Ashbaugh and colleagues described in that article, 4 of the 12 were aged 19 years or younger and may have been managed in pediatric critical care units today. That initial description has since evolved into the American European Consensus Conference (AECC) definition in 1994 and then the current Berlin definition of ARDS for adults and the Pediatric Acute Lung Injury Consensus Conference (PALICC) definition of pediatric ARDS (PARDS) [2–4]. Throughout these iterations, much attention continues to be paid toward understanding what conditions place patients at particular risk for ARDS development and what conditions contribute to worse ARDS clinical outcomes. This intense work is imperative in order to identify potentially modifiable factors that would decrease risk, improve monitoring of at-risk patients to prevent precipitous deterioration, and ultimately determine more personalized and precise approaches to management of those at highest risk or those with ARDS once established.

Risk factors associated with acute respiratory distress syndrome, whether in adults (ARDS) or pediatrics (PARDS), traditionally and originally consisted of the *diagnoses most often associated with ARDS or PARDS development.* This chapter takes these diagnoses into great account. Fortunately, this field of research has expanded to include relevant *comorbidities* associated with ARDS/PARDS development and/or severity. As the last 30 years have yielded important understanding into the pathobiology of ARDS/PARDS (see Chap. 3), so too have *biological markers* (aka biomarkers) and *markers associated with genetic risk* of ARDS/PARDS come to the forefront. Finally, discussions of ARDS/PARDS risk factors must inevitably dissect out whether the risk factors are associated with the *development* of ARDS/PARDS, and thereby factors impacting those patients *at risk of ARDS/PARDS development*, as well as those factors associated with better or worse *clinical outcome* once ARDS/PARDS has been established.

Finally, much of this work has now demanded that both clinicians and researchers refine our discourse to further acknowledge that, as a syndrome, certain subgroups of patients, oft termed endotypes or sub-phenotypes, must exist that ultimately can be at inherently greater risk of disease and/or have unique pathophysiological

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responses that may make these subgroups of patients more or less able to respond to certain treatment strategies. Accordingly, *prognostic risk factors* describe factors associated with subgroups of patients at inherently greater risk of ARDS/PARDS, whereas *predictive risk factors* identify subgroups of patients that are at greater/lesser likelihood of responding to certain treatment strategies based on inherent differences in their underlying pathophysiologic responses to illness/injury.

This chapter is intended to address all the areas outlined previously. These aspects inevitably dovetail significantly with (a) the epidemiology of PARDS, (b) pathophysiology of PARDS, and (c) relevant clinical outcomes of PARDS patients, both short and long term, each of which are covered in separate chapters in this book.

Identifying Patients at Risk

Identifying risk factors and understanding which patients are at risk for developing ARDS is significantly important to be able to develop preventative and early interventions. The US Critical Illness and Injury Trials Group (USCIIT): Lung Injury Prevention Study Investigators in 2013 developed a Lung Injury Prediction Score (LIPS) to identify patients at high risk for development of acute lung injury [5]. USCIIT researchers combined predisposing conditions (e.g., high-risk trauma, high-risk surgery, aspiration, sepsis, shock, and pneumonia) with risk modifiers such as alcohol abuse, acidosis, tachypnea, and FiO_2 greater than 0.35 to create this scoring system. The scoring system was able to identify patients at risk of developing ALI using a cutoff score of 4, with a positive likelihood ratio of 3.1 (95% CI 2.9–3.4) and a negative likelihood ratio of 0.4 (95% CI 0.3–0.5).

Similarly, with increasing use of noninvasive mechanical ventilation, both clinicians and researchers have wisely recognized that ARDS pathophysiology may begin before the onset of invasive mechanical ventilation, and identification of those patients before severe hypoxemia develops may be associated with improved survival [6, 7]. Accordingly, the PALICC authors also noted the importance of identifying pediatric patients earlier and proposed a definition for patients "at risk" of PARDS which requires new pulmonary infiltrates on chest radiograph within seven days of a "known clinical insult" and supplemental oxygen requirement delivered via an invasive or noninvasive mechanism that does not meet OI or OSI criteria for PARDS [8]. This "at risk" population will certainly be an ongoing and future target for research into prevention and risk modification in PARDS.

Comorbidities Associated with PARDS Development

Immunodeficiency

It has been long understood that both adult and pediatric patients with preexisting immunodeficiency are at increased risk of both development of ARDS and worse outcomes after ARDS [9]. In the largest ARDS epidemiologic study in adults (LUNG SAFE), 20.8% of patients with ARDS were identified as having some form of immunocompromised state [10]. These patients had proportionally more infections as the etiology of the ARDS and had worse outcomes, including higher ICU and hospital mortality. In pediatrics, much of the early data on immunodeficiency came from human immunodeficiency virus (HIV). Most recently, Dr. Kitchin and colleagues published their experience in 90 children with HIV admitted to the PICU in South Africa meeting AECC criteria in 2008–2009 in which the authors identify high rates of opportunistic infections (33% with *P. jirovecii*, 38% with cytomegalovirus) and overall 30% mortality [11]. Another significant population with immune dysfunction is patients with cancer or immunosuppression related to chemotherapy. In the Pediatric Acute Respiratory Distress syndrome Incidence and Epidemiology study (PARDIE), 8% of all PARDS patients were identified as having cancer and 13% had immune suppression [12]. The outcomes for the groups were a disheartening 51% and 46% mortality, respectively. Dr. Rowan and colleagues have focused on the outcomes of hematopoietic stem cell transplant (HSCT)

patients in the ICU (see Chap. 15). Their work has shown that HSCT patients who have respiratory failure often meet PARDS criteria (91% in the first week of mechanical ventilation) and their disease is often severe, with longer ventilation courses and increased mortality [13, 14].

Weight Extremes

There seems to be an interesting interplay between ARDS and body habitus in both adults and children. Results from the 2011–2012 National Health and Nutrition Examination Survey (NHANES) indicate that 3.5% of children and adolescents in the United States are underweight and 31.8% are overweight or obese [15, 16]. Both represent states of malnutrition and are known to be associated with a variety of comorbidities. Increasing BMI has been shown to be independently associated with increased risk of ARDS development. Further, while underweight adults with ARDS have high rates of mortality, obese individuals, particularly those with established ARDS, require longer intensive care unit (ICU) and hospital stays (LOS), but exhibit the lowest risk of in-hospital mortality when compared to other weight categories [17]. This has come to be known as the "obesity paradox." This "obesity paradox" has been reported in adults with sepsis or ARDS [18]. Obese individuals, who exhibit chronic inflammation and endothelial activation, surprisingly have reduced systemic inflammatory response with ARDS compared to those of normal weight [19], suggesting a possible protective attenuation of the immune response to critical illness [19]. In a cohort of 330 subjects, Ward and colleagues found that 28% of PARDS patients were obese, and the obesity paradox was observed in those whose PARDS was due to systemic illness [20]. Not surprisingly, the underweight exhibited the highest odds of in-hospital death.

Environmental Factors

Because of the acute onset and often clear catastrophic trigger, such as septic shock or major trauma, the importance of the environment and patient's air quality on ARDS development can be inappropriately discounted, unlike in disease processes such as asthma or chronic obstructive pulmonary disease. However, adult ARDS has been clearly shown to be affected by cigarette smoking, so it is not unreasonable to think that environmental smoke exposure could affect PARDS. In the adult ARDS population, Dr. Calfee and colleagues demonstrated that cigarette smoking by history and a biomarker of smoke exposure, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, were each associated with the development of ARDS in patients with sepsis [21]. Impaired fluid clearance, epithelial and endothelial effects, and immune modulation could all underlie this effect [21]. In an allied study, Reilly and colleagues studied 996 critically ill adult trauma patients in conjunction with air quality metrics in the 6 weeks prior to presentation. Interestingly, nitrogen dioxide, sulfur dioxide, and particulate matter <2.5 micrometers over the 6 weeks were significantly associated with ARDS development [22]. Further investigation into PARDS may reveal other predisposing environmental factors including environmental smoke exposure and ambient air pollution as risk factors for development of or more serious PARDS [23].

Age/Gender/Race and Ethnicity

It is well known that the immune system develops and assumes more complexity with age [24–26], and that children represent a more heterogenous patient population compared to adults with regard to predisposing conditions, etiology, and response to therapy [27]. The exact impact of age on risk of development of ARDS and severity of ARDS remains incompletely elucidated. Nonetheless, epidemiologic studies to date do not consistently endorse differential PARDS outcomes based on age, with some suggesting increasing risk with older age, but most studies suggesting no association of age with PARDS outcome [7, 9]. Similarly, these studies also do not show any differential risk of worse clinical outcomes with either male or female gender.

Similarly, risk factors for outcomes of ARDS patients from different racial and ethnic backgrounds are also incompletely investigated. Adult studies suggest increased risk of death in some African American and Hispanic ARDS cohorts [28] and differential response to treatments, as was determined post hoc in the NIH-funded Fluid and Catheter Treatment Trial [29]. Pediatric studies of PARDS patients, likely because of limited study size, have not consistently observed increased risk within racial or ethnic groups either. While the PARDIE study results did not indicate increased risk of death across different racial groups, mortality was significantly higher in Hispanic cohorts (24.4%) compared with non-Hispanic patients (14.8%) or those with other ethnicity (14.4%, $p = 0.013$) [12]. Finally, these studies do not address the racial or ethnic impact on the risks of development of ARDS or PARDS, which may have an entirely different risk profile and may better be studied from a genetic risk perspective. As an example, Dahmer and colleagues have determined genetic polymorphisms in the genes of factors involved in the splicing cystic fibrosis transmembrane regulator conductance associated with increased risk of pneumonia-associated PARDS development in African American and non-Hispanic Caucasian children [30]. Again, this area is likely to be more completely examined in the years to come.

Genetic Factors

Investigations focusing on the genetic contribution to PARDS development are inherently fraught with challenges including, but not limited to, (a) the wide array of disease states associated with PARDS development; (b) the PARDS diagnosis itself, by definition, being a syndrome rather than a clearly defined entity with a proven diagnostic confirmatory test; and (c) the large number of patients required to complete genomic studies with adequate power. That said, genomic approaches offer promising opportunities to identify novel mechanistic pathways of disease that may offer pharmacologic or other therapeutic targets in the future. Certainly, as latent class analytic strategies identify sub-phenotypes of ARDS patients with differential risk of response to therapy or distinct clinical outcomes, investigations of genetic variants may offer areas of common biology within sub-phenotypes or may identify previously unidentified sub-phenotypes. To date, although multiple single-nucleotide polymorphisms (SNPs) have been identified with some association to ARDS risk, almost all studies have been done in adults. Not surprisingly, reproducibility has been problematic. The most notable functional variants identified to date are variants encoding angiotensin-converting enzyme (*ACE*) and surfactant protein B (*SFTPB*), with the most potentially pharmacologically targetable SNPs identified to date being angiopoietin-2 (*ANGPT2*) and IL-1 receptor antagonist (*IL1RN*) [31]. To confirm the functional significance of dysregulated coagulation in contributing to worse outcome in ARDS, genetic studies from patients enrolled in the adult ARDSnet Fluid and Catheter Treatment Trial reported that genetic variants in thrombomodulin and endothelial protein C receptor genes were independently associated with mortality, independent of treatment trial allocation [32]. The finding that the *IL1RN* coding variant is associated with decreased risk of ARDS in adults supports the understanding that IL-1beta and other IL-1 pathway cytokines are causally implicated in ARDS risk [33]. However, in a study of 549 children with acute respiratory failure, Dahmer and colleagues were unable to identify genetic variants in the IL-1 pathway genes that were associated with PARDS [34]. Initiated in 2012, NHLBI hosted an exome sequencing project that includes an investigation of 45,000 SNPs from the exomes of adults with ARDS and healthy controls. Through this project, the regulatory gene arylsulfatase D (*ASRD*) was identified to be present in 22% of adults with ARDS and 4% of controls, and a protein coding gene, XK Kell blood group complex member 3 (*XKR3*), was present with a minor allele frequency of 37% in ARDS patients and 4% of controls [35]. More is certain to come.

Although many investigations are currently underway, far fewer publications exist on the genetic associations in established PARDS

patients or patients at risk for PARDS. Wei and colleagues identified linkage disequilibrium and different allelic or genotypic frequencies in nitric oxide synthesis 3 polymorphisms measured in 216 PARDS patients in comparison to 225 healthy controls [36]. As mentioned earlier, Perez-Marquez, Dahmer, and colleagues determined potential racial and ethnic contributions to PARDS development in pediatric patients with community-acquired pneumonia [30]. Specifically, this group identified 5 variants in cystic fibrosis transmembrane conductance regulator (*CFTR*) splicing factor genes independently associated with PARDS in African American children without cystic fibrosis but with PARDS secondary to community-acquired pneumonia. An additional variant was identified in non-Hispanic Caucasian children, also without cystic fibrosis, that was associated with increased risk of PARDS development. CFTR, a chloride channel in alveolar epithelial cells, has long been understood to be integral to maintenance of fluid homeostasis in the lung and impaired during ARDS as alveolar epithelial cell injury propagates.

Etiologies Associated with PARDS Development

Not surprisingly, more research has been completed into the risk factors associated with the development of ARDS in adults compared to pediatric populations. Diagnoses most commonly associated with adult ARDS include pneumonia, extrapulmonary sepsis, aspiration, noncardiogenic shock, and trauma [37, 38]. Understanding of the association with ARDS development has been so ingrained, that recent studies indicate that clinicians may "miss" ARDS diagnoses in those patients that present with no known risk factor [39].

One frequent assumption is that ARDS in pediatric patients is more often related to a direct lung injury than seen in adults. We can test this consideration by comparing the epidemiology of adult ARDS and PARDS through the lens of two large international cohort studies.

In adults, the Large Observational Study to Understand the Global Impact of Severe Respiratory Failure (LUNG SAFE) investigators recruited a sample of 29,144 patients from 459 ICUs and identified 3022 patients with ARDS using the Berlin definition [40]. Of those patients, 59.4% had pneumonia as a risk factor for ARDS, followed by 14.2% with extrapulmonary sepsis, 14.2% with aspiration, 7.5% with noncardiogenic shock, and 4.2% with trauma. No risk factor was identified in 8.3% of patients.

In pediatrics, the PARDIE study was an international point prevalence study surveying over 23,000 PICU admissions and 12,000 patients requiring mechanical ventilation [12]. Of those patients, 744 (3.2%) were identified as having PARDS based on PALICC criteria. Among PARDS patients, the most common risk factor was pneumonia or lower respiratory tract infection (63%), distantly followed by sepsis (19%), aspiration (8%), trauma (4%), other (3%), drowning (1%), and non-septic shock (1%). Therefore, although the Berlin and PALICC definitions for ARDS differ, the results of these two large epidemiologic studies strongly indicate that the etiologies of PARDS and ARDS may not be as disparate as is sometimes assumed.

Most descriptions of ARDS and PARDS break down the etiology into direct and indirect causes. The Pediatric Acute and Critical Care Medicine Asian Network (PACCMAN) published a study in 2018 comparing "pulmonary" versus "extrapulmonary" ARDS [41]. The "extrapulmonary" group included patients with sepsis, massive transfusions, burns, multi-trauma, and hemorrhagic shock and comprised 41 (13.4%) of the 307 patients with PARDS. In this cohort, the extrapulmonary group had higher mortality, higher proportion of multiple organ dysfunction, and higher median oxygenation index. A similar study in adults examined 417 patients with ARDS by AECC criteria: 250 (60%) with direct ARDS defined as pneumonia or aspiration and 167 (40%) with indirect ARDS defined as non-pulmonary sepsis or pancreatitis [42]. The authors showed similar mortality (28% direct vs 21% indirect) between the two groups, but the direct group had higher lung injury scores (3.0 vs

2.8) and the indirect group had more organ dysfunction (median 2 vs 1 organ system).

Direct Lung Injury

Primary Pulmonary Infections

Primary pulmonary infections were the most common cause of PARDS in the PARDIE study, underlying two-thirds of the cases of PARDS identified. These "direct" PARDS cases had lower mortality than "indirect" causes like sepsis and non-septic shock [12]. Primary pulmonary infections leading to ARDS can be related to a viral etiology, bacterial etiology, or both as in the case of influenza leading to a *Staphylococcus aureus* infection. Much attention has been paid to pandemic viruses that can lead to drastic increases in ARDS patients: influenza, including H1N1; Middle Eastern respiratory syndrome coronavirus; and severe acute respiratory syndrome coronavirus [43]. Interestingly, the extreme virulence of these coronavirus infections is now thought to be immune mediated, with very early and exaggerated activation of the complement cascade [44]. More commonly, viral etiologies are those that cause the upper respiratory infections and bronchiolitis cases commonly encountered in the pediatric intensive care unit: respiratory syncytial virus (RSV), adenovirus, rhinovirus, and human metapneumovirus [43, 45]. Similarly, bacterial causes of PARDS are often the common pathogens that cause community-acquired pneumonia including *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Staphylococcus aureus* [46]. As expected, immunosuppression also places patients at greater risk for fungal and parasitic causes of ARDS, including *Pneumocystis jirovecii* [46]. These patients retain a higher mortality regardless of ARDS severity [10]. Finally, as the PALICC definition now also allows for patients with chronic lung disease to be diagnosed with PARDS, we may see an increase in pathogens specific to technology-dependent and chronically ventilated patients as important PARDS etiologies soon.

Aspiration

Aspiration was identified as the third most common etiology of PARDS in the PARDIE study, underlying 8% of the incidence seen. Aspiration is most commonly thought of as aspiration of stomach contents but can also be from the aspiration of household chemicals, blood, and other substances. Swallowing dysfunction or altered consciousness places a patient at risk for inhalation of such pharyngeal contents. Further, the acidity of stomach contents can lead to direct pulmonary epithelial damage and neutrophilic inflammation [47], commonly described as "chemical pneumonitis." Bacteria from the digestive tract can also cause secondary aspiration pneumonia [47].

Trauma

The development of ARDS following trauma is multifactorial and can differ from other mechanisms leading to ARDS. It can be a result of both direct thoracic trauma, including pulmonary contusion, or secondary to inflammation and infection that develop after major trauma [48]. The pathophysiology of trauma-induced ARDS also seems to be different than other etiologies: biomarkers including von Willebrand factor antigen, intercellular adhesion molecule-1 (ICAM-1), and surfactant protein-D have been found to be lower in trauma patients than in other processes leading to ARDS [49].

Interestingly, both the LUNG SAFE and PARDIE studies described similar prevalence of trauma (4%) as an inciting factor for ARDS. Several studies have used the National Trauma Databank (NTDB) to evaluate the epidemiology of pediatric trauma-induced ARDS. Killien and colleagues examined 146,058 children <18 years old admitted to 460 level I or II adult or pediatric trauma centers from 2007 to 2016. ARDS incidence was 1.8% in all pediatric trauma patients and 3.8% in mechanically ventilated trauma patients. Injury severity score (ISS) was a strong risk factor for ARDS, and overall injury severity was more predictive of outcome than chest trauma alone [50].

The authors also identified that very few patients who went on to develop ARDS had a normal Glasgow coma scale (GCS) or respiratory rate on arrival to the emergency department (ED). The mortality in patients who developed ARDS was 20%. In Dr. Killien's study, motor vehicle crashes were the most common mechanism among those with ARDS. In another study using the NTDB, de Roulet and colleagues demonstrated that, in young children, non-accidental injury and near drowning were independently associated with the development of ARDS [51].

Indirect Lung Injury

Sepsis

Following respiratory infections, sepsis is the next most common etiology of PARDS [12]. The endothelial activation, cytokine-mediated inflammation, reactive oxygen species, and disruption of normal coagulation cascades present in patients with severe sepsis can lead to the development of diffuse alveolar damage [52]. Given that the inflammation in sepsis is thought to trigger the inflammation and cell damage in ARDS, studies have attempted to target this group specifically for anti-inflammatory therapies [53, 54]. A detailed discussion of sepsis is beyond the scope of this chapter, but further investigation into the pathophysiology and common pathways of both diseases can lead to therapeutic targets.

Transfusion Related

Transfusion of blood products is an uncommon but significant cause of acute lung injury and ARDS. Consensus definitions of transfusion-related acute lung injury (TRALI) mirror the AECC and Berlin definitions of ARDS except that lung injury and subsequent ARDS develop during or within 6 hours of the transfusion [55, 56]. TRALI may be considered a "two-hit" phenomenon with the first hit being the patient's disease process and the second hit being neutrophil activation and capillary leak [52, 57]. Both adult and pediatric investigators have confirmed that transfusions of multiple blood products, particularly those that are protein-rich, such as fresh frozen plasma and platelets, are associated with both development of ARDS (TRALI) and unfavorable outcomes of ARDS, including greater mortality [58–60].

Noninfectious Systemic Inflammation

Any disease process that results in a systemic inflammatory response places a patient at risk for ARDS. One classic example is the lung injury that develops with acute pancreatitis, which was also noted by Ashbaugh et al. in 1967. The inflammatory cytokines and chemokines released result in both vascular endothelial and alveolar epithelial damage, potentially exacerbated by pancreatic enzymes and a compromised intestinal barrier [61]. The common pathway of vascular permeability and fluid leak that often underlies ARDS follows. Another common mechanism of systemic inflammation is the ischemia and reperfusion that occurs during cardiopulmonary bypass for congenital heart defect surgical repair. This can lead to multiple organ dysfunction syndrome (MODS) including ARDS; however, outcomes are significantly better with MODS after bypass than other forms [62].

Modifiable Aspects of Care Delivery

Among all etiologies for ARDS, perhaps the most interesting and potentially meaningful area of focus is the potentially modifiable areas of the care we deliver to patients with acute respiratory failure. These methods of respiratory support, medications, and health care delivery are all potential targets to prevent the development of ARDS in at-risk patients. A large study by the Practice of Ventilation in critically ill adults without ARDS at onset of ventilation (PRoVENT) study group attempted to identify these factors [63]. This international, multicenter cohort study identified patients undergoing mechanical ventilation who were at risk of ARDS defined as a

Lung Injury Prevention Score of 4 or higher. Ventilator variables such as tidal volume, PEEP, and driving pressure were not associated with the development of ARDS in those at risk and those not at risk, but interestingly FiO_2 was higher in patients who developed ARDS. A noted limitation of this study as well as other efforts to prevent ARDS is the large number of patients who have ARDS at the time of intubation [64]. Raymondos and colleagues tested whether outcomes differed between ARDS patients managed at German university and nonuniversity hospitals and found a survival benefit in patients treated at university hospital [65]. Differences were seen in the use of higher FiO_2, lower PEEP, and higher driving pressure in the nonuniversity hospitals at the time of the study. Interestingly, this finding corroborates that of Noah et al. from 2011 wherein transfer to an ECMO center, even if the patient was then not cannulated for ECMO, conferred a survival benefit for those adults with H1N1-associated ARDS compared to matched non-ECMO referred patients [66]. While these observational data do not point towards clear reasons for the improved survival, they suggest that differences in our routine and supportive care of patients at risk for ARDS development can affect progression of disease.

Coupled with the acknowledgement that best chances for complete recovery rest on earlier initiation of appropriate therapies, these studies all indicate a need to identify patients at earlier timepoints in their course. To affect this next type of research, researchers are likely to enroll patients at locations other than the pediatric intensive care unit, including the emergency department, operating rooms, and acute care hospital wards. The mission of the National Institutes of Health–funded PETAL network (Prevention and Early Treatment of Acute Lung Injury, http://petalnet.org) includes partnering ICUs with EDs for earlier diagnosis and initiation of supportive measures. In pediatrics, in 2015, the PALICC yielded internationally accepted, comprehensive definitions for PARDS, patients at risk for PARDS, and patients with complex comorbidities previously oft excluded from PARDS-related research, such as chronic lung disease and congenital heart disease populations. The at-risk group is now defined as patients either on noninvasive positive pressure via nasal interface or patients on nasal cannula, either via traditional or heated high flow nasal cannula, with specified oxygenation deficits [8]. In the wake of the establishment of these pediatric-specific definitions, the PARDIE investigators recently completed an international, observational study of PARDS and at risk for PARDS patients. Initial results are now published on the traditional PARDS cohort with results related to the at-risk population, including data on potentially modifiable aspects of care, soon forthcoming [12].

Less Common Etiologies of ARDS

Case reports and case series describe the development of ARDS following episodes causing local or systemic inflammation including pulmonary air embolus [67], fat embolism [68], Still's disease [69], and malaria [70, 71]. Neurogenic pulmonary edema has been described in the setting of severe neurologic injury, potentially related to a large sympathetic surge following the injury [72].

Biomarkers Associated with PARDS Onset and at Risk for PARDS Development

Clearly the pathophysiologic processes of inflammation, vascular endothelial injury, alveolar epithelial injury, fibrosis, and hypercoagulability may be triggered and initiated well before patients are admitted to intensive care units [73]. Biomarker studies in children, as in adults, have identified evidence of lung injury even in the earliest days of hypoxemia and, in up to 25% of cases, before invasive mechanical ventilation has been initiated [37, 74].

Several researchers have observed elevations of markers of vascular endothelial injury at the onset of PARDS diagnosis. Flori and colleagues

found that the highest levels of von Willebrand factor antigen were measured early in the course of PARDS [75] and Yehya et al. reported similar findings with angiopoietin-2, ANG2 [76]; both are vascular endothelial injury markers. Markers specific for alveolar epithelial injury are more difficult to measure in plasma. Flori and colleagues found early elevations of soluble intercellular adhesion molecule-1, sICAM-1 [77], also a marker of macrophage activation, and Yehya observed elevated levels of soluble receptor for advanced glycation end products, sRAGE, at PARDS diagnosis [76]. Sapru and colleagues identified early activation of multiple markers of the inflammatory and coagulation cascades [78, 79]. Zinter et al. observed early evidence of matrix metalloproteinase release into the plasma, an indicator of early-onset fibrosis, again at PARDS onset. Finally, the pathogenesis of ARDS is felt to be mediated by both pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), biomolecules that can perpetuate an inflammatory response. Circulating nucleosomes are released after cellular injury into the bloodstream, acting as DAMPs, and contributing to the severity of ARDS. Yehya et al. have measured circulating nucleosomes in children with PARDS and found striking and independent associations with mortality and non-pulmonary organ failure and severity of oxygenation defect [80]. Most of these studies included PARDS patients who were not only invasively mechanically ventilated but also those patients meeting PARDS criteria while on noninvasive ventilation, which suggests that pathophysiology can be identified a bit earlier in these cascades.

These studies all reflect biomarkers associated with PARDS onset. As described previously, the next phases of research must strive to identify at-risk patients before they develop PARDS. Identification of these risk factors for development may help clinicians at the bedside to adjust monitoring and/or initiate lung protective management strategies earlier in the patients' course in order to prevent PARDS development entirely. Similarly, better identification of those patients at risk for PARDS development may enable researchers to develop novel therapies that can be initiated earlier in the patient's course and, likely, using noninvasive modalities (i.e., inhaled treatments, alternate modes of noninvasive respiratory support).

The RESTORE trial of sedation management in pediatric acute respiratory failure enrolled pediatric patients with acute respiratory failure requiring invasive mechanical ventilation secondary to primary pulmonary or airway disease [81]. As such, patients with acute respiratory failure secondary to trauma or surgery were excluded. Nonetheless, the RESTORE study has allowed for potential identification of children with acute respiratory failure yet *prior to* PARDS onset. Genetic Variation and Biomarkers in Children with Acute Lung Injury (BALI; R01HL095410) was a prospective ancillary study to the multisite clinical trial, Randomized Evaluation of Sedation Titration for Respiratory Failure (RESTORE; U01 HL086622) (22). BALI was designed to examine the association of specific plasma protein and genetic biomarkers with PARDS among prospectively enrolled children with acute respiratory failure. Twenty-two of the 31 PICUs participating in RESTORE volunteered to participate in this study. A total of 69% of the patients (n = 378) met the criteria for PARDS and 83% of children (n = 312) with PARDS met criteria on the day of intubation (study day 0); another 11% (n = 42) met criteria on study day 1, and the remaining 6% met criteria on study days 2–5. The level of plasma IL-1ra was significantly greater at intubation through day 3 in those with PARDS compared with those without PARDS ($p < 0.0001$). In addition, multivariable regression analysis of data across all days demonstrated a significant association of IL-1ra (OR, 1.30; 95% CI, 1.10–1.52; $p = 0.002$) and day ($p < 0.05$) on presence of PARDS, independent of age and PRISM-III. Additional data from BALI related to other markers of inflammation, plasma surfactant protein measurement, and markers of dysregulated coagulation are forthcoming. Despite this work and although RESTORE enrolled patients with acute respiratory failure,

approximately 90% of patients meeting PARDS criteria did so within the first day of RESTORE enrollment, thereby again limiting the opportunity to find biomarkers that can be measured prior to PARDS onset and within a time frame to allow clinicians to use these marker measurements to initiate preventative therapies. These data corroborate nicely with adult data from the LUNG SAFE study wherein only 7% of adults that eventually developed ARDS did so after day 2 of acute hypoxemic respiratory failure [40].

Latent Class Analysis and Identification of ARDS and PARDS Sub-phenotypes

To date, no pharmacologic treatment has been conclusively proven effective in decreasing mortality or morbidity in adults or children with ARDS [82, 83]. The failure of the pharmacologic treatments tested thus far has recently been attributed, in part, to heterogeneity in patients with ARDS. Dr. Iwashyna and colleagues developed simulation models to demonstrate that heterogeneity in cohorts of patients with acute respiratory failure can significantly impact clinical trial results by: (a) showing no benefit for the entire cohort resulting in a negative trial although a high-risk subgroup (sub-phenotype) of patients may actually benefit from the treatment and (b) showing benefit for the entire cohort resulting in a positive trial though a subgroup (sub-phenotype) of patients may incur harm from the treatment [84]. The recent consensus in the field is that strategies aimed at *prognostic* (identifying high-risk patients) and *predictive* (selecting patients who are likely to respond to treatment based on differences in the underlying pathology) enrichment should be used in studies of ARDS patients to identify targeted therapies that have a higher likelihood of reducing morbidity and mortality.

Recently, Drs. Calfee and Delucci have used latent class analysis (LCA) to identify two novel sub-phenotypes in adult ARDS patients with different biomarker profiles, clinical and biological characteristics, clinical outcomes, and response to treatment [85–87]. *Their team has since independently replicated the same two ARDS sub-phenotypes using data from additional NHLBI-funded adult ARDS trials* (Table 4.1). The hyperinflammatory ARDS sub-phenotype, characterized in part by higher plasma inflammatory biomarkers (interleukin-6 (IL-6), IL-8, soluble tumor necrosis factor receptor-1 (sTNFr-1), plasminogen activator inhibitor-1 (PAI-1), angiopoietin-2 (Ang-2), receptor for advanced glycation end products (RAGE), and decreased protein C, is associated with 20–30% higher mortality and approximately 10-day longer length of mechanical ventilation (MV). The hyperinflammatory patients may preferentially benefit from higher PEEP and restrictive fluid strategies. The two sub-phenotypes appear to be stable to at least 3 days after meeting ARDS criteria. There are no studies identifying PARDS sub-phenotypes in children primarily because until recently there were no large cohorts of children with PARDS. Once again, this is assuredly "next to come" for this patient population.

Table 4.1 Differential response to treatment in ARDS sub-phenotypes

	Mortality in intervention hypoinflammatory sub-phenotype	Mortality in intervention hyperinflammatory sub-phenotype	Mortality in control hypoinflammatory sub-phenotype	Mortality in control hyperinflammatory sub-phenotype
ALVEOLI[a]	24%	42%	16%	51%
FACCT[a]	26%	40%	18%	50%
HARP[b]	17%	32%	16%	45%

[a]90-day mortality
[b]28-day mortality

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5 Imaging and Monitoring in Pediatric Acute Respiratory Distress Syndrome

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Abbreviations

AVDSf	Alveolar dead space fraction
CT	Computed tomography
EA_{di}	Electrical activity of diaphragm
EIT	Electric impedance tomography
F_IO_2	Fraction of inspired oxygen
FRC	Functional residual capacity
LIS	Lung injury score
NVE	Neuroventilatory efficiency
OI	Oxygen index
OSI	Oxygen saturation index
P/F	P_aO_2/F_IO_2
P_aO_2	Partial pressure of oxygen
Paw	Mean airway pressure
P_{di}	Transdiaphragmatic pressure
P_{dimax}	Maximum inspiratory transdiaphragmatic pressure
PE_{max} expiratory	Muscle strength
P_{es}	Esophageal pressure
PET	Positron emission tomography
P_{ga}	Gastric pressure
PI_{max}	Global inspiratory
PRP	Pressure–rate product
RIP	Respiratory inductive plethysmography
S/F	S_pO_2/F_IO_2
S_pO_2	Oxygen saturation
T_i	Inspiratory time
TTI	Tension–time index
TT_{mus}	Noninvasive TTI
T_{tot}	Total respiratory cycle time
X-ray	Radiograph

Part One: Imaging

Examination and proper understanding of chest imaging are paramount in diagnosing and treating PARDS. In this section, we will summarize the role of each imaging modality from the point of view of assessment and diagnoses of PARDS, and as a tool to assess treatment effect (Table 5.1).

Chest X-Ray

Overview

A chest radiograph (X-ray) is fundamentally important in the diagnosis and management of

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Table 5.1 Chest imaging in the diagnosis and management of PARDS

Imaging	Clinical and physiological information	Advantages	Weakness/drawbacks	Risks and unknown
X-ray	Etiological diagnosis PEEP adjustment (recruitment) Detection of complications	Available at bedside	Poor sensitivity and specificity Large interobserver variability	Radiation exposure On-demand or routine
CT scan	Etiological diagnosis PEEP adjustment (homogeneity, recruitability)	Higher sensitivity	Challenges in timely follow-up Resolution dependency	Radiation exposure Risk of transport
Ultrasound	Etiological diagnosis PEEP adjustment (homogeneity, recruitability) Differentiate new comorbidity Heart and lung interaction Evaluation of diaphragm function	Repeatability No radiation exposure	Technically difficult Challenges in quantification	Tolerance Infection
EIT	PEEP adjustment (homogeneity, recruitability) Pulmonary perfusion	Real-time monitoring Intuitive visual aid No radiation exposure	Technically difficult Affected by thoracic shape/wall	Skin injury or discomfort
PET	Regional lung perfusion Pulmonary vascular permeability Metabolic activity of inflammatory lung cells	Combinable with other imaging No radiation exposure	Technically difficult Long duration of procedure	Risk of transport

PARDS, having played a key diagnostic role since the original definition of ARDS [1–3]. It has also been recognized as an important modality to ascertain and check the correct position of medical devices as well as to detect complications such as air leak. However, its poor diagnostic sensitivity, appropriate frequency of routine chest X-ray in the PARDS management, and high interobserver variability have been subjects of debate.

Diagnosis

For more than two decades, the evaluation of the extension and distribution of ARDS lung opacities was limited to chest X-rays [1]. In the Berlin ARDS definition, the radiographic criterion is more explicit, specifying that it should include bilateral opacities, consistent with pulmonary edema not fully explained by effusions, lobar/lung collapse, or nodules [2]. In adult ARDS, when the radiological criteria of the previous ARDS definition were strictly applied (bilateral chest X-ray infiltrates), the sensitivity was good, but specificity was low. ARDS does not necessarily translate into the histologic appearance of diffuse alveolar damage. The primary argument to include bilateral infiltrates in the definition of ARDS was to allow for discrimination between localized processes such as lobar pneumonia and diffuse inflammatory processes [1]. However, the sensitivity of chest X-rays is low to detect pulmonary parenchymal inflammation and edema, which compounded by high interobserver variability further compromises the value of chest X-rays in PARDS [4, 5]. For this reason and others, the new PARDS criterion advocated the removal of the requirement for bilateral infiltrates from the definition [6].

Use in Management

Generally, a chest X-ray is repeated regularly to monitor the progression of the disease, detect complications, and check the correct position of tubes and catheters. The optimal frequency of chest X-rays in children with PARDS is not established. Although some adult studies reported a possible benefit of an on-demand chest X-ray strategy to decrease its utilization in mechanically ventilated patients without affecting quality of care or safety, a recent systematic review con-

cluded that the safety of abandoning routine chest X-rays in patients admitted to the ICU remained uncertain [7, 8]. In the pediatric cohort, routine (once a day) chest X-rays have been associated with a higher likelihood of management change or intervention. However, given the advancement of other less-invasive diagnostic imaging techniques such as ultrasonography, the necessity of routine versus adoption of on-demand chest X-rays should be considered [9].

Automation of Imaging Diagnosis

In spite of its limitations, chest X-ray continues to be an important tool in the management of PARDS, owing to its simplicity, relatively low cost, and widespread availability. A recent large international epidemiological study suggests that the proportion of patients with bilateral infiltrates increased with increasing severity of PARDS, and these were associated with higher mortality compared to unilateral infiltrates [3]. Artificial intelligence has been used to assist in standardizing the interpretation of chest X-rays and may have a role in PARDS [10].

Chest Computed Tomography

Overview

Chest Computed Tomography (CT) plays an important role in the diagnosis and management of PARDS. Chest CT can provide a better understanding of the distribution of poorly aerated pulmonary regions of PARDS lung, and the effect of gravitational forces on disease distribution.

Diagnosis

Chest CT enables a precise assessment of lung aeration, consolidation, or overdistension through direct visual analysis or quantitative measurements of Hounsfield Unit in the single voxel [11]. Lung compartments at different degrees of aeration, from totally nonaerated to hyperinflated tissue, can be identified through analysis of voxels representing a certain region of the lung [12, 13]. Modern multislice CT scanners have even better sensitivity and may give us more insights into PARDS [11].

Use in Management

Role of chest CT as a monitoring tool to guide ventilator setting and recruitability assessment has been well studied in an adult population [11, 12, 14–16]; it has been recognized as the gold standard to target PEEP and VT by assessing recruitment and hyperinflation. Modern multislice CT can be helpful in assessing the results of various recruitment maneuvers and provide more precise diagnostic information compared to single-slice CT [11, 17, 18]. In the pediatric population, only a case series examined the feasibility of evaluation of lung aeration by chest CT following a recruitment maneuver [19]; hence, the clinical impact of assessment of lung aeration in PARDS remains unclear. Because chest CT carries important risks associated with radiation exposure and the need to transport a critically ill patient to the scanner [20–23], it is not routinely performed in PARDS.

Ultrasound

Overview

Lung ultrasound is widely used in contemporary pediatric practice due to its simplicity, reproducibility, and lack of exposure radiation. It can be used in differentiating PARDS from other conditions, and in the evaluation of treatment effects. However, ultrasound evidence in PARDS is still scarce with respect to its validity and technical standardization.

Diagnosis

Anatomical structures with gas-filled spaces do not transmit ultrasound waves. Therefore, one can only obtain real structural images from a consolidated lung or a lung surrounded by pleural effusion. Air in the lung can create "artifacts" with various patterns, which could help us to understand certain pathophysiological conditions. Normal healthy or hyperinflated lungs create a horizontal pattern of artifacts parallel to the pleural line called "A-lines," while the partial loss of aeration leads to a longitudinal laser pattern of artifacts called "B-lines." The patterns of spatial distributions and number of B-lines can be used to assess the grades of aeration. Particularly, we can see

multiple B-lines in the ARDS lung with a heterogeneous and non-gravity-dependent distribution, pleural thickening, and diminished lung sliding [13, 24, 25]. Ultrasound images can be semiquantitatively assessed using the four sonographic findings: normal pattern, multiple spaced B-lines, coalescent B-lines, and consolidation [25].

Use in Management

Lung ultrasound can be used to monitor aeration changes and effects of therapy including recruitment maneuver. In adult patients, lung ultrasound has been well validated to detect conditions such as pleural effusions, cardiogenic pulmonary edema, alveolar–interstitial syndrome, ventilator-associated pneumonia, pleural effusion, and pneumothorax, and compares favorably to chest X-ray in critically ill patients, with very high diagnostic accuracy, specifically for both pneumothorax and pleural effusions [13, 24–29]. It can also be used to assess heart–lung interactions, including the intracardiac right-to-left shunting to guide therapeutic interventions in ARDS patients. Nonetheless, the evidence for routine use of lung ultrasound in the pediatric population is still somewhat limited [30, 31].

Lung reaeration by ultrasound can be assessed by tracking changes in sonographic findings, including evaluation of response to recruitment maneuvers. For instance, a patient with ARDS with diffuse loss of aeration has a higher level of PEEP-induced lung recruitment when compared to patients with focal loss of aeration. A-lines correspond to normally aerated or hyperinflated lung, well-spaced B lines correspond to moderate loss of aeration, coalescent B-lines correspond to severe loss of aeration, and a tissue-like pattern indicates complete loss of aeration.

Lung ultrasound can be performed at the bedside, thus avoiding the possible risks associated with transporting unstable children. It could also lead to a reduction in the number of chest X-rays and CT scans, thus reducing radiation exposure. Lung overinflation, technical difficulty with subcutaneous emphysema, the presence of large thoracic dressings (e.g., patients following chest trauma or burns), or marked obesity can limit the performance of lung ultrasound. Proper training is required to correctly perform and interpret the findings of a lung ultrasound examination. Lung ultrasound usually takes longer to perform compared to other imaging modalities, such as X-ray, an issue that could limit its tolerability by some of the sicker patients with PARDS.

Ultrasound of Diaphragm

Evaluation of the diaphragm by ultrasound has recently become a common practice in the PICU. Abnormal diaphragmatic imaging (i.e., thickness and motility) can be observed in conditions such as phrenic nerve injury or prolonged mechanical ventilation in PARDS [32].

Electric Impedance Tomography

Overview

Electric Impedance Tomography (EIT) is a non-invasive bedside monitoring technique that enables dynamic real-time evaluation of lung volume and regional lung changes. EIT quantifies relative changes in local impedance of lung; therefore, normal or pathologically stable structures such as pleural effusions are functionally muted and are not visualized. In other words, the lung is a good candidate for EIT because its impedance is closely related to the degree of parenchymal inflation. In children, typically, chest EIT can be performed by placing an electrode belt around the thorax, between the third and the sixth intercostal spaces. The resulting images represent the impedance changes occurring in a cross-section of the thorax [33–35].

Use in PARDS

EIT can detect existing heterogeneity in regional ventilation during mechanical ventilation and during recruitment maneuvers. Changes in EIT patterns can distinguish between recruited and derecruited lung regions. Decreased lung aeration in dependent regions and compensatory overdistension in nondependent regions can be seen in EIT during the progression of PARDS. EIT has also been studied to assess the regional distribution of pulmonary perfusion and its relationship with lung ventilation [36–39].

EIT has been well validated in an adult subjects against other imaging techniques that assess

lung volume. However, several factors may affect its output and resolution, such as electrode position, conformational changes of chest wall, and diaphragm. Research focusing on improving image reconstruction algorithms, creating dedicated algorithms for specific clinical applications, improving its connectivity with modern mechanical ventilators (including noninvasive ventilators), and developing ways of reducing artifacts due to the changes in thoracic shape, is ongoing [40].

Positron Emission Tomography

Positron emission tomography (PET) is a functional imaging technique based on the administration of a molecule labeled with a radioactive isotope that decays with the emission of a positron. PET is versatile; it can quantify regional perfusion, pulmonary vascular permeability, ventilation, aeration, metabolic activity of inflammatory cells, enzyme activity, and pulmonary gene expression. Combining PET measurements of perfusion and shunt can identify redistribution of perfusion toward derecruited regions as the mechanism for the worsening oxygenation that is sometimes observed with recruitment maneuvers or application of PEEP. One should be cautious when using PaO_2 as an index of PARDS severity or response to recruitment strategies if the distribution of perfusion is unknown [41–43].

While routine PET scanning of PARDS patients is not feasible, PET could be useful in selected cases to detect early PARDS development, or to monitor the efficacy of anti-inflammatory treatment. Combined availability of PET with other imaging modalities such as CT scan or Magnetic Resonance Imaging (MRI) could make multimodality imaging a valuable tool to further our understanding of PARDS.

Part Two: Nonimaging Monitoring

Children with PARDS should, at a minimum, undergo continuous monitoring of heart and respiratory rates, continuous pulse oximetry, and blood pressure measurements. Those monitored parameters can be utilized for diagnosis of PARDS, and to assess its severity and progression during the course of treatment. In this section, we describe and summarize respiratory system variables related to PARDS management, which are derived from measurements in a non-airway circuit, including oxygen and ventilatory parameters, and severity scores (Table 5.2).

Respiratory Variables Derived from Additional Monitoring

Lung Compliance

In complement to the tidal volume and positive inspiratory pressure, these are continuously monitored on the ventilator; monitoring of respiratory system compliance can help assess PARDS progression. In clinical practice, the dynamic compliance measurement [Vt (ml/kg ideal body weight)/(PIP-PEEP (cmH_2O)] (normal range 1.5–2 ml/kg/cmH_2O) is preferred to static or quasistatic compliance measurements that are more difficult to obtain. Of note, although the PIP can be used to calculate compliance in patients undergoing pressure-controlled ventilation, the plateau pressure (Pplat) is preferred in patients undergoing volume-controlled ventilation. The Pplat should be measured during an end-inspiratory hold and in the absence of active spontaneous breathing [44].

Transpulmonary Pressure

During mechanical ventilation, transpulmonary pressure measurements can be estimated as the airway pressure (Paw) (a surrogate for alveolar pressure) minus the esophageal pressure (P_{es}) (a surrogate for pleural pressure). Transpulmonary pressure, the pressure across the lung that gives rise to pulmonary ventilation, is crucial to our understanding of respiratory mechanics and clinical decision makingregarding PEEP adjustment in PARDS. Although transpulmonary pressure has been well studied in the adult population, limited evidence exists in patients with PARDS [45–50]. We can calculate work of breathing from intrinsic PEEP or any cause of decreased respiratory system compliance by using the Campbell diagram, or the pressure–rate product

Table 5.2 Parameters monitored in the management of children with acute respiratory distress syndrome (hemodynamic monitoring excluded)

Monitoring and measurement	Clinical indication and information	Equipment required	Specific considerations
Respiratory system variables derived from additional monitoring			
Lung compliance	Severity assessment	Pressure and tidal volume on the ventilator	Dynamic compliance Plateau pressure measure
Esophageal manometry	Measuring transpulmonary pressure PEEP adjustment Prevention of ventilator induced lung injury	Esophageal balloon Pressure monitor or ventilator	Technical difficulty
Work of breathing, pressure–rate product	Adequacy of support PEEP adjustment	Esophageal balloon Pressure monitor or ventilator	Technical difficulty
Corrected minute ventilation	Severity assessment	Ventilator ABG or CBG	Standardized minute ventilation of children: Approximately 150 mL/kg/min Largely a research tool
Functional residual capacity	Severity assessment PEEP adjustment	Ventilator with special function or dedicated device	Simple and automated bedside techniques required
Ratio dead space/tidal volumes (V_D/V_T)	Severity assessment and disease progress Weaning success indicator	Volumetric capnography ABG or CBG	End-tidal CO_2 should be used as a reliable surrogate for arterial or capillary CO_2 when a correction method is validated Peripheral venous blood gas also does not accurately predict arterial gas
Alveolar dead space fraction	Severity assessment and disease progress	Volumetric or time-based capnography ABG or CBG	
Respiratory inductance plethysmograph	Estimating ventilator volume and work of breathing Apnea detection	Respiratory inductance plethysmography	Dual and single band techniques Challenging to control artifact in nonsedated patients
3D computed imaging system	Estimating ventilator volume and work of breathing Apnea detection	Specially equipped bedside video cameras	Contactless automated techniques
Oxygenation and ventilation parameters and severity scores			
P/F and OI	Severity assessment Diagnosis and prognosis assessment	ABG Ventilator	Requiring arterial blood gas sampling Patients need to be on ventilator for OI
S/F ratio and OSI	Severity assessment Diagnosis and prognosis assessment	Ventilator	Patients need to be on ventilator for OSI
Lung injury score	Severity assessment	Chest x-ray ABG Compliance	Noninvasive score using oxygen saturation for P_aO_2
Ventilation index	Severity assessment	ABG or CBG	Arterial blood gas required and patients need to be on ventilator
Continuous arterial gas monitoring	Ventilator settings and adjustment	Specific arterial catheter	No widely available device

Table 5.2 (continued)

Monitoring and measurement	Clinical indication and information	Equipment required	Specific considerations
Respiratory system variables derived from additional monitoring			
Continuous CO_2 monitoring	Accuracy of the support	Ventilator, monitor, or specific analyzer	Capnography or transcutaneous monitor can be used
Respiratory muscle activity			
$P_{0.1}$	Respiratory drive Extubation readiness	Ventilator with specific function	Need to be on mechanical ventilation to measure non-invasive P0.1
Tension–time index	Respiratory drive Weaning strategy	Esophageal and gastric pressure catheter	Need to be on mechanical ventilation to measure non-invasive TTI
PE_{max}, PI_{max} Sniff P_{di}, Gilbert index	Response of respiratory muscle training	Ventilator Pressure measuring device	Voluntary measurements of maximum P_{di}: Sniff procedure Gilbert index: Relative contribution of the diaphragm to inspiration
Electrical activity of diaphragm	Respiratory drive (phasic activity); synchronization PEEP adjustment (tonic activity)	Ventilator with specific function Special nasogastric tube	V_T/EA_{di}: Neuroventilatory efficiency (NVE)
Phrenic nerve stimulation	Function of the diaphragm	Needle and implanted wire stimulation (invasive, not recommended) Transcutaneous electrical stimulation Magnetic stimulation	

(PRP; esophageal pressure change x respiratory rate) or pressure–time product [51]. The role of these variables considering different levels of PEEP and tidal volume on the partitioned respiratory mechanics, stress (i.e., transpulmonary pressure at the end of inspiration), and strain (the change in volume to the functional residual capacity) is unknown in PARDS.

Functional Residual Capacity

Optimizing Functional residual capacity (FRC) is critically important in the management of patients with PARDS because of the smaller elastic retraction forces and a lower relaxation volume that makes them more prone to airway collapse. FRC can be affected by the ventilator mode and settings such as PEEP, respiratory rate, and I:E ratio [52, 53]. Although assessing and understanding FRC could lead to a physiology-cased strategy for managing PARDS, its applicability has been limited due to lack of reliable and straightforward bedside measuring techniques [54].

Ratio Dead Space/Tidal Volumes, Alveolar Dead Space Fraction

Physiologic dead space is the sum of anatomical dead space (volume of the conducting airways not participating in gas exchange) and alveolar dead space (volume of gas in the respiratory zone that does not participate in gas exchange). Abnormalities of pulmonary blood flow and injury to the microcirculation are a characteristic feature of PARDS; hence, physiological dead space is expected to be elevated [55–61]. Capnography enables the calculation of the ratio of dead space to tidal volume, end-tidal alveolar dead space fraction (AVDSf), and ventilation index [62]. The ratio of dead space to tidal volume can be measured using volumetric capnography and $PaCO_2$ from a properly timed blood sample. It can be calculated using such as the Enghoff modification of the Bohr equation [63]. Similar information can be obtained using the end-tidal AVDSf where end-tidal CO_2 is substituted for the mixed expired CO_2, although

there may be situations when AVDSf may not be a good surrogate for V_D/V_T, such as in patients with lower airway obstruction.

Respiratory Inductive Plethysmography

Respiratory inductive plethysmography (RIP) measurements of timed respiratory mechanics, including tidal flow volume loops and thoracoabdominal asynchrony, reflect respiratory system resistance and compliance. RIP is relatively simple to perform and only requires two elastic bands placed around the chest and abdomen (i.e., dual band measurement). Although it is not designed as a monitor and has possible drawbacks such as discomfort due to the placement of the probes, RIP may provide a useful measure of respiration in conscious patients, especially those undergoing noninvasive ventilation, such as high flow nasal cannula, where one would otherwise lack the ability to measure tidal volume [64–68].

3D Computed Imaging System

While respiratory rate (RR) and ventilator tidal volume can be easily measured by the mechanical ventilator for the intubated patient, assessment of minute ventilation and effort of breathing of the spontaneously breathing patient is more challenging. Many techniques of noninvasive respiration monitoring have been reported, but most of them are unsuitable for the clinical environment due to the size of the machine or poor patient tolerance [69]. A novel noninvasive contactless 3D imaging system that captures motion data for the anterior and lateral surfaces of the torso and is capable of measuring respiratory variables, including spontaneous tidal volume, has been developed [70].

Oxygenation and Ventilation Parameters and Severity Scores

P/F and S/F Ratio, Oxygenation and Oxygen Saturation Index

Initial degree of hypoxemia correlates well with outcomes in PARDS. Several indexes aiming at evaluating the degree of hypoxia in PARDS have been studied and are routinely used in clinical practice, such as P/F ratio (P_aO_2:F_IO_2 ratio), oxygen index (OI = $F_IO_2 \times Paw/P_aO_2$; Paw: mean airway pressure), and oxygen saturation index (OSI: $F_IO_2 \times Paw/S_pO_2$).

P_aO_2/F_IO_2 Ratio

Partial pressure of oxygen (P_aO_2)/fraction of inspired oxygen (F_IO_2) ratio has been widely used in the diagnosis and management of PARDS [71]. Given the challenges of placing arterial catheters in small children, especially when patients are not sedated or mechanically ventilated, PaO_2 measurements are not routinely and practically obtainable. Therefore, the utility of P/F ratio in children has been questioned, particularly as a disease indicator or prognostic factor [59, 72–74].

Oxygen Index

OI has been used as an entry criterion and to stratify risk in PARDS studies. OI has an inherent advantage over P/F ratio in that it incorporates Paw (a measure of respiratory support) and may have a more reliable correlation than P/F ratio with mortality in children [72, 75–77]. In a single-center cohort study, it is suggested that OI could reflect the severity of oxygenation failure at any point in time in acute hypoxemic respiratory failure and does have an impact on length of mechanical ventilation and mortality. In a recent international epidemiological study, PARDS severity groups proposed by PALICC using OI measurements rather than P/F ratio have been shown to have important prognostic relevance, with patients with higher OI being at particularly high risk [3].

S_pO_2/F_IO_2 Ratio and Oxygen Saturation Index

Pulse oximetry is now widely used in PICUs, which has led to a reduced frequency of peripheral arterial catheter utilization [75, 78]. This is particularly true in patients suffering from mild or moderate PARDS. In children without an arterial line, PaO_2 cannot be easily measured, so the P/F ratio and OI cannot be calculated. In other words, children with mild-to-moderate hypoxemia that would likely meet Berlin criteria may

not be screened for PARDS due to the lack of a documented qualifying P_aO_2. Because the oxyhemoglobin dissociation curve is nearly linear when S_pO_2 is 80–97%, S_pO_2 has been proposed as a substitute for P_aO_2 in PARDS. A prospective study in adults with ARDS suggests that S_pO_2/F_IO_2 (S/F) ratio can be a reliable surrogate for the P/F ratio when S_pO_2 is ≤97% [79]. A PARDS retrospective study has shown similar results, suggesting a positive association with mortality [76]. This study also demonstrates that OSI, which substitutes SpO_2 for P_aO_2 in the OI equation, is an acceptable surrogate for P/F ratio in PARDS, with a reasonably good sensitivity and specificity, and good correlation with mortality [76].

Lung Injury Score and Ventilation Index

Various physiological measurements and scoring systems have been proposed and assessed for grading severity of illness in PARDS and predicting mortality. The lung injury score (LIS), proposed by Murray et al., has been commonly utilized to assess severity of illness in studies of adult ARDS, and has also been validated in PARDS [76, 77]. A higher LIS could identify the need for deploying rescue therapies, and changes in LIS over time have also been used as a primary outcome to study the efficacy of certain interventions [80, 81]. A large cohort study of adult ARDS reported that both LIS and the Berlin definition severity categories were associated with increased in-hospital morbidity and mortality. However, the predictive validity of both scores was marginal and there was no additive value of LIS over the Berlin criteria [81]. Noninvasive LIS applying S/F for P/F ratio has also been validated in PARDS [77]. Ventilation index (VI) (P_aCO_2 (in mm Hg) × peak airway pressure (in cmH_2O) × respiratory rate (breaths/min)/1000) has been shown to have prognostic value in PARDS [62, 82]. A small single-center study reported that higher VI (>65) could be a reliable prognostic indicator in PARDS.

Continuous Arterial Gas Monitoring

Peripheral blood gas sampling does not accurately predict arterial blood gases. Frequent blood gas sampling can be challenging, considering the risk of iatrogenic anemia, particularly in small infants. Arterial blood gases can be continuously monitored using special arterial catheters and have been studied in the research arena [83–89]. Although several prospective studies in neonates attest to the accuracy and reproducibility of an intra-arterial continuous monitoring device (Paratrend7; Diametrics Medical Inc., United Kingdom), it has subsequently been withdrawn from the market and no comparable devices exist as of today for this purpose [83, 85, 89].

Continuous CO_2 Monitoring

Carbon dioxide can be noninvasively monitored by capnography when patients are on conventional mechanical ventilation. End-tidal CO_2 monitoring can provide useful and predictive information, including dead space evaluation. However, that is not the case during high-frequency oscillatory ventilation. Although it has not been well studied in PARDS, transcutaneous CO_2 monitoring can substitute arterial CO_2 or mixed venous CO_2 in continuous monitoring [90–96].

Respiratory Muscle Function

Respiratory muscle dysfunction is known to develop in mechanically ventilated patients. To that effect, some have advocated maintaining patient breathing effort during mechanical ventilation; yet due to the limited availability and knowledge of tools to monitor respiratory muscle function in PARDS, evidence regarding clinical effect and benefits of such a strategy are still very limited.

Neural Respiratory Drive ($P_{0.1}$)

Respiratory drive measurement may be used to evaluate extubation readiness. Airway pressure (Paw) generated in the first 100 ms of inspiration ($P_{0.1}$) has been used as an index of neural respiratory drive. This delay prevents any reaction from the patient in response to occlusion. It can be measured in most conventional mechanical ventilators and has been successfully used in critically ill ventilated children. However, the value of $P_{0.1}$ in predicting extubation readiness has been reported with conflicting results [97–100].

Tension–Time Index

Understanding the effectiveness of breathing effort and load on the respiratory muscles is crucial when predicting extubation readiness. The Tension–time index (TTI) of the diaphragm (TT_{di}) is derived by relating the mean transdiaphragmatic pressure per breath (P_{di}) to the maximal inspiratory transdiaphragmatic pressure (P_{dimax}) and the inspiratory time (T_i) to the total respiratory cycle time (T_{tot}) [101–103]. It can be a fraction of maximal effort that the diaphragm performs during the contraction time. The difference between esophageal (P_{es}) and gastric pressure (P_{ga}) is used to calculate P_{di}. Measurement of the TT_{di} requires the use of balloon catheters. A noninvasive TTI measurement (TT_{mus}), based on airway pressure, has been developed and studied in children [104, 105]. One of the advantages of TT_{mus} is that it reflects the contribution of all the inspiratory muscles, rather than being specific to the diaphragm muscle. Measurement of TT_{mus} would be useful in a variety of settings such as in selecting a strategy for weaning from prolonged mechanical ventilation.

Pressure and Flow Recordings

A maximal static inspiratory and expiratory maneuver can be obtained in mechanically ventilated patients to evaluate global inspiratory (PI_{max}) and expiratory (PE_{max}) muscle strength. PI_{max} and PE_{max} can be used as a measure for respiratory muscle function and possibly to monitor the response of respiratory muscle training. They can also be measured during brief disconnection by using a handheld pressure-monitoring device, which requires patient cooperation [106].

Voluntary measurements of maximum P_{di} can be obtained by having the patients inspire as forcefully as possible against a closed airway or by having the patient sniff forcibly. Sniff P_{di} appears to be more reproducible than maximum inspiratory P_{di} [107]. The Gilbert index can be used to determine the relative contribution of the diaphragm to inspiration [28]. The higher the index, the greater is the contribution of the diaphragm to the total inspiratory effort. One must keep in mind that the index can be a negative value with a paralyzed diaphragm. To estimate the energy expenditure of the diaphragm, the TTI and pressure–time product of the diaphragm can be calculated using P_{di}. These indices are frequently used for research purposes, but without dedicated software, they are impractical for routine clinical use. However, one should keep in mind that P_{di} is influenced by the positive pressure of the mechanical ventilator, so ideally, it should be measured during spontaneous breathing.

Electrical Activity of Diaphragm

Electrical Activity of Diaphragm (EA_{di}) is a method of monitoring respiratory muscle unloading and patient-ventilator synchrony. EA_{di} has been validated in clinical practice using a technology developed for the neurally adjusted ventilator assist (NAVA) mode of ventilation [108–115]. EA_{di} reflects the respiratory drive and is correlated with other indicators such as $P_{0.1}$. EA_{di} has a wide range of application in PARDS management. Visual inspections of flow and pressure waveforms using EA_{di} can be used to detect patient–ventilator asynchrony. Increased value of EA_{di} during expiration period may suggest increased efforts to create larger end-expiratory lung volume [108, 116, 117]. EA_{di} may also help in the monitoring of respiratory muscle loading, patient–ventilator synchrony, and efficiency of breathing in critically ill patients. The ratio of actual EA_{di} to peak EA_{di}, observed during a 20-second inspiratory occlusion, is a measure of the patient's breathing effort. A small ratio suggests excessive ventilatory support, whereas a larger ratio indicates inadequate unloading of the respiratory muscles. The ratio between VT and EA_{di} also represents neuroventilatory efficiency (NVE) of the diaphragm. An improved NVE can indicate that a patient generates adequate VT with a lower level of EA_{di}, while a higher value of EA_{di} suggests the opposite. NVE is affected by changes in diaphragm function and a patient's load of breathing. Decreased value of a ratio between P_{di} and EA_{di} (i.e., neuromechanical efficiency) indicates the development of diaphragm weakness, whereas an increase value suggests a recovery.

Phrenic Nerve Stimulation

Phrenic nerve stimulation can provide valuable information regarding the mechanical function of the diaphragm, and how its contractile force is transformed into pressure. Four techniques have been developed: needle stimulation and implanted wire stimulation are both invasive and currently not recommended, while transcutaneous electrical stimulation and magnetic stimulation have been more extensively studied and have minimal reported side effects [118, 119]. The integrity of the phrenic nerve in response to stimulation can be used to calculate phrenic nerve conduction time, which helps in the detection of phrenic nerve injury, and currently is extensively used in research settings [118–121].

Conclusion

Chest X-ray is currently mandatory for the diagnosis of PARDS and to detect complications such as air leak or equipment displacement but lacks interrater reliability. Various other imaging techniques are being studied in PARDS research but are not routinely performed. The monitoring of vital signs and ventilator parameters, including oxygenation and CO_2 removal, is important in the assessment of PARDS severity and to guide management. The monitoring of various respiratory system parameters requires continued development so as to be useful in children, and further research is needed to assess their potential impact in patients with PARDS.

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6 Conventional Mechanical Ventilation in Pediatric Acute Respiratory Distress Syndrome

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Introduction

Pediatric acute respiratory distress syndrome (PARDS) represents a small number of pediatric intensive care unit (PICU) admissions. However, it is often considered as one of most challenging conditions to manage. Conventional mechanical ventilation (MV) is used to support the majority of children with PARDS. This chapter will cover key principles that clinicians may find helpful when using MV in children with PARDS. Use of noninvasive ventilation, nonconventional MV (e.g., high-frequency oscillatory ventilation), ancillary therapies (e.g., surfactant), and weaning from MV are all covered in other chapters of this book.

Pathophysiology and Principles of Management of PARDS

It is important for the clinician to consider both the unique aspects of the pediatric respiratory system (Table 6.1) and the pathophysiology of PARDS. The interdependent arrangement of the alveoli equalizes airway pressure between neighboring alveoli. This design reduces both collapse and overdistension [1]. ARDS disrupts alveolar interdependence by causing alveolar edema and surfactant deactivation. This disruption in alveolar microanatomy results in alveolar wall strain and subsequently heterogeneous ventilation. Forces applied by MV (i.e., tidal volume and

Table 6.1 Differences in pediatric and adult pulmonary anatomy and physiology

Characteristics	Pediatrics	Adults
Impact on airway resistance with reduction in airway radius (e.g., airway edema)	Greater increase	Smaller increase
Chest wall compliance	Greater compliance	Less compliance
Functional residual capacity	Lower	Higher
Respiratory muscle reserve	More reliance on diaphragm	Less reliance on diaphragm
Metabolic requirement	Higher	Lower

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peak inspiratory pressure) to a heterogeneous lung result in uneven stress within the lung tissue, producing alveolar strain, which is a primary mechanism of ventilator-induced lung injury (VILI) [2–5]. Supportive care geared to providing sufficient oxygenation and ventilation while avoiding secondary lung injury is a mainstay in the management of PARDS [6]. A fundamental principle should always be to titrate oxygenation and ventilation to optimize potential benefits while minimizing the risks of causing injury with the ventilator [7]. The aim of MV in ARDS is to convert from heterogeneous to homogenous lung ventilation to minimize VILI.

The Pediatric Acute Lung Injury Consensus Conference (PALICC), consisting of 27 experts from 8 countries, published recommendations for the management of PARDS after a 2-year conference process and three face-to-face meetings [8]. The panel reached strong agreement on 132 out of 151 recommendations [8]. Unfortunately, definitive data do not exist in several areas of PARDS. In those cases, recommendations were generated based on expert opinion, which may have relied on available adult or neonatal data. The lack of pediatric-specific data can be attributed to the challenges in conducting randomized controlled trials in PARDS secondary to the heterogeneity in pathophysiology, a relatively lower incidence of PARDS, and prior weaknesses in defining PARDS. Similar consensus efforts were made by The European Society for Paediatric and Neonatal Intensive Care in 2017 via the Paediatric Mechanical Ventilation Consensus Conference (PEMVECC) consisting of 15 international European experts who provided recommendations in various aspects of pediatric MV [9].

Modes of Mechanical Ventilation

A full review of all modes of conventional MV is beyond the scope of this book. In one international multicenter study, the three modes most commonly used in children with ARDS were pressure-controlled ventilation (PCV), volume-controlled ventilation (VCV), and pressure-regulated volume control (PRVC). In all three modes, the clinician programs the ventilator rate, the positive end expiratory pressure (PEEP), the fraction of inspired oxygen (FiO2), and the pressure support. The main differences between the three modes are whether the pressure or the volume is prescribed and whether the breath is sculpted with decelerating or constant gas flow. It must be noted that no mode of conventional ventilation has been demonstrated to be definitely superior in improving outcomes in pediatrics [8, 10].

Pressure-controlled ventilation – In PCV, the clinician programs the peak inspiratory pressure (PIP) and each breath is delivered over a preset inspiratory time (I_T). Therefore, the tidal volume will be variable, based mainly on the respiratory mechanics of the patient. In order to quickly achieve the PIP, the flow rate is initially high, and then decreases (decelerates) to maintain the PIP for the duration of the breath. There are several potential advantages of PCV compared to VCV. Some studies show that PCV leads to higher mean airway pressures and thus improved oxygenation [11, 12]. At the same time, PIP is lower for a given tidal volume with PCV, which may reduce the risk of VILI [13]. PCV may also be more comfortable for the patient and reduce work of breathing and ventilator asynchrony [14, 15]. The main limitation of PCV is that tidal volume, and therefore minute ventilation, is not prescribed and may vary as a patient's respiratory mechanics change. This can lead to inadequate ventilation as compliance worsens or excessive volutrauma as mechanics improve if attention is not paid to the actual tidal volume.

Volume-controlled ventilation – With VCV, the clinician programs the tidal volume on the ventilator. The ventilator uses the prescribed tidal volume and the prescribed I_T to determine the correct flow to deliver. The flow is constant for the duration of the breath, sometimes termed a "square wave" flow pattern. While the tidal volume will be consistent between breaths, the PIP will vary depending on lung mechanics. The theoretical disadvantages of VCV are the oppo-

site of the advantages listed in the above paragraph: lower mean airway pressure leading to worsened oxygenation, higher PIP leading to VILI, and reduced patient comfort. However, VCV enables the prescription of the minute volume, which may be especially beneficial when tight control of arterial carbon dioxide tension is important (e.g., intracranial hypertension, pulmonary hypertension, single ventricle physiology, etc.).

Dual-controlled ventilation (e.g., PRVC) – PRVC is intended to give the best of both worlds: the physiologic benefits of decelerating flow patterns with the clinical benefit of a prescribed minute ventilation. In PRVC, the clinician sets the tidal volume (as in VCV), but each breath is delivered with a decelerating flow pattern (as in PCV). With each breath, the ventilator adjusts the inspiratory flow rate to achieve a preset tidal volume. If the delivered tidal volume is low, the ventilator increases inspiratory pressure on the following breath. PRVC allows effective breath-by-breath tidal volume delivery while controlling PIP and adapting to changing respiratory mechanics in the patient. For many clinicians, PRVC has become the default mode for all mechanically ventilated children, including those with PARDS.

Oxygenation and Ventilation Goals

Specific oxygenation and ventilation goals may vary between patients and often within the same patient over time. The evolving pathophysiology of PARDS is patient-specific and may change in the same patient during the disease course. It is important to emphasize that clinicians need to consider the benefits of achieving optimal oxygenation against the risks of therapeutic interventions leading to pulmonary injury. Several adult and pediatric studies noted that increased systemic oxygen saturation has not been correlated with improved outcomes [7, 16, 17]. Of note, in the ARDS network low VT trial, the 12 mL/kg VT cohort had higher systemic oxygenation saturation levels than the 6 mL/kg VT cohort, but the low tidal volume group had better outcomes [7]. Furthermore, a recent trial in 434 critically ill adults showed that mortality (11.6% vs. 20.2%) and morbidity were lower in those randomized to a lower SpO2 target (94–98% vs. 97–100%) [18]. Possible explanations include immunomodulating effects of hyperoxia, free radical–induced lung injury, and higher systemic oxygen saturation requiring increased (i.e., injurious) ventilator settings. The recommended approach by PALICC was staged permissive hypoxemia depending on the severity of PARDS [19, 20]. PALICC recommended higher PEEP and lower systemic oxygenation goals with worsening ARDS [8]. In the PALICC guidelines, the PEEP recommendation for mild ARDS is <10 cm H_2O, with goal systemic oxygen saturation of 92–97%. The experts further recommended that lower goal systemic oxygen saturation levels of 88–92% be considered for more severe ARDS [8]. The concept of permissive hypoxemia is attractive as it may reduce the risk for VILI, but clinicians must balance that concept with the need to provide adequate tissue oxygen delivery. Therefore, PALICC recommended monitoring central venous saturation and markers of oxygen delivery to guide setting optimal patient-specific oxygenation goals [8, 10]. In addition, the long-term impact of permissive hypoxemia has not been definitely studied. Thus, clinicians must individualize permissive hypoxemia after considering potential risks of long-term damage to end-organs as well as the potential benefits of limiting ventilator support, including FiO_2. Such an approach is especially cautioned in patients who are pregnant or have pulmonary hypertension or acute intracranial pathology.

Permissive hypercapnia is recommended by PALICC in moderate-to-severe ARDS to minimize VILI [8, 10]. Adult data strongly support better ARDS outcomes with permissive hypercapnia, lower VT, and pressure-limited ventilation [21, 22]. PALICC recommended a pH range of 7.15–7.30. Similar to oxygen saturation, insufficient data exist to determine a safe lower

pH limit. PALICC cautions against permissive hypercapnia in pregnant patients and those with intracranial hypertension, severe pulmonary hypertension, certain congenital heart diseases, and hemodynamically significant ventricular dysfunction. Again, clinicians should carefully assess each scenario to implement an optimal management strategy.

Tidal Volume (VT)

In the pediatric population, unlike our adult counterparts, a randomized control trial focused on tidal volume in ARDS does not exist. Pediatric providers must rely on observational data or extrapolate from adult-based recommendations of using a tidal volume (VT) of 6 mL/kg [7]. In a prospective multicenter observational study, Erickson et al. [23] studied 103 children below 16 years of age with a diagnosis of ARDS as defined by the American-European Consensus Conference. Overall mortality in this cohort was 35% during hospitalization. Interestingly, higher tidal volumes were associated with improved outcomes after adjusting for illness severity. The average maximum VT among all patients was 9.3 mL/kg (IQR: 7.8–11.6 mL/kg), and higher volumes were significantly associated with a lower odds of mortality ($p = 0.03$). The average median VT was 8.0 mL/kg (6.4–9.0), and higher volumes trended toward lower mortality ($p = 0.08$). Similar findings were observed in a retrospective single center study by Khemani et al. [24] The cohort had 198 children below 18 years of age with an overall mortality of 20%. During the first 3 days of ventilation, median VT was not significantly different between survivors and nonsurvivors. The majority received pressure-controlled ventilation (>90%) and were ventilated with a VT of 6–10 mL/kg. After controlling for diagnostic category, age, delta P (PIP-PEEP), PEEP, and severity of lung disease, VT was not associated with mortality. Interestingly, higher VT was associated with more ventilator-free days in children with less severe lung disease as assessed by dynamic compliance. In a recent meta-analysis by de Jager et al. [25], which included 8 studies with 1756 patients, mortality rates ranged from 13% to 42%. A relationship between VT and mortality was not identified when VT was dichotomized at 7, 8, 10, or 12 mL/kg. Moderate-to-substantial heterogeneity was observed in all pooled analyses. Some observational studies reported improved outcomes with higher tidal volumes of greater than 5–8 mL/kg [23, 24, 26, 27], and only one identified an association of lower mortality with VT 8 mL/kg as compared with VT 10 mL/kg [28]. In a recent prospective multicenter observational study of 23-PICUs in China, 345 infant and young children were diagnosed with PARDS as defined by American-European Consensus Conference definition. The reported mortality was 32.8% in this cohort. VT levels were not associated with mortality during the first 7 days. Furthermore, VT at levels of <6, 6–8, 8–10, and > 10 mL/kg showed no association with mortality in the first 3 days. Infants with more severe disease as indicated by higher oxygenation index (OI) and higher pediatric risk of mortality score III (PRISM III) were associated with higher mortality [27].

These observational pediatric studies seem to contradict the adult-based VT 6 mL/kg recommendation [7]. However, caution should be exercised while interpreting the observational studies. It is important to note that most pediatric patients were ventilated with pressure-limited modes of ventilation. Therefore, it could be speculated that children with more severe lung disease (i.e., poorer lung compliance) were ventilated with a lower VT than less severe counterparts. PALICC recommended using "patient-specific" VT according to disease severity. VT should be 3–6 mL/kg predicted body weight for patients with poor respiratory system compliance and closer to the physiological range of 5–8 mL/kg for patients with better preserved respiratory system compliance [8, 10]. The experts from PEMVECC had a strong agreement and recommended targeting physiological VT (5–8 mL/kg) and avoiding VT > 10 mL/kg ideal body weight [9].

It is important to note that PALICC and PEMVECC recommend using ideal/predicted body weight to determine optimal VT [9, 10]. The use of predicted weight to calculate VT is based on the assumption that volutrauma may be minimized by delivering VT appropriate to the

patient's lung capacity [7]. Martin et al. proposed unisex calculations to predict ideal body weight that can be used in pediatric patients [29]. The Center of Disease Control and Prevention (CDC) has published gender- and age-based growth charts that can be used to estimate ideal body weight (https://www.cdc.gov/growthcharts/clinical_charts.htm accessed Dec 4, 2018). Once the patient's height/length is measured, the predicted ideal body weight corresponding to the height/length percentile can be determined easily [30].

Peak and Plateau Pressure

The ARDS Network trial demonstrated significantly lower peak and plateau pressure (25 ± 6 vs. 33 ± 8 cm of H_2O, $p < 0.001$) in the lower VT cohort, and a linear association between mortality and peak inspiratory pressure (PIP) [7]. A recent international prospective observational study in adults (LUNG SAFE) showed higher PIP was associated with worsening from mild to moderate-severe ARDS [31]. Pediatric data are consistent with the adult literature. Studies by Khemani et al. and Erickson et al. showed a linear association between higher PIP and increased mortality [23, 24]. PALICC recommended the plateau pressure be limited to 28 cm H_2O. Those experts allowed for slightly elevated plateau pressure of 29–32 cm H_2O in patients with decreased lung compliance (i.e., increased chest wall elastance) [8]. In pediatrics, it should be noted that the use of variable flow ventilation and uncuffed endotracheal tubes prompts substitution of PIP with plateau pressure. In addition, an improvement in lung protection is achieved as the plateau pressure must always be the same or lower than the PIP, depending on the inspiratory airway resistance.

Positive End-Expiratory Pressure (PEEP)

Optimal PEEP is required to prevent alveolar collapse at end-expiration while avoiding overdistension, which can cause VILI and reduce right heart filling (and subsequently cardiac output). In other words, adequate PEEP titration is required to prevent atelectrauma in ARDS. In a randomized control trial of 549 adults, Brower et al. demonstrated no improvement in outcomes with higher PEEP (13.2 ± 3.5 cm H_2O) as compared to lower PEEP (8.3 ± 3.2 cm H_2O) when goal plateau-pressure (<30 cm H_2O) and VT (6 mL/kg of predicted weight) remained within recommended ranges [32]. Similar results were found in subsequent randomized trials by Meade et al. and Mercat et al. [33, 34] Of note, these trials used PEEP/FiO_2 tables as suggested by the ARDS Network study to determine higher versus lower PEEP levels but did not analyze PEEP in association with alveolar collapse [32]. Interestingly, recent meta-analyses suggest the association of higher level of PEEP with lower mortality in more severe ARDS (defined as PaO_2/FiO_2 ≤ 200 mmHg) [35, 36]. However, similar results were not seen in more mild ARDS. Unfortunately, there are a lack of prospective trials regarding PEEP management in PARDS.

PALICC recommended that, in absence of clear pediatric data, moderately high PEEP (10–15 cm H_2O) should be titrated in severe PARDS to the observed oxygenation and hemodynamic response [8]. However, in severe PARDS, PEEP >15 cm H_2O can be considered, provided peak and plateau pressure remained in the range described as above [8]. PALICC stressed the importance of monitoring markers of oxygen delivery, lung compliance, and hemodynamics with every increment or decrement of PEEP. PEMVECC had no recommendation on how much PEEP should be used. PEMVECC experts had a strong agreement that high PEEP titration is needed in severe disease by keeping a balance between hemodynamics and oxygenation. However, there is no defined method to set best PEEP [9]. Although there is no consensus regarding PEEP titration methods, previous studies have used PEEP/FiO_2 titration tables recommended by ARDS network [7, 32, 34]. Interestingly, observational data in both pediatrics and adults highlight that clinicians often use lower PEEP than the levels recommended in ARDS management [8, 7, 37]. Pediatric intensivists have a tendency to use higher FiO_2 over PEEP for hypoxemia during ARDS management.

Several pediatric studies confirm the uncommon use of the ARDS network PEEP/FiO_2 table recommendation [38–40]. In general, pediatric clinicians seem to have a reluctance to increase PEEP >10 cm H_2O particularly in the younger age group [41, 38–40]. A recent multicenter retrospective trial of 1134 patients with PARDS showed that patients managed with lower PEEP relative to FiO_2 compared to the ARDS network recommendations had higher mortality than children whose care aligned with ARDSnet tables [42]. In summary, there are no clear data to suggest best PEEP levels and titration method in PARDS. It is important to emphasize that markers of oxygen delivery, respiratory system compliance, and cardiovascular status should be closely monitored as PEEP is increased.

Driving Pressure

The relative importance among lower VT, lower plateau pressure, and higher PEEP is uncertain. Respiratory system compliance in ARDS is a strong determinant of volume received by the remaining functional lung. Driving pressure (ΔP) is a newer concept defined as VT/respiratory system compliance (or plateau pressure minus PEEP), where VT is intrinsically normalized to functional lung size (instead of predicated lung size in healthy persons). Recent adult data ($n = 3562$) have shown closer association of driving pressure to ARDS mortality than PIP, PEEP, or VT alone [43]. A 1-SD increment (approximately 7 cm H_2O) in driving pressure was associated with increased mortality (relative risk of 1.41, 95% CI 1.31–1.51, $p < 0.001$). Relative risk remained high even in patients receiving recommended plateau pressures and VT (RR 1.36, 95% CI 1.17–1.56, $p < 0.001$). No corresponding data or recommendations exist in the pediatric population.

Recruitment Maneuvers

Lung recruitment depends on several factors including respiratory system compliance, type of lung disease (focal versus diffuse alveolar process), and time course of lung disease. Patients with reduced lung compliance show relatively poor response to recruitment maneuvers when compared to patients with reduced chest wall compliance [44]. Limited adult data have shown an improvement in oxygenation with recruitment maneuvers in patients with preserved chest wall compliance [45]. However, a recent trial of recruitment maneuvers and titrated PEEP showed an increase in mortality among adults with ARDS [46].

With limited adult data and lack of pediatric data, significant controversy continues to exist surrounding the application and best approach regarding recruitment maneuvers. PALICC recommended the use of gradual increase or decrease in PEEP for careful recruitment. However, sustained inflation was not recommended [8, 10].

Patient-Ventilator Synchrony

Optimal patient-ventilator synchrony is of paramount importance in patients receiving MV. Achieving the optimal patient-ventilator synchrony can reduce the peak pressure and, thus, subsequently reduce the risk of VILI. Lack of synchrony between patient and mechanical ventilator can contribute to patient discomfort, dyspnea, increased energy expenditure by increasing respiratory muscle fatigue, and increased work of breathing [47]. In addition, asynchrony can lead to measurement errors in the assessment of breathing frequency and readiness to wean [48]. Difficulties in weaning may result in prolonged MV, increased ICU and hospital length of stay, increased likelihood of tracheostomy, and even increased mortality [47, 49, 50]. It is important that clinicians pay close attention to ventilator settings regardless of the mode of ventilation and titrate them according to disease evolution in a patient to optimize patient-ventilator synchrony. The goal of sedation in mechanical ventilated patients is to achieve patient comfort while maintaining safety, and it should not be used as a primary approach to prompting patient-ventilator synchrony. Excessive sedation may prolong the length of MV and increase the

risk of complications in mechanically ventilated patients [51, 52]. Patient-ventilator synchrony should be achieved by close monitoring of respiratory mechanics and airway graphics, and appropriate titration of ventilator settings including inspiratory trigger and cycle time.

Summary

Unfortunately, a lack of definitive pediatric data regarding management of PARDS exists even after years of extensive research and experience. Given this lack of definitive data, variation in practice is likely to exist for individual patient scenarios as well as across clinicians and institutions. It is important to note that the clinician must frequently assess ventilator settings as the natural course of PARDS pathophysiology evolves regardless of strategy chosen. It is important to stress that the current literature does not support any ventilation mode to be superior to any other. Although PALICC has provided the pediatric community with an age-specific PARDS definition, the pediatric critical care community still must validate the proposed criteria, correlate the classification of severity with outcomes, and assess conventional as well as alternative ventilation strategies. Until definitive pediatric data become available, the majority of recommendations will continue to rely on expert opinion and extrapolation of data from adults.

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7 Nonconventional Mechanical Ventilation for Pediatric Acute Respiratory Distress Syndrome: High-Frequency Oscillatory Ventilation and Airway Pressure Release Ventilation

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Introduction

Pediatric acute respiratory distress syndrome (PARDS) is a manifestation of severe, life-threatening lung injury [1, 2]. The prevalence of PARDS may be as high as 10% of all children admitted to the pediatric intensive care unit (PICU) with mortality rates ranging up to 40–50% in the more severe subsets [3]. Mechanical ventilation (MV) is intimately linked with the daily care of critically ill children admitted to the pediatric intensive care unit (PICU) and has added significantly to survival. However, numerous experimental studies have also shown that MV induces a pulmonary inflammation (biotrauma) that may aggravate pre-existing lung injury (double-hit). This is known as ventilator-induced lung injury (VILI) [4, 5]. Furthermore, the resultant inflammation is not limited to the lung; inflammatory mediators can enter the systemic circulation and lead to organ failure. As a consequence, patients do not die from lung injury, but from multiple system organ failure (MSOF) linked to VILI [6]. Two main mechanisms have been attributed to play a role in VILI: the delivery of excessive tidal volume (Vt) – coined volutrauma – and the repetitive opening and closure of alveoli (coined atelectrauma) [7].

At present, there is no available treatment for VILI. In fact, care of ventilated patients has shifted toward a "less intervention" philosophy over the past decade. This includes less ventilation to protect the lung from VILI rather than more ventilation to normalize blood gas levels. This concept is known as lung-protective ventilation (LPV). LPV is built on the delivery of small Vt to avoid volutrauma and a certain level of positive end-expiratory pressure (PEEP) to prevent cyclic alveolar collapse. The importance of volutrauma was underscored by the ARDS Network landmark study in critically ill adults with ARDS, showing that ventilation with low Vt and pressure limitation (i.e., 6 mL/kg ideal bodyweight and plateau pressure $\leq$ 32 cmH_2O) resulted in significantly lower mortality compared to traditional Vt and no pressure limitation (i.e., 12 mL/kg ideal bodyweight and plateau pressure $\leq$ 50 cmH_2O) [8]. Subsequent studies showed that using higher levels of PEEP to prevent alveolar collapse led to a better outcome

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than using lower levels of PEEP, especially in patients with more severe ARDS [9]. However, certain patients may need even lower Vt to prevent regional tidal hyperinflation and the optimal level of PEEP is unknown [10].

The clinical relevance of VILI is unclear in critically ill children [11]. To date, a pediatric counterpart of the ARDS Network trial has never been (and is highly unlikely to be) performed, leaving pediatric critical care practitioners in the dark regarding what the best Vt is for their individual patient [12]. However, pediatric critical care practitioners may have already found the solution in targeting the optimal Vt in PARDS. Unlike in adult critical care, pediatric intensivists tend to use pressure-controlled (PC) ventilation instead of volume-controlled (VC) ventilation [13]. The delivered Vt then depends on the compliance of the respiratory system (Crs) and reflects the amount in inflatable lung (baby-lung) [14]. Use of these modes makes sense as part of LPV as pediatric studies in PARDS established a direct relationship between inspiratory pressures and mortality but not between Vt and mortality [15–17]. Alternatively, high-frequency oscillatory ventilation (HFOV) and airway pressure release ventilation (APRV) are, at least theoretically, justifiable modes to be used in the context of LPV because they target the two major determinants of VILI. Interestingly, both modes are usually referred to as nonconventional because they are most commonly used as rescue in case of refractory hypoxemia and/or hypercarbia. However, one can argue that there is nothing nonconventional about these modes and that they should be considered as just another tool in the intensivist's arsenal. This chapter focuses on the theoretical and practical aspects of HFOV and APRV and discusses the clinical evidence supporting their use in PARDS.

High-Frequency Oscillatory Ventilation

Description of HFOV

HFOV was originally developed for the treatment of neonatal respiratory distress syndrome [18]. The device generates a continuous distending pressure (CDP), often referred to as mean airway pressure (mPaw), through introduction of bias flow into the circuit. This CDP generates and maintains end-expiratory lung volume (EELV), attenuating atelectrauma. Pressure oscillations are superimposed on the CDP at a frequency (F) of 3–15 Hz by an electromagnetically driven piston membrane apparatus. The oscillatory pressure amplitude (ΔP) is highly attenuated over the endotracheal tube and the airways and results in the delivery of a very small Vt, usually lower than the anatomical dead space (1–2 mL/kg) [19]. Hence, HFOV is, at least theoretically, an ideal tool for LPV in ARDS.

HFOV allows for the decoupling of oxygenation and ventilation. For this purpose, the operator has to set the CDP, F, power, inspiratory-to-expiratory (I:E) ratio, FiO_2 and circuit bias flow. Simply put, oxygenation is dependent on EELV (which is controlled by the CDP) and the FiO_2. The power of the piston membrane is set to generate pressure oscillations (displayed on the device as ΔP) that determine the delivered Vt; CO_2 clearance ($\dot{V}CO_2$) is relatively independent of lung volume but influenced by F and the square of Vt ($\dot{V}CO_2 = F \times Vt^2$). The I:E ratio is usually set at 1:2.

Physiologic Benefits

Observations made in animal studies indicate that HFOV might be preferable over CMV given its more beneficial effects on oxygenation, lung compliance, attenuation of the pulmonary inflammation and histologic injury, and better alveolar stability, even though higher pressures than accepted as plateau pressure (Pplat) during CMV are delivered [20–22]. Additional benefits of HFOV include a better distribution of ventilation resulting from the short inspiratory times compared to CMV and the presence of an active expiratory phase resulting from the generation of negative pressures and thereby preventing gas trapping and dynamic hyperinflation [23]. However, the beneficial effects of HFOV are less clear in animal models when control groups were modeled to a more LPV approach as nowadays used in daily clinical practice [24].

The mechanisms of gas exchange during HFOV are complex and not fully understood. These include pendelluft (i.e., movement of gas between lung regions with different time constants), convective gas transport (i.e., transport of gas into alveoli secondary to the vacuum left after absorption of oxygen into capillaries), Taylor dispersion (i.e., passage of oxygenated gas from rapid central jet into the deeper bronchial tree), enhanced molecular diffusion near the alveolo-capillary membrane and enhanced mixing in the large airways due to turbulence (Fig. 7.1) [25]. Pendelluft is of importance for lung units with long time constants and for those alveoli that are not reached by the Vt, whereas convective gas transport plays an important role in larger airways.

Clinical Evidence in Children

Pediatric critical care practitioners cherish HFOV as rescue intervention, despite the lack of solid scientific evidence. To date, there is only one randomized controlled trial (RCT) reporting the effects of HFOV on mortality (Table 7.1) [26]. This RCT was performed 25 years ago in five centers spanning a 3½-year period. In that crossover study, 58 patients of whom 55% had PARDS according to the American-European Consensus Conference (AECC definition), and an oxygenation index (OI) > 13 demonstrated by two consecutive measurements over a 6-hour period were randomized to HFOV ($N = 29$) using a strategy of aggressive increase in CDP targeted at $SpO_2 \geq 90\%$ with $FiO_2 \leq 0.6$, or CMV ($N = 29$)

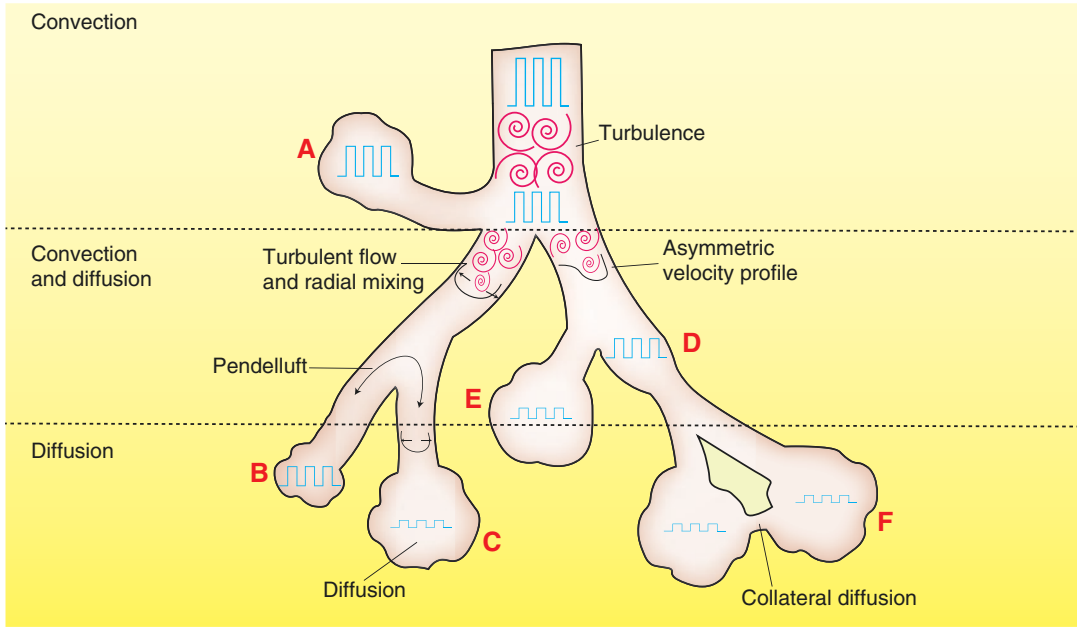

Fig. 7.1 Mechanisms of gas exchange and pressure transmission during high-frequency oscillatory ventilation. Mechanisms include pendelluft (i.e., movement of gas between lung regions with different time constants), convective gas transport (i.e., transport of gas into alveoli secondary to the vacuum left after absorption of oxygen into capillaries), Taylor dispersion (i.e., passage of oxygenated gas from rapid central jet into the deeper bronchial tree), enhanced molecular diffusion near the alveolo-capillary membrane and enhanced mixing in the large airways due to turbulence. The oscillatory pressure applied at the airway opening is dampened by the resistance and inertance of the endotracheal tube and central airways. Proximal alveoli (A) are subjected to the same oscillatory pressure as the central airways, but the more distal from the airway opening, the more the oscillatory pressure is dampened, especially in compliant alveoli (C) but to a lesser extent in poorly compliant or not fully recruited alveoli (B). Increased peripheral airway resistance causes a higher pressure transmission to more proximal alveoli (E) but a lower pressure amplitude in alveoli distal of the airway resistance (F)

Table 7.1 Summary of published pediatric randomized controlled trials or observational case-control studies evaluating the outcome effect of high-frequency oscillatory ventilation (HFOV) or airway pressure release ventilation (APRV) in critically ill children with a variable degree of pediatric acute respiratory distress syndrome (PARDS)

First author [ref]	Study design	Study period (years)	Sample size	Percentage PARDS	Main findings	Comments
High-frequency oscillatory ventilation						
Arnold [25]	RCT Five centers	3.5	58	55 (AECC)	Survival similar between HFOV (66%) and CMV (59%) Lower need for O_2 supplementation at 30 days with HFOV (21% vs. 59%, $p = 0.039$)	Cross-over trial, conducted in pre-ARDS network trial era Heterogeneous study population
Samransamruajkit [26]	RCT Single center	2	16	100 (AECC)	Survival higher with HFOV (1%), then CMV (44%)	Study not designed to examine effects on patient outcome
Samransamruajkit [27]	RCT Single center	1	18	100 (Berlin)	Number of deaths similar between HFOV and CMV ($N = 1$ in both groups)	Study not designed to examine effects on patient outcome
Gupta [28]	Retrospective case-control 85 centers	2	9177	Unknown	In matched analysis, mortality significantly higher with HFOV (17% vs. 8%, $p < 0.001$) In matched analysis, mortality significantly higher with early HFO (i.e., <24 hours of intubation, 18% vs. 8%, $p < 0.001$) Length of MV and PICU stay significantly longer for HFOV vs. CMV	Propensity matching to overcome confounding by indication not done with variables that are commonly used in the decision-making when to go to HFOV No mention of HFOV and CMV strategy
Bateman [29]	Post-hoc case-control	4	2449	90 (PALICC)	Mortality rates not different between early HFOV (<24–48 hours of intubation) vs. CMV/Late HFOV in children most likely to have early HFOV (25% vs. 17%, $p = 0.09$) Length of MV and PICU stay significantly longer for early HFOV vs. CMV/Late HFOV	No mention of HFOV or CMV strategy Unclear how many patients really had PARDS (classification only made on OI)
Airway pressure release ventilation						
Lalgudi Ganesen [30]	RCT Single-center	1.5	52	100 (Berlin)	Trial stopped prematurely for increased harm with APRV (53.8% vs. 26.9% control, $p = 0.089$) Comparable VFDs APRV with control Comparable oxygenation APRV with control	Planned sample size was 52 per arm CMV protocol based on pediatric prone studies

AECC American-European Consensus Conference, *APRV* airway pressure release ventilation, *CMV* conventional mechanical ventilation, *HFOV* high-frequency oscillatory ventilation, *PARDS* pediatric acute respiratory distress syndrome, *RCT* randomized controlled trial

with a strategy utilizing PEEP and limited inspiratory pressures. Patients with obstructive airway disease, intractable septic or cardiogenic shock, or nonpulmonary terminal diagnosis were excluded. Targeted blood gas values were equal for each group. The intention-to-treat analysis showed that HFOV did not improve survival (HFOV 66% vs. 59%) or total ventilator free days (VFD) (HFOV 20 ± 27 vs. 22 ± 17) compared with CMV. However, the percentage of survivors requiring supplemental oxygen at 30 days was significantly lower in the HFOV group (21% vs. 59%, $p = 0.039$), suggestive of less lung injury. Furthermore, mortality was only 6% ($N = 1/17$) in patients who were exclusively managed on HFOV, in contrast to 42% ($N = 8/19$) for patients who failed CMV and were transitioned to HFOV and 40% ($N = 4/10$) in those exclusively managed with CMV, although these numbers were too small to draw any firm conclusions.

Samransamruajkit et al reported the results of a small single-center study comparing HFOV ($N = 7$ patients) with CMV ($N = 9$ patients) with AECC defined ARDS in a 2-year study period [26]. Although their study was not designed and thus powered to address this, survival was higher with HFOV (71%) compared with CMV (44%) and predicted by plasma levels of soluble intercellular adhesion molecule (sICAM) 1. The same group of investigators randomized 18 children with severe PARDS according to the Berlin Criteria to HFOV or CMV and a lung volume optimization maneuver in both groups [28]. They observed a significantly better improvement in oxygenation in patients randomized to HFOV, but again their study was underpowered to detect effects on patient outcome (in fact, only two patients died).

The controversy surrounding HFOV has been further fueled by two case-control studies. Gupta et al reported increased mortality and morbidity in patients managed with HFOV compared with CMV when they analyzed the data from the virtual PICU (vPICU) database [29]. Included in this study were 9177 patients from 98 institutions receiving MV aged 1 month to 18 years in the Virtual PICU System database from January 1, 2009, through December 31, 2011. For analytical purposes, patients were stratified by type of ventilation (HFOV vs. CMV); patients managed on the oscillator were stratified by early (i.e., within 24 hours of intubation) of and late HFOV (i.e., after 24 hours of intubation). Propensity matching to overcome confounding by indication (i.e., the sickest patient is the most likely to get the intervention) was used for matching. Comparisons between matched patients showed a significant difference in mortality (overall HFOV vs. CMV: 17% vs. 8%, $p < 0.01$; early HFOV vs. CMV: 18% vs. 8%, $p < 0.01$) and a significantly longer time spent on the ventilator for HFOV patients, challenging the use of HFOV.

Bateman and coworkers performed a post-hoc analysis of data from the Randomized Evaluation of Sedation Titration for Respiratory Failure (RESTORE) study with propensity matching to match for severity of illness comparing early HFOV (i.e., within 24–48 hours of intubation) with a group of children managed only with CMV or with CMV and late HFOV (CMV/late HFOV) [31]. For analytical purposes, they studied $N = 213$ children with the highest likelihood of early HFOV based on the propensity score. In-hospital mortality rates at day 90 were not different between the HFOV and CMV/late HFOV groups (25 vs. 17%, $p = 0.09$), but patients managed with the oscillator spend significantly more time on the ventilator in both quintiles with the highest risk of early HFOV.

Summarizing, the published pediatric clinical data are not supportive of HFOV. However, there are certain aspects that need to be considered when interpreting those data. The Arnold trial was performed during an era when the approach to CMV does not reflect current practices and the first study by Samransamruajkit et al did not report their CMV strategy [26]. Only in their second study did they mention their CMV settings, which could be appreciated as lung-protective [28]. The Gupta study is problematic to interpret, since important clinical variables that influence the decision to initiate HFOV, such as metrics of oxygenation and ventilator settings, were not available for propensity matching, thus challenging the true relevance and clinical impact of this study [32–34]. And finally, the data from the RESTORE study that

was used by Bateman et al is influenced by the fact that, in that trial, decisions about MV mode and ventilator weaning strategy were left to the discretion of the treating physician [31].

Clinical Evidence in Adults

In the early 2000s, three RCTs comparing HFOV as first-line strategy with CMV in adult patients with ARDS reported improved oxygenation and – although not significant – lower mortality in patients randomized to HFOV [35–37]. A subsequent meta-analysis of all available adult and pediatric RCTs confirmed a potential mortality benefit of HFOV, although much can be said about the ventilatory management in the control groups not being compatible with what is nowadays appreciated as LPV [38]. However, continued use of HFOV in adults became highly controversial following the outcome of two large RCTs. No benefit on patient outcome was observed in the Oscillate for Acute Respiratory Distress Syndrome (OSCAR) trial that compared HFOV using a novel device with nonprotocolized CMV in 795 patients admitted to centers with little HFOV experience [39]. More worrisome however were the outcomes of the Oscillation for Acute Respiratory Distress Syndrome Treated Early (OSCILLATE). This study was stopped prematurely after inclusion of 548 out of 1200 planned patients due to increased mortality (47% vs. 35%, $p = 0.005$) and worse secondary outcomes in the HFOV group [40]. Unlike OSCAR, OSCILLATE was conducted in centers with previous HFOV experience and made use of a strictly protocolized CMV control arm. Including the results of these two later trials, an updated meta-analysis confirmed no outcome benefit of HFOV over CMV, challenging the routine use of HFOV in adults with moderate-to-severe ARDS [41, 42].

Why Did HFOV Fail to Improve Outcomes?

The question is whether the results of the pediatric and adult RCTs confirm that HFOV is not beneficial, or if the patient outcomes were determined by how the oscillator was used [43, 44]. Thus, one could question whether HFOV was applied in its most optimal fashion in those, in a manner that takes full advantage of the properties of HFOV. These issues (among others) include identification of the patient who will benefit the most from HFOV, the timing of cross-over from CMV to HFOV, and determining the best oscillator settings.

Indications for and Timing of HFOV

The indications for HFOV are ill-defined and are usually dictated by personal preferences of the attending physician and institutional bias. In general, HFOV is only considered as a rescue approach when CMV fails, but it could be argued that it should be considered earlier in the PARDS trajectory to minimize VILI and prevent exposure to noxious ventilator settings. There is virtually no pediatric data supporting this concept, except for one small observational study of 26 patients reporting significantly higher 30-day survival rates (58.8 vs. 12.5%) when HFOV was employed within 24 hours rather than as rescue [45]. OSCILLATE attempted to study the effects of early HFOV within 72 hours of ARDS diagnosis. However, in that study, patients could have been on the ventilator for up to 14 days prior to randomization, making it less clear what the true effects of early HFOV are [40].

Some authors have proposed the use of a specific oxygenation index (OI) or the PaO_2 /FiO_2 ratio as threshold in deciding when to transition a patient to HFOV. Two pediatric trials used, respectively, an OI > 13 and 15 as cut-off values [26, 27]. A recent re-evaluation of the OSCILLATE trial showed that a mortality benefit of HFOV could only be expected in adults with severe ARDS (i.e., PaO_2 /FiO_2 less than 100) [46], suggesting that HFOV as a rescue intervention should only be considered in the sickest of patients.

Lung Volume Optimization Maneuvers

Lung volume is the main determinant of oxygenation in diffuse alveolar disease during HFOV. Simply put, PaO_2 increases linearly with

lung volume up to a certain point when alveoli become overdistended [47]. This suggests that an open-lung strategy (i.e., opening up the lung and keeping it open) by (repeated) recruitment maneuvers (RMs) should be considered when switching from CMV to HFOV. Remarkably, RMs seem not to be the standard of care when initiating HFOV [48]. This may be explained by a lack of clinical studies reporting beneficial effects of RMs, or even the best approach to RMs in HFOV, and the presumed enhancement of the underlying inflammatory process [49]. The only guidance comes from one neonatal lamb model study investigating four different RM approaches: a stepwise pressure increase over 6 minutes, a 20 second dynamic sustained inflation either one or repeated six times, and a standard approach (setting CDP directly at start) [50]. This study showed that a stepwise pressure increase produced the greatest gain in lung volume and resolution of atelectasis. A sustained inflation of 30–35 cmH_2O for 20–30 seconds was used in the small study by Samransamruajkit et al, whereas the adult OSICLLATE study applied 40 cmH_2O for 40 seconds [28, 40]. However, such a nonindividualized approach to lung volume optimization does not take the patient's respiratory system mechanics into account, thereby leading to overdistension or not fully recruited lung units in a clinically unidentifiable group of patients [44]. We have adopted an individualized, staircase incremental–decremental CDP titration as part of an open-lung approach to HFOV (Fig. 7.2). Such an approach is feasible and safe in terms of hemodynamic consequences while allowing for sufficient gas exchange [51].

Additional benefits of optimization of the end-expiratory lung volume include a better distal dampening of the pressure oscillations. This is because pressure oscillations are less dampened in lungs with ongoing atelectasis, thus exposing the conducting airways and alveoli to injurious higher pressure swings (Fig. 7.2) [24]. With reduced compliance in unresolved atelectasis, there is a marked increase in transmission of the peak-to-trough ΔP to the alveoli and bronchi. Another, at least theoretical, benefit of RMs is that it allows oscillating the patient on the deflation limb of the P–V curve, thereby avoiding, at least in part, injurious hyperinflation and atelectasis [20, 52–54]. By doing so, a lower CDP is needed to maintain the same amount of EELV than on the inflation limb because of the hysteresis of the respiratory system.

Achieving the Lowest Tidal Volume

The delivered Vt during HFOV is determined by numerous factors, including resistance of the respiratory system (Rrs) and oscillator settings such as oscillatory power (magnitude of membrane displacement), F in Hertz (Hz), I:E ratio, position of the membrane, endotracheal tube (ETT) length and diameter, and presence of ETT leakage [55–59]. The ETT constitutes the major work load to the oscillator and is an important determinant of Vt [60]. Vt is proportional to the ETT inner cross-sectional area because the impedance of the ETT exceeds the impedance of the lung [61, 62].

In clinical practice, it is common to set F and power according to the patient's age, ventilator settings, and observation of chest wiggle. However, from a physiological perspective, it seems more appropriate to use the highest possible F in PARDS. First, the higher the F, the smaller is the Vt because changes in F are inversely proportional to the distal oscillatory pressure amplitude [63]. It will subsequently be easier to stay within the limits of the safe zone (i.e., the zone with the smallest risk of injurious hyperinflation or atelectasis) of the P–V loop. Second, collapsed lung regions are more easily opened at higher F [64]. Third, the delivered Vt is more equally distributed as it becomes less dependent on regional compliance at higher F [23]. However, finding the best F can be challenging. Venegas et al have proposed that setting the oscillatory F is dictated by the corner frequency (Fc) of the lung, $Fc = 1/(2\pi RC)$, where R is resistance and C compliance [65]. Fc defines the optimal frequency at which there is adequate gas transport during HFOV in combination with the least injurious pressures and is influenced by the underlying disease (Fig. 7.3). It is increased in lung diseases characterized by short time constants and low compliance such as in

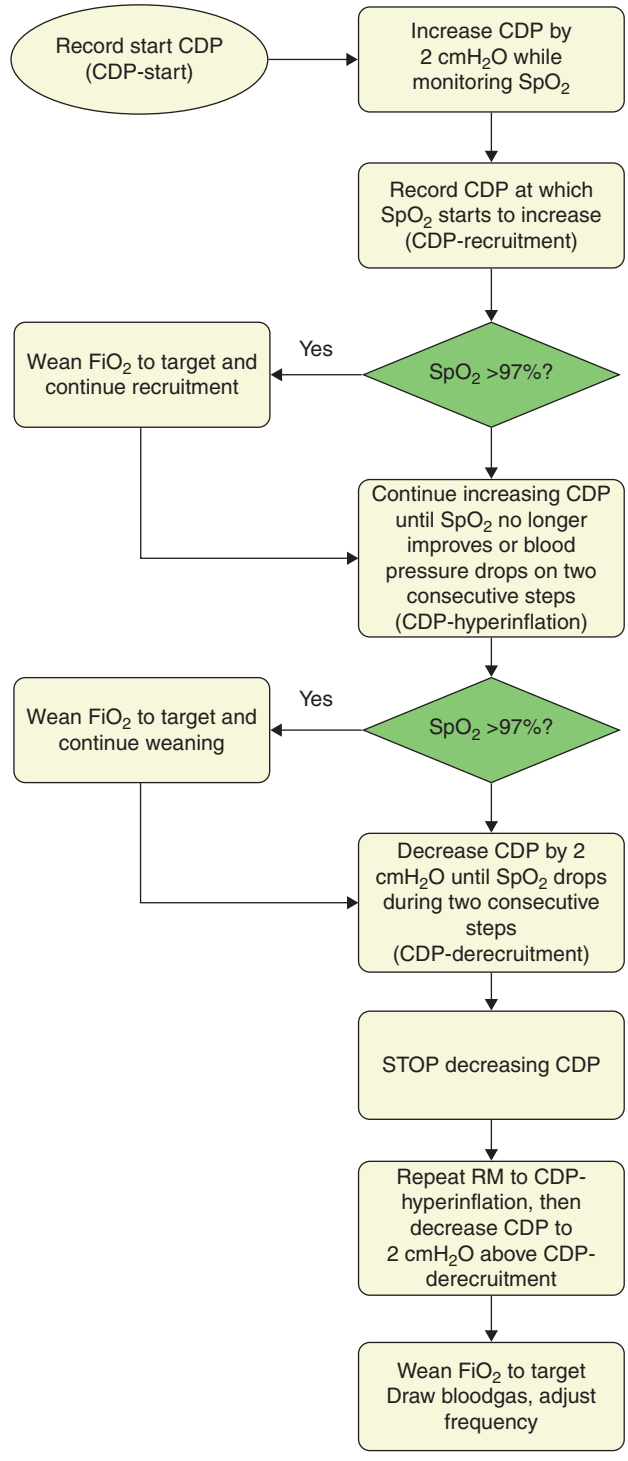

Fig. 7.2 Outline of the staircase incremental–decremental titration of the continuous distending pressure (CDP) after switching to high-frequency oscillatory ventilation (HFOV)

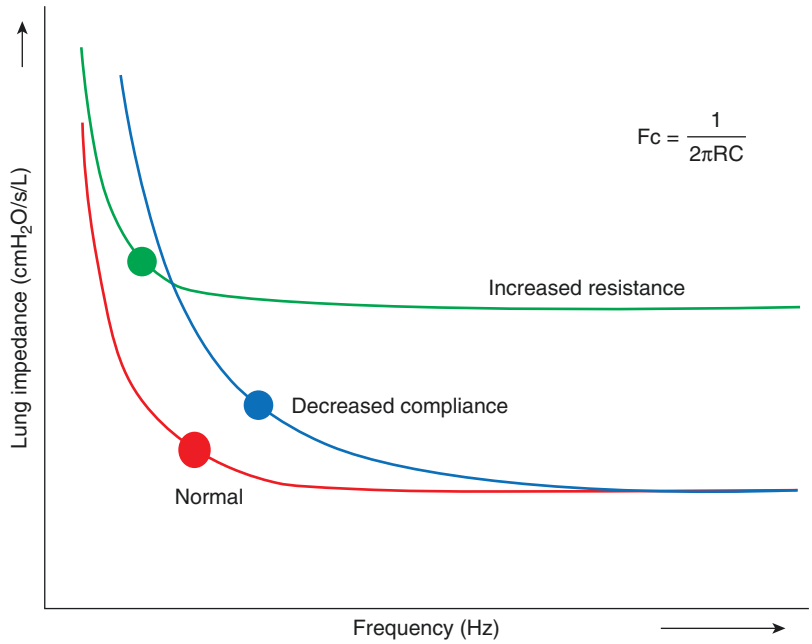

Fig. 7.3 Concept of corner frequency (Fc) of the lung in patients with decreased compliance, such as PARDS and increased resistance, such as obstructive airway disease. Fc (graphically depicted by the dot) defines the optimal frequency at which there is adequate gas transport during HFOV in combination with the least injurious pressures. Fc is calculated by 1/2πRC, where R is resistance and C compliance

PARDS. Importantly, F is intimately linked with ΔP. Basically, the higher the ΔP, the larger is the Vt. Yet, we (unpublished data) and others have observed in bench test studies that Vt was smaller when combining high F (15 Hz) and high power (set to achieve a ΔP of 90) compared with low F (5 Hz) and low power settings as the distal pressure amplitude was much lower but still associated with a sufficient CO_2 elimination [66].

Airway Pressure Release Ventilation

Description of APRV

Airway Pressure Release Ventilation (APRV) was first described in 1987 as a mode to deliver two levels of continuous positive airway pressure (CPAP) while allowing for spontaneous breathing throughout the respiratory cycle [67]. Unlike traditional CPAP, both oxygenation and ventilation are supported during APRV. A continuous high flow is delivered to the patient, only interrupted by intermittent opening of the expiratory valve, resulting in a decrease in circuit pressure allowing gas outflow and thereby enhanced CO_2 removal from the lungs as well as emptying of the anatomic dead space. Unlike CMV, the breath begins at an elevated baseline and ends with the deflation from high pressure to a low pressure. This driving pressure gradient establishes the delivered Vt allowing for ventilation, which is (as with PCV) affected by Crs and Rrs. Hence, APRV is considered a time-triggered, pressure-limited, and time-cycled intermittent mode of ventilation with an inversed inspiratory-to-expiratory ratio [68]. Of note, APRV is in fact an inverse ratio mode of PCV if spontaneous breathing is absent.

The operator has to set the high (Phigh) and low (Plow) pressure as well as the time (T) intervals of these pressures (Thigh and Tlow). Oxygenation is determined by the FIO_2 and Thigh. Usually, Phigh is set to match the plateau pressure (Pplat) during CMV (targeting Pplat <30 cmH_2O), but the approach to setting Plow and Thigh and Tlow is highly variable [68]. Thigh can be set somewhere between 4 and 10 seconds and is dictated by oxygenation. For Plow and Tlow, there are roughly two concepts: (a) using a constant Tlow and nonzero Plow to prevent complete end-expiratory lung deflation and a Thigh

that is approximately 90% of the total cycle time, or (b) setting Tlow dictated by lung mechanics (to achieve an end-expiratory flow: peak expiratory flow (PEF) ratio of ±50–75%), Plow at zero and Thigh >90% of the total cycle time – the inherent short Tlow thus prevents complete end-expiratory lung emptying [69, 70]. How both are ultimately set is dictated by the desired level of CO_2 elimination. The combination of these settings results in a mPaw calculated by ((Phigh ∗ Thigh) + (Plow ∗ Tlow)) / (Thigh + Tlow). The prolonged inspiratory time may lead to the development of intrinsic PEEP (PEEPi), which should be avoided because of its adverse cardiovascular effects.

Physiologic Benefits

The potential benefits of APRV are linked to a presumed reduced risk of volutrauma inherent to the pressure limitation with this mode, and therefore, the delivered Vt is affected by Crs and Rrs (as with PCV). In line with the open-lung concept, the risk for atelectrauma may be reduced because APRV delivers a higher mPaw than on PCV. Numerous animal studies have shown improved oxygenation and some reduced lung injury with APRV [30]. However, the true potential benefit of APRV is probably linked to spontaneous breathing, which makes it appealing. Critical care practitioners have adopted the philosophy of maintaining spontaneous breathing in mechanically ventilated patients as much as possible. This dogma is based on early work showing that Vt was directed toward the dorsal, well-perfused regions of the lung in anesthetized adults without lung injury when they were in the supine position [71]. These beneficial effects of spontaneous breathing were confirmed in experimental and clinical studies of lung injury [72, 73]. Explanations for these beneficial effects include reduced shunt fraction, improved distribution of Vt toward the dependent lung zones, and less lung inflammation [74–76]. In addition, spontaneous breathing may allow for a better patient–ventilator synchrony and a potential decrease in sedation and analgesia. To date, however, these beneficial effects have not been demonstrated in children.

Clinical Evidence in Children

The pediatric literature on APRV is mainly limited to case reports, case series, and retrospective and prospective observational cohort studies with small sample sizes. In most cases, APRV was employed as rescue intervention and overall results in terms of oxygenation and ventilation were not universally confirmed. In 2018, Lalgudi Ganesan et al reported the outcomes of the first RCT comparing APRV with CMV in Berlin-defined PARDS (Table 7.1) [69]. In this open-label, parallel-designed RCT, children aged 1 month to 12 years were randomized within 24 hours of PARDS diagnosis and 72 hours of ventilation to APRV or CMV. Remarkably, randomization was unbalanced as there were more girls and patients suffering from more severe hypoxia in the APRV arm. In the APRV group, Phigh was set 1–2 cmH_2O above Pplat with a maximum of 30 cmH_2O and subsequently titrated targeting Vt 6–7 mL/kg IBW and Thigh at 4 seconds; Plow was set at 0 cmH_2O and Tlow was terminated when the expiratory flow had decreased to approximately 75% of the peak expiratory flow. Ventilator algorithms used in the two prone positioning trials by Curley et al were used for patients randomized to CMV [77, 78]. HFOV was used as rescue mode when predefined hypoxia criteria were met. Although the study was designed to include 26 patients per randomization arm, it was stopped prematurely at 50% enrollment because of increased mortality in the APRV group (53.8%) compared to CMV (26.9%), yielding a relative risk for death of 2.0 (95% CI 0.97–4.41). Cause of death in these patients was refractory hypoxemia in almost half of the patients, whereas the remaining patients died from MSOF. The primary endpoint VFDs were significantly lower in the APRV arm (9.7 ± 11.1 days) compared to the CMV arm (14.2 ± 10.4 days).

In summary, the available pediatric literature does not support the use of APRV in PARDS.

Current Evidence in Adults

Clinical studies in adults with ARDS have reported improved oxygenation, ventilation, and lung mechanics when comparing APRV with CMV, although most of these studies were not restricted to patients with severe ARDS [30]. However, different results in terms of patient outcome have been reported. Putensen et al found improved cardiovascular performance and arterial oxygenation as well as fewer ventilator and ICU days when comparing APRV with PCV, whereas others found no effect on clinically relevant outcomes in two RCTs [79, 80]. Similarly, conflicting observations have been made in prospective and retrospective cohort studies [81–83].

Why Did APRV Fail to Improve Outcomes?

Although not novel, use of APRV is limited to a certain number of centers and requires greater experience than traditional PCV. As with HFOV, there is no clear understanding of what optimal initial and titration APRV settings are effective. Furthermore, concerns related to APRV must be better understood, and include the effect of high transpulmonary pressures during spontaneous breathing, along with cyclical derecruitment and Vt variability during the release time [69].

Practice Recommendations and Future Prospects

It can thus be concluded that there is a big difference between the presumed theoretical LPV effects of HFOV and APRV and their relationship with patient outcome. To date, both HFOV and APRV have not been shown to improve outcomes in children with moderate-to-severe ARDS. In fact, some adult and pediatric trials were stopped prematurely because the intervention caused harm. However, does this truly mean that we should discontinue use of HFOV or APRV indefinitely? It can safely be concluded that both ventilator modes suffer from similar issues: a lack of understanding of how to appropriately use these modes. In summary, we don't really know how to set the device tailored to the need of the individual patient nor do we really know which patient might actually benefit from either one of these modes. Furthermore, the question is still open if both modes are similar in terms of LPV (Fig. 7.4). APRV makes

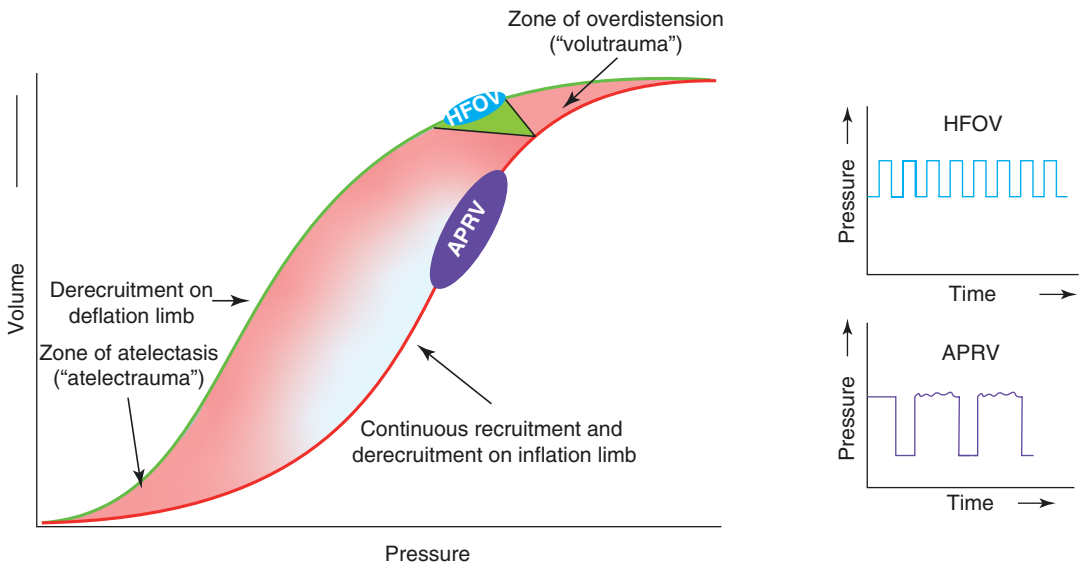

Fig. 7.4 Position of high-frequency oscillatory ventilation (HFOV) and airway pressure release ventilation (APRV) on the pressure–volume loop. Whereas APRV is positioned on the inflation limb, optimal use of HFOV means that it is positioned on the deflation limb after a lung volume optimization maneuver

use of spontaneous breathing, but is this really desired in the context of severe lung injury where spontaneous breathing may augment lung injury because of increased transpulmonary pressure [84]? Another major difference between the two modes is their position on the P–V loop. While HFOV makes use of the hysteresis of the lungs and oscillates on the deflation limb in the safe zone of ventilation, meaning that the same EELV is maintained at a lower pressure compared with the inflation limb [44], APRV ventilates on the inflation limb of the P–V loop where there is a continuum of alveolar recruitment and derecruitment, which is considered undesirable [52]. At the same time, there are major drawbacks associated with HFOV that favor the use of APRV. These include possible need for heavy sedation and or continued use of neuromuscular blockade, device noise, and probably most important, lack of monitoring tools to assist the physician in finding the optimal settings [85]. Most HFOV devices cannot display P–V loops and although some modern day oscillators can display Vt, it is unclear if measuring Vt can aid in identifying the best oscillator settings. These are all subjects of ongoing and future research.

So, where does this leave the physician? At present, no recommendations can be supported by rigorous evidence. The Pediatric Mechanical Ventilation Consensus Conference (PEMVECC) recommended that HFOV may be considered if conventional ventilation fails, using an open-lung strategy to maintain optimal EELV [86]. These recommendations mirrored the recommendations from the Pediatric Acute Lung Injury Consensus Conference (PALICC). This expert panel recommended that HFOV should be considered as an alternative ventilatory mode in patients with moderate-to-severe PARDAS in whom Pplat exceeds 28 cm H_2O in the absence of clinical evidence of reduced chest wall compliance [87]. PALICC also recommended that the optimal lung volume in HFOV should be achieved by exploration of the potential for lung recruitment by a stepwise increase and decrease of the mean airway pressure (continuous distending pressure) under continuous monitoring of the oxygenation and CO_2 response and hemodynamic parameters. Both PEMVECC and PALICC did not make any recommendations on the use of APRV. Our personal preference is to consider HFOV in the presence moderate-to-severe lung injury rather than APRV. This approach is based on the change in thinking about spontaneous breathing, which brings APRV into consideration later in the clinical trajectory, when the patient has improved and might benefit from spontaneous breathing instead of using it as an early primary mode of ventilation. There are no pediatric data to support this assumption, although bench work and limited data in adults suggested that APRV would be more protective in limiting lung stress and strain in ARDS when associated with spontaneous breathing [88]. We have moved away from the concept of HFOV being just a rescue mode of ventilation, but have adopted a liberal threshold for HFOV when PIP (in case of PC ventilation) or Pplat >28–32 cmH_2O and PEEP >8 cmH_2O and FiO_2 > 0.6 and a rise in the oxygenation index (OI) on three consecutive measurements that are 1 hour apart [51].

It is needless to say that large RCTs are needed to examine the role of HFOV or APRV in the management of children with moderate-to-severe PARDS. The PRone and OScillation PEdiatric Clinical Trial (PROSpect) is currently underway examining the effects of prone positioning and HFOV in children with severe PARDS (www.prospect-network.org). The primary outcome of this 2 by 2 randomized adaptive trial is ventilator-free days (VFDs), whereas secondary outcomes include, among others, mortality and trajectory of organ failure. The study is expected to complete in 6 years.

Conclusion

Nonconventional modes of ventilation such as HFOV and APRV are just another mode of ventilation. Use of these modes makes sense from a physiologic perspective, but these theoretical benefits have so far not been translated into improved meaningful outcomes in children with moderate-to-severe PARDS. Much needed studies are eagerly awaited.

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8 Ventilator Weaning and Extubation Strategies for Children with PARDS

Adrienne Randolph

This chapter will provide an overview of strategies for discontinuing ventilator support in children with pediatric acute respiratory distress syndrome (PARDS) [1], as also recently reviewed by Hess and Randolph [2], by reviewing the following topics:

- How clinicians can assess whether children should be assessed for extubation readiness?
- The indications for ventilator weaning and which parameters to evaluate.
- Use of spontaneous awakening and spontaneous breathing trials.
- Ventilator modes commonly used in the process of weaning.
- How to determine when ventilator liberation is facilitated by a tracheostomy?
- Use of weaning and extubation protocols.
- Comparing criteria for use in assessing readiness for extubation in children.
- Use of noninvasive ventilation, high-flow nasal cannula, and other supports to optimize extubation success.

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Introduction

Most children diagnosed with PARDS require intubation with prolonged mechanical ventilator support during lung recovery. Fluid overload, sedation, neuromuscular weakness, and impaired clearance of secretions can prolong need for ventilator support. Many strategies have been used to discontinue mechanical ventilator support in children, where the ultimate goal is permanent liberation. *Weaning* is a strategy where the amount of ventilator support is gradually decreased while continually assessing patient tolerance. In the mid-1990s, a large multicenter study showed that many adults with acute respiratory failure do not require weaning and can be extubated after the underlying disease process is treated and they are awake and able to maintain their airway [3]. A multicenter trial then showed that most children who pass a spontaneous breathing trial (SBT) can be extubated successfully, requiring no additional support aside from supplemental oxygen [4]. Children that fail their SBT, however, require thorough evaluation to determine underlying reasons for failure. Sedation, neuromuscular weakness, and difficulty in clearing secretions are common reasons for SBT failure. Children with PARDS have many risk factors for developing neuromuscular weakness such as prolonged mechanical ventilator support with immobility, exposure to steroids, and use of neuromuscular-blocking agents. Therefore, children recovering from PARDS may require

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Table 8.1 Recommendations for discontinuing ventilatory support in children with PARDS modified from Macintyre [5]

Recommendation 1: In children with PARDS requiring mechanical ventilation for more than 24 hours, the causes that contribute to ongoing ventilator dependence should be systematically evaluated at least once daily. The goal is to reverse all possible ventilatory and nonventilatory issues impeding the ventilator discontinuation process
Recommendation 2: Children with PARDS receiving mechanical ventilation for respiratory failure should undergo a formal assessment of discontinuation potential if they meet the following criteria: a. The underlying cause for respiratory failure is likely reversed, b. their oxygenation and pH is acceptable, c. they are hemodynamically stabile, and d. their capacity to initiate spontaneous breaths is sufficient
Recommendation 3: Formal discontinuation assessments for children receiving mechanical ventilation for respiratory failure related to PARDS should be performed during spontaneous breathing rather than while the patient is still receiving substantial ventilator support. Tolerance of reduction to FiO2 < 50% and an initial brief period of spontaneous breathing can be used to assess the capability of continuing onto a formal spontaneous breathing trial (SBT). There are no firm criteria with which to assess patient tolerance during SBTs but the respiratory pattern, the adequacy of gas exchange, hemodynamic stability, and subjective comfort all should be considered. Children tolerating an SBT lasting 30–120 minutes should be considered for permanent ventilator discontinuation
Recommendation 4: Extubation (the removal of the artificial airway) from a child recovering from PARDS who has successfully passed an SBT should be based on assessments of airway patency and the ability of the patient to protect the airway. A patient should be assessed prior to extubation to determine if early initiation of NIV or HFNC may facilitate the transition to complete ventilator liberation
Recommendation 5: Children recovering from PARDS who are receiving mechanical ventilation for respiratory failure that fail an SBT should have the cause for the failed SBT determined. Once reversible causes for failure are corrected, subsequent SBTs should be performed once every 24 hours, or more frequently, if the cause is oversedation. After failing an SBT, they should receive a stable, nonfatiguing, and comfortable form of ventilatory support
Recommendation 6: Weaning and ventilator discontinuation and sedation management protocols designed to give nonphysician healthcare professionals more autonomy have been successfully developed and implemented in pediatric intensive care units and may facilitate ventilator discontinuation
Recommendation 7: Tracheostomy should be considered after an initial period of stabilization on the ventilator when it becomes apparent that a child recovering from PARDS will require prolonged ventilator assistance (>14–30 days). Tracheostomy then should be performed when the child appears likely to gain benefit and is still expected to require prolonged ventilator support. Children requiring high levels of sedation to tolerate an endotracheal tube and those with profound neuromuscular weakness should be considered for tracheostomy early, and reassessed daily with risk–benefit assessment
Recommendation 8: Unless there is evidence for clearly irreversible disease (e.g., high spinal cord injury or advanced neurodegenerative condition), a child recovering from PARDS requiring prolonged mechanical ventilator support for respiratory failure should not be considered permanently ventilator dependent until many months of ventilator liberation attempts have failed
Recommendation 9: Ventilator liberation strategies in children with PARDS requiring prolonged mechanical ventilation should be systematic, slow paced, and usually include gradually lengthening self-breathing trials
Recommendation 10: Transfer to a rehabilitation center specializing in weaning and providing high-level physical therapy may optimize the efficiency of the process of ventilator liberation in some children with PARDS

ongoing respiratory support after extubation to decrease the risk of reintubation. Noninvasive ventilation (NIV) (e.g., CPAP or BiPAP), high-flow nasal cannula (HFNC), and/or cough-assist devices can assist patients who are severely deconditioned. A temporary tracheostomy is required in some children with PARDS for secretion management or to facilitate more prolonged ventilator weaning. These topics will be reviewed in detail in the sections below.

Evidence-based recommendations for Weaning and Discontinuing Ventilatory Support were published in 2001 by a task force of individuals from three professional societies [5]. In Table 8.1, these recommendations have been modified for application in children recovering from PARDS. In 2007, an International Consensus Conference focusing on adult patients suggested that ventilator discontinuation could be categorized as simple, difficult, or prolonged as follows [6].

- *Simple*: Patients who successfully extubate after the first SBT.
- *Difficult*: Patients who fail the initial SBT and require up to 3 SBTs or as long as 7 days from the first SBT to achieve successful liberation from the ventilator.
- *Prolonged*: Patients who fail at least 3 SBTs or require >7 days from the first SBT to achieve successful ventilator discontinuation.

Although not formally applied, this stratification may be useful for categorizing ventilator discontinuation in children recovering from PARDS; proportionately, those with severe ARDS are more likely to be in the difficult or prolonged categories than children recovering from less severe lung injuries.

Assessing Readiness for Ventilator Discontinuation

Has the Severity of PARDS and Its Underlying Trigger Improved?

Strategies for providing lung protective mechanical ventilator support should be provided while aggressively treating the underlying disease process that triggered PARDS (e.g., infection, pancreatitis, aspiration, etc.). Once the patient achieves sufficient recovery, the process of discontinuing mechanical ventilatory support should begin. For practitioners following a PARDS management protocol, such as the one developed by the ARDS Clinical Research Network [7], which was modified by Curley et al. [8] for use in the pediatric prone positioning clinical trial, parameters for decreasing levels of ventilator support based on oxygenation and ventilation will be specified.

Is the Child Hemodynamically Stable?

Before attempting to discontinue mechanical ventilator support, pediatric patients should be hemodynamically stable. This may be defined as absence of clinically significant hypotension (i.e., requiring no vasopressor therapy or only low-dose) and active myocardial ischemia or its risk should have resolved. Although serum B-type natriuretic peptide (BNP) – a marker of fluid overload, which can rise during an SBT due to left ventricular failure – has been used in clinical studies to guide fluid restriction and diuresis in adult patients [9], the majority of children with PARDS have recovered cardiovascular function by the time that ventilator weaning is initiated.

Is Gas Exchange Acceptable?

There are no strict parameters for categorizing when children are ready for ventilator discontinuation using gas exchange criteria, but assessing adequacy of gas exchange is important. Generally, children with $SpO_2 > 92\%$ on an $FIO_2 \leq 0.5$ and PEEP ≤ 7 cm H_2O have adequate oxygenation to initiate the process. Parameters for ventilation will vary but those with arterial pH is >7.35 (or venous pH >7.30) with an acceptable minute ventilation for age and weight can usually tolerate a trial. When high minute ventilation is required due to high dead space and/or high CO_2 production, children may not be able to sustain this level for a prolonged period spontaneous breathing.

Is the Level of Sedation Titrated for the Child to Be Easily Awakened but Calm?

Before the process of ventilator discontinuation can proceed, the child must be able to consistently initiate spontaneous inspiratory efforts. The level of sedation commonly impedes this process [4]. Therefore, it is recommended that children tolerate a spontaneous awakening trial (SAT) before they undergo formal assessment of ability to tolerate ventilator discontinuation with an SBT [10]. Children are considered to have passed the SAT if they consistently open their eyes to verbal stimuli. If they do not, sedation should be decreased and then restarted at a decreased level (usually half the previous dose) and then titrated to achieve a pre-

specified sedation target (e.g., awake and calm) using a scale that is customized for children. The State Behavioral Scale is a validated customized sedation scale for children [11]. Use of short-acting sedatives, such propofol or dexmedetomidine, can be implemented fully or in part as part of sedative weaning as they do not impede spontaneous respiration as much as narcotics or benzodiazepines. However, prolonged use of propofol in children must be restricted due to the risk of propofol infusion syndrome [12]. Although use of a protocol for titrating narcotics and benzodiazepines in mechanically ventilated children, many of whom had PARDS, did not shorten time to extubation, overall, children on the protocol were more awake and had less overall narcotic exposure [13].

Is the Patient Profoundly Weak?

Respiratory muscle strength is also an important consideration. Children whose respiratory muscle strength is impeded due to critical illness myopathy/polyneuropathy or neurologic injury are at higher risk for extubation failure [14]. These patients should have their maximum airway pressure during airway occlusion (aPiMax) measured. In children with low aPiMax, considerations for need for prolonged mechanical ventilation and individualized weaning strategies are important.

Ventilator Weaning Strategies

The course of mechanical ventilation in children including the time period considered "weaning" is shown in Fig. 8.1 [15]. There have been no clinical trials comparing different methods of weaning from mechanical ventilation limited specifically in children intubated for severe hypoxia. In a heterogeneous group of children with respiratory failure from pulmonary and neurologic etiologies including PARDS, there was

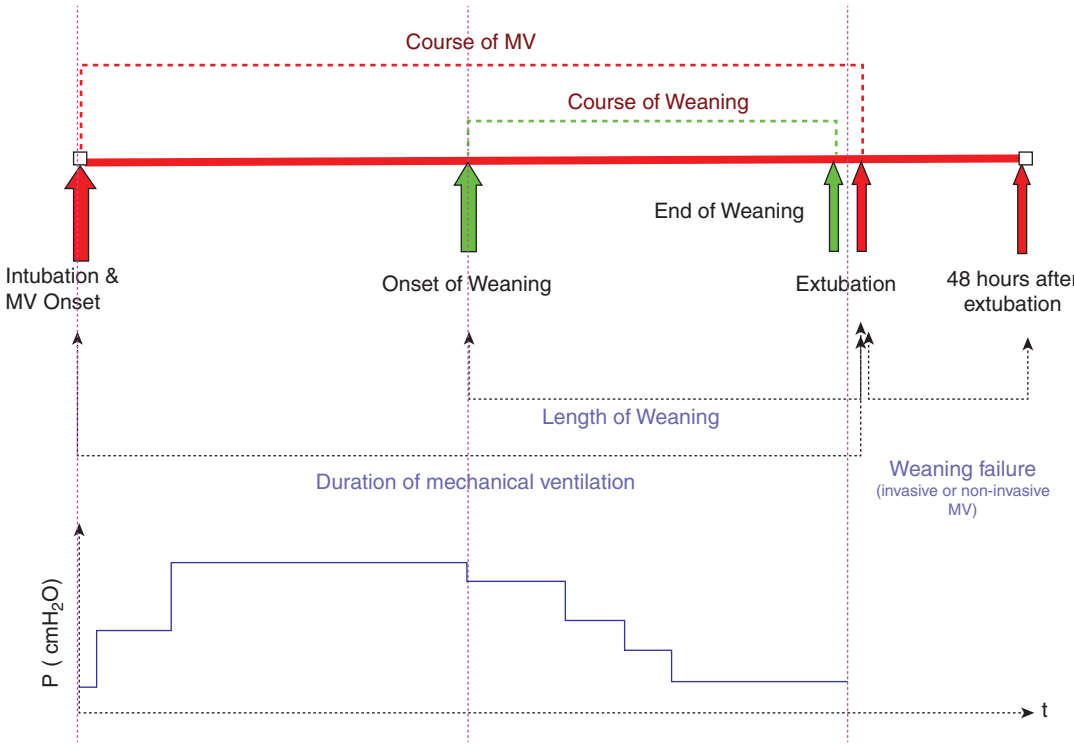

Fig. 8.1 The course of mechanical ventilation in children. (Courtesy of Christopher Newth, MD and adapted from Newth et al. [15])

no difference between physician-driven weaning versus two different pressure support ventilation (PSV)-based weaning protocols [4]. In this trial, the physician-driven PSV protocol required a clinician to stepwise decrease the amount of pressure support, aiming to maintain an exhaled tidal volume goal (Fig. 8.2). The other pressure support weaning arm used an automated mode on the ventilator called Volume Support to achieve the same goal but targeting minute ventilation, with continuous adjustment of pressure support. In the "usual care" arm, clinicians used a mix of modes including synchronized intermittent mandatory ventilation (SIMV) with a stepwise decrease in set rate, PSV and CPAP. Although all children failed an SBT (called the extubation readiness test) prior to randomization, the median duration of time in weaning was between 1.6 and 2 days in the three study arms.

There is no evidence to support a specific mechanical ventilator weaning method for children with PARDS, so continuous assessment is essential, with titration of the amount of support downward as the patient recovers. Randomized trials evaluating automated systems of weaning were systematically reviewed by Rose and colleagues [16], and there is some evidence that automated systems can reduce weaning duration significantly with a concomitant decrease in duration of mechanical ventilation and number of patients receiving a tracheostomy. Although these trials included patients with ARDS and pediatric trials were included, they were not focused specifically on this population. Therefore, an adequately powered multicenter randomized controlled trial is needed to evaluate the safety and efficacy of automated systems of weaning young children with PARDS.

Spontaneous Breathing Trials

In the 1990s, two randomized, controlled trials in adult patients were published [17, 18] that showed performing a once or twice daily SBT in patients meeting screening criteria enabled successful extubation in the majority of patients compared to synchronized intermittent mandatory ventilation (SIMV) weaning (gradual reduction in mandatory breath rate) or PSV weaning. Most adult patients were successfully extubated after passing the first SBT, which was a finding that was replicated in children [4]. The two adult and pediatric studies included patients with ARDS. In patients that failed the initial SBT, no difference in duration of mechanical ventilation was seen between PSV versus usual care in children [4]. However, once or multiple daily SBT was superior to PSV and SIMV weaning in one multicenter randomized trial in adults [18]. This evidence shows that adult and pediatric patients who tolerate an SBT for 30–120 minutes should be considered for a trial of extubation, because they are likely ready for liberation from mechanical ventilator support.

The resistance of an endotracheal tube is associated with its radius and length. Therefore, smaller tubes were believed to have higher resistance, necessitating that, along with the pressure needing to be generated against the ventilator valves, small children be supported with some PSV during their testing to decrease risk of fatigue and failure (Fig. 8.2). This belief has been challenged by Khemani and colleagues who showed that use of PSV may overestimate the patient's chance of success by providing too much ventilator support and recommended use of CPAP alone for SBTs [19, 20]. In older patients, especially those with neuromuscular weakness or afterload-sensitive left ventricles, a T-piece trial can be used to estimate ability to tolerated extubation.

An SBT in children can be performed with a low level of PSV (5–10 cm H_2O) titrated upward for smaller endotracheal tubes over low PEEP (4–5 cm H_2O) as shown in the protocol in Fig. 8.2, or can be performed on CPAP of 5 cm H_2O. Use of inspiratory pressure automatically titrated to overcome endotracheal tube resistance (i.e., tube compensation) is another option that is used in adult patients [2]. Tube compensation adjusts the level of PS according to the size of the endotracheal tube and inspiratory flow; it compensates for the resistance through the endotracheal tube. The resistance caused by upper airway edema after extubation may, however, be similar to the resistance caused by the endotracheal tube (ETT) [21].

PRESSURE SUPPORT WEANING PROTOCOL*

Physician to review in entirety in conjunction with a Respiratory Therapist

- ☐ Patient is on a ventilator that delivers pressure support
- ☐ Physician to review pain and sedation orders with RN
- ☐ PEEP ≤ 7 cm H_2O and FiO_2 ≤ 60%
- ☐ Check inspiratory rise time and flow sensitivity (adjust if necessary)

Initiate Pressure Support Patient's Ideal Body Weight:_____kg

PS min by ETT size: 3.0 to 3.5 ETT = 12 cm H_2O; 4.0 to 4.5 = 10; 5.0 to 5.5 = 8; ≥ 6.0 = 6 cm H_2O

ETT size =_____ PS min = _____cm H_2O

1. Change to PS mode on PS min + 2 cm H2O
2. Adjust PS to achieve exhaled VT of 5-7 ml/kg (____ to ____ ml) and hold for 4 hours.

ADJUST FIO_2 AND PEEP

Maintain SpO_2 ≥ 95%

- If SpO_2 ≥ 95% on FiO_2 ≤ 0.60, decrease PEEP by 1 cm H_2O Q4 hours (PEEP ≥ 8 cm H_2O for > 4 hrs = weaning cessation, see back of page)
- Once PEEP is ≤ 5 cm H_2O, then wean FiO_2 to ≤ 50%

If SpO_2 < 95%, then return to previous setting, notify MD, and hold PEEP wean for 4 hrs.

PRESSURE SUPPORT ADJUSTMENT

*****Goal is to wean to PSmin keeping exhaled VT between 5 to 7 ml/kg*****

- If exhaled VT **≥7 ml/kg** (____ml) **at any time** *OR* VT **≥ 5 ml/kg** (____ml) **for ≥ 4 hours** then **wean PS** by 2 cm H_2O and reassess in 30 minutes. Evaluate Q4 hrs.
- See EXTUBATION READINESS. *When PSmin (____) is reached, see* **Extubation** *at bottom of page.*
- If exhaled VT are consistently **< 5 ml/kg** (____ml) then **increase PS** in 2 cm H_2O increments to achieve tidal volumes of ≥5 ml/kg *AND* do not wean PS for at least 4 hours.
  Spontaneous RR goal: age > 5 years (10 to 35 bpm); age 2-5 years (15 to 40 bpm); age 6 months to 2 years (15 to 45 bpm); age < 6 months (20 to 55 bpm)
- RR is > RR goal? →YES: (a.) Could be from anxiety alone. Evaluate sedation/analgesia. (b.) If anxiety appears to be from excessive work of breathing, increase PS 2 cm H_2O until RR is in range.
- RR is < RR goal? → YES: If oversedated, decrease sedation/analgesia.

EXTUBATION READINESS

❑ PS ≤16 cm H_2O and SpO_2 ≥ 95% on PEEP ≤ 5 cm H_2O and FiO_2 ≤ 0.50 for a minimum of 4 hours
If the above criteria are met, once ***every 24 hours with Physician approval*** you may perform an ***Extubation Test*** by placing patient on PS min (___) and monitoring exhaled tidal volumes.

If exhaled tidal volume is consistently < 5 ml/kg (___ml) **AND/OR** SpO_2 < 95 % on PEEP ≤ 5 and FiO_2 ≤ 0.50 **AT ANY TIME**, then return to previous PS setting, hold for 4 hours then decrease stepwise to PSmin as specified in **PRESSURE SUPPORT ADJUSTMENT** above.

Extubation

Once patient is ***on PSmin*** and ***for ≥ 2 hours*** (1.) Exhaled tidal volumes are ≥ 5ml/kg **AND** (2.) SpO_2 ≥95% on PEEP ≤ 5 and FiO_2 ≤ 0.50, then proceed to **Extubation**

* This protocol was used in a clinical trial: Randolph AG, et al. JAMA 2002; 288:2561-2568.

Fig. 8.2 Example of a ventilator discontinuation protocol

In a multicenter study of 182 mechanically ventilated pediatric patients, an SBT (called an ERT or extubation readiness test) was performed for children meeting screening criteria as follows [4]. Patients were placed on PEEP ≤5 or FIO_2 ≤ 0.5. If they maintained SpO_2 > 94%, they were then converted to PS titrated to the size of the endotracheal tube (e.g., 3.0–3.5 mm, then PS = 10 cm H_2O; ≥ 5.0 mm, then PS 6 cm H_2O). The great majority of children passed the

ERT, and of these, 88% were extubated with the great majority (87%), requiring no additional ventilator support. This finding was replicated using a similar protocol in the RESTORE study that was evaluating a sedation protocol in children mechanically ventilated for acute respiratory failure [13]. In children with an oxygenation index of six or lower, passing the ERT described above had a positive predictive value of 93% for successful extubation within 10 hours [22].

SBT Failure: Recognition and Management

A failed SBT is stressful both physiologically and psychologically for patients and families. Reviewing multiple pediatric studies, Newth and colleagues proposed a list of criteria for failing an SBT or ERT, which are shown in Table 8.2 [15]. Parameters for tachycardia and tachypnea will vary by age [4] given that young children have higher heart rates and respiratory rates. It is important to recognize when psychological factors are driving the changes in vital signs, and verbal reassurance, parental presence or, if these fail, pharmacologic measures may be needed. When it is deemed that the child has failed the SBT, ventilator support should be re-established with the goal of providing patient comfort. The mode of mechanical ventilation and specific settings may vary.

Table 8.2 Proposed criteria for ERT/SBT failure in children recovering from PARDS

Clinical criteria
Diaphoresis
Nasal flaring
Increasing respiratory effort
Tachycardia (increase in HR > 40 bpm)
Bradycardia
Cardiac arrhythmias
Hypotension
Apnea or hypopnea
Laboratory criteria
Increase of $P_{ET}CO_2$ > 10 mmHg
Decrease of arterial pH < 7.32
Decline in arterial pH > 0.07
PaO_2 < 60 mmHg with an FiO_2 > 0.40 (P/F O_2 ratio <150)
SpO_2 / FiO_2 declines >5%

Modified from Newth et al. [15]

After a child recovering from PARDS fails the SBT and has been returned to comfortable ventilator settings, a systematic assessment of the reasons for failure should be performed. With correction of the cause of the failed SBT, another SBT is done 24 hours after the failed SBT. There are a number of reasons that may explain why a child recovering from PARDS failed an SBT that the clinician may evaluate and address, as reviewed by Hess and Randolph [2]:

- *Excessive respiratory muscle load*: high airways resistance and low compliance.
- *Auto-PEEP*: increases the pleural pressure needed to initiate inhalation.
- *Cardiac dysfunction*: left heart failure when intrathoracic pressure decreases with the transition from positive pressure ventilation to spontaneous breathing.
- *Respiratory drive*: increase (acidosis, pain) or decrease (narcotics) in respiratory drive. Decreased respiratory drive can be caused by oversedation or by underappreciated neurologic injury.
- *Respiratory muscle weakness*: either preexisting or acquired (critical care myopathy, diaphragm paralysis).
- *Electrolyte imbalance*: low levels of potassium, magnesium, phosphate, and calcium can impair ventilatory muscle function.
- *Nutritional support*: overfeeding can elevate carbon dioxide production, leading to hypercarbia whereas lack of sufficient protein and calories can lead to catabolism and muscle loss.
- *Fever and infection*: increases oxygen consumption and carbon dioxide production, resulting in an increased ventilatory requirement.
- *Major organ system failure*: renal failure can lead to fluid shifts and metabolic acidosis; neurologic impairment can lead to alteration in respiratory drive and ability to manage secretions.
- *Technical issues*: endotracheal tube obstruction from secretions and malposition of endotracheal tube should be ruled out.

Use of Clinical Decision Support (CDS) Protocols

Use of clinical decision support (CDS) protocols to guide mechanical ventilator management of children with PARDS is feasible and may be helpful, especially in improving compliance with the above recommendations [23, 24]. Optimally, these protocols will include instructions that improve consistency of evaluating children based on best clinical evidence with input from clinical experts. CDS protocols are designed to complement and enhance clinical decision making and be used as a tool in the hands of an expert clinician [25]. They are not a replacement for clinical judgment, and their application should be individualized for each patient. Successful CDS protocols require input from multidisciplinary teams, including respiratory therapists and nurses who are essential for protocol implementation and monitoring, and for timely feedback to the physician. Ventilator discontinuation protocols are common in adult ICUs in the United States, [26] and are increasingly used in pediatric ICUs. Elements of a ventilator discontinuation protocol are shown in Fig. 8.2 [4, 27].

Blackwood et al. [28] conducted a Cochrane systematic review and meta-analysis on the use of ventilator discontinuation protocols. The review comprised 11 trials that included 1971 patients. Compared with usual care, the mean duration of mechanical ventilation in the protocol group was reduced by 25% (95% CI 9–39%), the duration of weaning was reduced by 78% (31–93%,), and ICU stay by 10% (2–19%). The results of this systematic review support the use of ventilator discontinuation protocols.

Extubation

After a child successfully completes an SBT, a decision about when and how to extubate must be made. Prolonging extubation in a patient that can be successfully extubated can lead to preventable complications such as atelectasis, ventilator-associated infection, and endotracheal tube obstruction. However, patients that fail extubation and require reintubation have worse clinical outcomes including prolonged hospital stay and higher mortality [29]. Therefore, a reintubation rate of zero would mean that many children may be remaining on the ventilator longer than necessary but a high reintubation rate (e.g., >30%) may be putting too many children recovering from PARDS at risk. An acceptable reintubation rate for children with PARDS is likely between 10% and 20%. No single predictor or index of predictors has been shown to be highly accurate for extubation failure in mechanically ventilated children [15], and there are no studies specifically testing extubation predictors solely in children with PARDS.

Some children deemed to be at high risk of extubation failure can be transitioned to NIV or HFNC support to help them remain free of the endotracheal tube. HFNC has been shown to reduce reintubation versus conventional oxygen in adults at low-risk for reintubation, and to be noninferior to NIV in high-risk patients [30, 31]. The multidisciplinary team – including physicians, nurses, and respiratory therapists – should "huddle" and make a clear plan for when and how to remove the endotracheal tube, with a plan for determining when extubation has failed and how the patient will be rescued.

A patient's ability to clear secretions, their neurologic status, and their ability to maintain their upper airway must be assessed prior to extubation. Children recovering from PARDS who have poor neurologic function but who are able to manage their secretions may be able to be successfully extubated, whereas children with increased secretions and depressed neurologic status are at high risk for failing extubation. Some recommendations for how to assess these [2] are listed below:

- *Secretion assessment*: In adult patients, inability to generate a cough peak flow >60 L/min, and secretions ≥2.5 mL/h have been reported to increase the risk of reintubation [32]. Accurate assessment of the strength of a cough using peak flow and quantifying the volume of secretions is difficult in intubated children and is usually subjective. Need for frequent suctioning, especially in patients requiring suctioning at least hourly, is a potential risk factor for extubation failure. However, some chil-

dren's secretion burden may decrease after extubation. Some patients with a weak cough who are not burdened by heavy secretion volume may be able to extubate successfully. Use of an insufflation-exsufflation cough-assist device may help with secretion management.

- *Neurologic status assessment*: Can the patient perform simple tasks either on command or after stimulation? These tasks may include opening eyes, following an object with the eyes, grasping a caregiver or parent's hand, or pushing with their feet against resistance. The effect of neurologic function on airway protection is not clear. Lack of a gag reflex itself is not a strict contraindication for extubation, but the patient must be watched very closely for aspiration and re-intubated quickly if it seems that secretions are pooling in the back of the throat without a reflexive cough. It is possible to proceed with extubation despite poor neurologic function; however, some clinicians prefer tracheostomy to the high risk of extubation failure. Many patients who are unable to follow commands, but have the ability to clear pulmonary secretions, can be safely extubated [33]. Bach has shown that a cough-assist device can help with airway clearance in patients with neuromuscular weakness [34], and this device may also help children who are weak during PARDS recovery.

Upper airway obstruction following extubation is a risk factor for extubation failure in children and can occur from subglottic or supraglottic airway swelling [35]. Deflating the endotracheal tube cuff and measuring the amount of pressure delivered before hearing an air leak around the endotracheal tube (delivering up to 30 cm H_2O) has commonly been used to assess the potential for postextubation stridor, but is has been shown to be an inaccurate predictor. Although the absence of leak (positive test) with the cuff-leak test portends a higher risk of upper airway obstruction, the test itself may lead clinicians into unnecessarily delaying extubation [36, 37]. In part, this may be due to the fact that there is not a standard method for performing a cuff-leak test and interpretation of it is subjective [38, 39].

Use of steroids (e.g., dexamethasone) prior to extubation is acceptable if there are no contraindications in patients with suspected upper airway swelling [38]. In published meta-analyses, the incidence of postextubation laryngeal edema was decreased in adults and children receiving intravenous corticosteroids at least 12 hours prior to extubation who received multiple doses [40–42]. Use of corticosteroids even 4 hours pre-extubation may have an effect [43].

Extubation Failure

Tachypnea, retractions, tachycardia, and increasing hypoxia are all signs that a child is struggling after extubation. It is important to identify this pattern quickly and intervene to rescue the child so that morbidity is prevented, including aspiration and atelectasis, that can impair recovery from PARDS. In patients with severe distress, intubation may need to be performed quickly. However, most children can be assessed for remediable factors and interventions can be performed to assist them in remaining extubated. In stridulous children, use of inhaled racemic epinephrine and corticosteroids may help to reduce airway swelling. In children who are oversedated with insufficient respiratory drive, further reduction in their sedative wean is indicated. In children having difficulty managing their secretions, suctioning and use of a cough-assist device may be helpful. Positioning of older patients out of bed into a chair and use of incentive spirometry (or blowing pinwheels or bubbles) can help to prevent development of atelectasis.

NIV is increasingly used in the pediatric intensive care unit. It is commonly used in children recovering from PARDS after extubation. It can be used either to facilitate removal of the endotracheal tube and/or to prevent reintubation in a patient who appears to be failing extubation [44–46]. In the "huddle" prior to extubation, the clinical staff should determine if the patient may benefit from transition directly to NIV support. Children recovering from PARDS who repeatedly fail an SBT may benefit from direct transition to NIV for a trial of extubation. Children who use NIV at baseline often benefit from direct transfer to NIV using settings at or higher than

their baseline settings. It is important not to delay reintubation if a patient who is rescued with NIV postextubation requires escalating settings, as this may lead to worse clinical outcomes. HFNC may also be used post extubation for prevention of failure or for rescue, but this technology has even less data supporting the safety of its use than NIV.

Summary of Key Learning Points

Modified from Hess and Randolph [2].

- Improvement in the severity of PARDS, adequate gas exchange, adequate respiratory drive, and hemodynamic stability are essential before children with PARDS can proceed to the ventilator liberation process.
- No single parameter accurately predicts the ability of a child to wean from the ventilator or to be successfully extubated.
- The best way to determine whether a child recovering from PARDS can be potentially liberated from the ventilator is by undergoing a spontaneous breathing trial (SBT). The SBT has been called an extubation readiness test (ERT) in many pediatric studies.
- The SBT should be individually modified according to the child's baseline characteristics.
- Providing too much support during the SBT may overestimate the chance of extubation success.
- A failed SBT can be due to many reasons, and it is important to systematically evaluate and intervene before repeating an SBT to optimize success.
- In children, oversedation and upper airway obstruction are common and remediable reasons failing a trial of extubation.
- Some children recovering from PARDS may benefit from extubation directly to NIV or HFNC to facilitate more rapid liberation from the endotracheal tube.

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9 Noninvasive Respiratory Support in Pediatric Acute Respiratory Distress Syndrome

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Introduction

The incidence of pediatric acute respiratory distress syndrome (PARDS) is estimated to be quite low, accounting for approximately 2.3–3.2% of pediatric intensive care unit (PICU) admissions worldwide [1, 2]. However, up to one-third of these children will die during hospital admission, making it imperative for clinicians to continue investigation of novel therapeutic modalities [1]. Invasive mechanical ventilation (IMV) is the predominant mode of respiratory support for children with PARDS [2, 3], but potential risks including ventilator-associated lung injury, ventilator-associated infections, and need for potentially harmful neurosedatives and neuromuscular blockade make consideration of alternative, noninvasive modes of respiratory support especially important [4].

There is a growing body of literature describing the benefits of noninvasive ventilation (NIV) use in acute respiratory failure (ARF). Children successfully managed with NIV have shorter lengths of stay, shorter duration of ventilatory support, and decreased mortality compared to children treated with invasive ventilation [5, 6]. These benefits are best described in children receiving continuous positive airway pressure (CPAP) or high-flow nasal cannula (HFNC) for bronchiolitis [7, 8], and bilevel intermittent positive airway pressure (BiPAP) for asthma [9]. In adults, first-line therapy with NIV is considered standard of care in cardiogenic pulmonary edema [10], and acute exacerbation of chronic obstructive pulmonary disease [11]. While frequently used in the management of adult patients with acute hypoxemic respiratory failure including acute respiratory distress syndrome (ARDS) [12], the effectiveness of NIV is unclear [13, 14]. Evidence examining the use of different modes of NIV in this patient populations is generally limited to observational studies and few randomized controlled trials, which include heterogeneous patient populations with conflicting results [15, 16].

Similarly, there is inconclusive evidence to support the use of NIV children with PARDS [2] or those "at risk" for PARDS (ARF-PARDS) [17]. Due to lack of data to support the routine use of NIV (specifically noninvasive positive pressure ventiation), current consensus guidelines recommend against its use in moderate-to-severe PARDS, but suggest clinicians may consider its early implementation in children with mild

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PARDS [18]. The wide availability, ease of use, and low-risk profile of NIV make it an attractive alternative to IMV, and despite lack of compelling evidence of its benefits in PARDS, it has been used with increasing frequency in the PICU [4]. Therefore, practitioners should be familiar with the variety of available technologies and patient interfaces.

For the purposes of this chapter, we will consider the following modes of NIV: HFNC, CPAP, BiPAP, neurally adjusted ventilatory assist (NAVA), and negative pressure ventilation (NPV).

History and Epidemiology

The modern era of NIV began with the first widely used iron lung, developed by Drinker and Shaw in Boston in 1929 [19, 20]. Used to treat ARF in adults and children with polio, its size, expense, and challenges with patient accessibility, immobility, and comfort limited its practicality. Twenty years later, use of the iron lung was supplanted by invasive mechanical ventilation [21]. Negative pressure ventilation still remains a useful treatment in the armamentarium for acute respiratory failure [22], but the use of HFNC, CPAP, and BiPAP predominantly accounts for the recent popularity of NIV [5].

Current HFNC use in the PICU is reported to be as high as ~23% of all admissions [5], with many clinicians considering it a first-line therapy [23, 24]. The prevalence in HFNC use is mostly because of its role in treatment in bronchiolitis, with other common indications include asthma, postextubation respiratory support, and respiratory distress associated with congenital heart disease [5, 25]. A diagnosis of PARDS necessitates full face-mask BiPAP or CPAP ≥5 cm H_2O, but children receiving HFNC may be classified as "at risk for PARDS" [26]. The literature describing HFNC use in these patients is sparse [17]. In a single-center observational study including critically ill adults employing a now obsolete ARDS definition, HFNC was used as first-line therapy for nearly one-third of patients with acute lung injury/ARDS [27].

Noninvasive positive pressure ventilation (NPPV), including CPAP and BiPAP, is similarly rising in popularity in the PICU, with utilization increasing from 11.6% to 18.2% over a 7-year period in an Italian multicenter study [28]. Essouri et al. studied over 3000 critically ill children and showed BiPAP use increased from <1% of admitted patients to nearly 7%, over a 5-year period [29]. Smaller, single-center studies show similar trends. Common indications for CPAP and BiPAP use include bronchiolitis, pneumonia, and postoperative respiratory failure [28, 29].

Despite conflicting data to support its routine use in ARDS/PARDS, many practitioners express a willingness to use NPPV as a treatment [4], and it is frequently employed as a first-line modality [2]. In a recent international, multicenter, prospective observational study including 708 children with PARDS, NPPV was used in 22.6% of patients. This is an increase from the previous decade, when an international cross-sectional study of 59 PICUs showed that only 8.5% of children meeting criteria for acute lung injury/ARDS criteria were treated with NPPV [3].

Physiology of NIV in PARDS

NPPV is beneficial in patients with upper airway obstruction including neuromuscular disease, [30] in children with diseases of respiratory compliance, including pneumonia, and increased lower airway resistance, such as asthma or viral bronchiolitis. PARDS is a heterogeneous lung disease, and the predominant pathophysiology may be dependent, in part, upon the etiology of PARDS and concurrent comorbidities. Therefore, the potential benefit of NIV will depend upon the lung pathology for each patient. The clinical syndrome of PARDS begins with disruption of the alveolar epithelial-endothelial barrier, leading to an accumulation of protein-rich, inflammatory fluid in the alveoli. This ultimately manifests clinically as hypoxemia, infiltrates, increased dead space, decreased compliance, and decreased functional residual capacity (FRC) [31]. Different modes of NIV improve gas exchange and respiratory mechanics in different ways, and the choice

of NIV mode and patient interface is dependent upon a multitude of disease and patient factors that the clinician must consider concordantly.

In patients with restrictive lung disease, compliance is decreased, and chest wall expansion is limited. Acute processes including infection, effusion, alveolar or interstitial edema, and chronic processes such as neuromuscular dysfunction or thoracic cage abnormalities can all contribute to restrictive lung disease. The resultant decreased FRC and decreased tidal volume lead to a compensatory increase in respiratory rate necessary to maintain minute ventilation. Furthermore, the decreased FRC can lead to further alveolar collapse and progressively worsening lung compliance. CPAP raises inspiratory pressures above atmospheric pressure through application of positive end-expiratory pressure (PEEP). By decreasing the inspiratory work of breathing, the patient generates higher tidal volumes and FRC is increased. BiPAP applies PEEP and augments inspiration with delivery of pressure or volume support, thereby increasing tidal volume, augmenting minute ventilation, and unloading fatigued respiratory muscles. Application of positive pressure may also decrease alveolar edema to improve gas exchange.

Children with acute hypoxemic respiratory failure are likely to benefit from HFNC. Based on recent randomized controlled trials in children and infants with bronchiolitis, HFNC may be superior to standard low-flow nasal cannula [32, 33] and similar to CPAP [34] in prevention of treatment failure requiring escalation of care. While use of HFNC precludes a diagnosis of PARDS based on current consensus definitions, children requiring this level of support may meet the "at risk for PARDS" criteria [26]. There is no firm evidence to date recommending HFNC use in these patients, but the potential benefits of HFNC are multifactorial. Application of high-flow conditioned gas causes reduction in inspiratory resistance at the high-resistance nostrils and nasal passages, washout of nasopharyngeal dead space with oxygen-rich gas, reduction of metabolic work with delivery of heated, humidified gas, improved mucociliary clearance, and application of low levels of positive pressure [35–37]. Together, these mechanisms may improve respiratory mechanics and gas exchange in children with acute respiratory failure.

NPV is not well described in the pediatric respiratory failure [22]. Potential advantages include improved secretion management and oral care, and augmentation of cardiac output [38] by increasing right ventricular preload. In NPV, the thorax is exposed to subatmospheric pressure, leading to expansion of the thoracic cage and resultant decrease in pleural and alveolar pressures. The resultant pressure gradient augments the patient's inspiration and relieves respiratory fatigue.

Patient Selection

The primary goal of NIV in patients with PARDS is to provide adequate gas exchange by eliminating CO_2 and improving oxygenation, decrease work of breathing, and avoid intubation or reintubation. This can be achieved by optimizing FRC and recruitment of the alveoli.

For most children with ARF and PARDS, the indications to use NIV is usually due to lower respiratory tract disease, the need to avoid intubation in cases where IMV is contraindicated or strongly undesirable [18, 39–43], and to aid in extubation (Table 9.1).

Table 9.1 Indication of NPPV in PARDS

Acute lower respiratory tract diseases
Bronchiolitis
Pneumonia
Pulmonary edema
Acute chest syndrome
Atelectasis
Avoidance of intubation or re-intubations
Do-Not-Intubate (DNI) or comfort-measures-only (CMO)
Immunocompromised status
Neuromuscular disorders
Neurological illnesses
Cystic fibrosis
Restrictive lung disease (e.g. severe scoliosis)
Postoperative respiratory insufficiency
Postextubation respiratory insufficiency
Aid to successful extubation
Overlap with invasive mechanical ventilation to facilitate early weaning and extubation

The successful use of NIV in parenchymal lung diseases has been well described for decades. NPV was the first modality of NIV used back in the 1930s throughout the 1950s during the polio epidemic, and then recently with more recent evidence to support its effectiveness in patient with bronchiolitis and other causes of parenchymal lung diseases like pneumonia [22]. NPPV, including CPAP and BiPAP, is an effective modality to support pediatric patients with mild and moderate acute respiratory insufficiency [18, 28, 42, 44–48] associated with bronchiolitis, pneumonia [49, 50], status asthmaticus [41], pulmonary edema, and atelectasis. In a large retrospective study by Ganu et al. including 520 children with bronchiolitis, 285 patients were supported with NIV. Of the NIV-supported patients, 237 (83.2%) needed only NIV and 48 (16.8%) failed and required intubation. Patients successfully supported by NIV had significantly shorter median length of stay compared to those requiring invasive ventilation and those who failed NIV (2.38 ± 2.43 vs. 5.19 ± 6.34 vs 8.41 ± 3.44 days, respectively; $p < 0.001$) [42].

In a prospective study, Munoz-Bonet et al. [50] reported using NIV in 47 episodes for 37 patients with acute hypoxic respiratory failure with an 80% success rate. NIV-failure was due to progression of respiratory failure and was observed between 3 and 87 hours (average 33.6 ± 29.6 hours) after initiation. Heart rate and PCO_2 significantly improved after NIV implementation. Maximum mean airway pressure of 11.5 cmH_2O and oxygen requirements more than 60% predicted NIV failure.

While its association with favorable outcomes makes the use of NIV an attractive alternative to IMV, appropriate patient selection is paramount because failure of NIV has been associated with higher morbidity and mortality in acute hypoxic respiratory failure and PARDS. Because of lack of strong consistent data, current consensus guidelines do not support the routine use of NIV in patients with moderate to severe PARDS [26]. Therefore, clinicians should be judicious with its use, selecting only patients in whom the most benefit is expected.

In some patient populations, the potential benefit of NIV may far outweigh the risk of initiation of IMV. NIV could be the only appropriate ventilation modality for terminally ill patients with Do-Not-Intubate (DNI) or comfort-measures-only (CMO) status in place. Implementing NIV in these circumstances could be needed to get through an acute illness or to provide comfort at the end of life [51].

In pediatric oncology and immunocompromised patients, the risk of mortality associated with IMV makes a trial of NIV warranted and desirable. While survival of this group of critically ill patients has improved, mortality associated with acute respiratory failure and PARDS remains high [52–54]. These patients continue to represent a challenging population in critical care units. It is estimated that about 40% of these patients requires intensive care admission throughout the disease course. Development of ARF/PARDS and associated complications with IMV are major determinants of poor outcomes. Recent advances in respiratory support, especially NIV, have allowed more options to support these patients early on while in the PICU.

NIV has been suggested as the first modality of respiratory support in mild and possibly moderate PARDS in immunocompromised patients [18, 26, 52, 53, 55–58]. In a retrospective Italian study, Piastra et al. [54] showed that NPPV use was feasible in immunocompromised/oncology patients with PARDS. Out of 23 immunocompromised children with PARDS requiring mechanical ventilation, 13 (56%) were successfully supported with NPPV. The NPPV-successful group had a shorter ICU and hospital stay, less hospital-acquired infections, and lower reported incidence of septic shock. In another retrospective study, Fuchs et al. [59] investigated the mortality rate and the clinical variable related to the use of NPPV in 41 immunocompromised children with ARF. Eleven were successfully supported with NIV, of which 8 had recurrence of respiratory insufficiency within 27 days. The study showed that lower FiO_2, lower SpO_2/FiO_2 ratio, and bacterial septicemia were predictive of NIV success, while fungal septicemia and culture-negative acute respiratory insuf-

Table 9.2 Contraindication of NPPV in PARDS

Respiratory arrest
Cardiac arrest
Hemodynamic instability (shock)
Severe PARDS
The need for immediate intubation
Rapid progression of neuromuscular illness
Rapid worsening of neurological status
Inability to handle oropharyngeal secretions
Impaired gag or cough reflex
Recent esophageal or gastric surgery
Uncooperative patient
Severe agitation
Facial trauma
Basal skull fracture with CSF leak
Facial burns
Untreated pneumothorax

ficiency were predictive of NIV failure. In addition, the overall prognosis of ARF in immunocompromised children was independent of the NIV failure. In a more recent large retrospective cohort study, Pancera et al. reported a NIV success rate of 74.2% in 120 immunocompromised children with ARF. Solid tumors and cardiovascular dysfunction predicted NIV failure [60].

Weaning and early extubation is desired in patients with PARDS. NIV has been proposed to facilitate early weaning from IMV, most commonly by implementing NPPV preemptively in high-risk patients (e.g., neuromuscular illnesses) immediately after extubation, especially following pulmonary complications after major surgical procedures [61–63]. NPPV has been used to treat postextubation ARF in adults and pediatrics for decades to avoid reintubation with encouraging results.

Anecdotally, clinical practices suggest the use of NPPV concurrently with IMV to facilitate separation from the ventilator despite "higher ventilator settings" than the usual practice.

Contraindications for the use of NPPV in PARDS are shown in Table 9.2. Careful patient selection is paramount for the success of NIV in children. Clinicians must be aware of all medical conditions and comorbidities before applying NPPV to minimize the risk of potential complications (Table 9.3).

Table 9.3 Complications of NPPV

Inadequate gas exchange
Pulmonary aspiration
Gastric distention and perforation
Pressure sores (face, nose)
Eye injury and irritation/conjunctivitis
Barotrauma (pneumothorax, pneumomediastinum)
Agitation

High-Flow Nasal Cannula

The use of HFNC in pediatric acute hypoxemic respiratory failure has increased over the last decade, with nearly one-quarter of all children admitted to the PICU receiving this form of respiratory support [5]. The popularity of HFNC is likely related to its ease of use, portability, patient tolerability, and success in treating perinatal lung disease and viral bronchiolitis [33, 64]. Clinicians may also choose to use HFNC in children at risk for development of PARDS, although there are limited data describing these patients [17].

HFNC likely improves work of breathing and gas exchange in hypoxemic respiratory failure via reduction in inspiratory resistance, washout of nasopharyngeal dead space with oxygen-rich gas, reduction of metabolic work with delivery of conditioned gas, improved mucociliary clearance, and application of nominal levels of positive pressure [35–37]. The HFNC system includes the following basic elements: (1) a source of pressurized and blended oxygen and air; (2) a water reservoir attached to a heated humidifier; (3) a heated circuit that maintains temperature and humidity of the gas; and (4) a nonocclusive cannula interface.

With initiation of HFNC, the clinician sets the gas temperature, the FiO_2, and the flow rate. We recommend an initial gas temperature 1–2 °C below body temperature. The initial HFNC FiO_2 should be chosen based on patient's need and physiology, and adjusted to target a chosen oxygen saturation (SpO_2). While there is no consensus regarding the ideal gas flow rate, there is evidence to support weight-based dosing [34]. Modest respiratory support is provided with flow rates between 0.5 and 1.0 L/kg/min, while increas-

ing the flow to 1.5–2.0 L/kg/min may attenuate intrathoracic pressure swings to further reduce work of breathing [65]. Flows greater than 2 L/kg/min may not provide additional benefit [66].

Continuous Positive Airway Pressure (CPAP)

CPAP, similar to other forms of NIV, may be considered both for patients "at risk for PARDS" and in those with mild and moderate PARDS to avoid complications of IMV. However, intubation and mechanical ventilation should not be delayed and must be considered early in patients without signs of improvement or with worsening respiratory status within the first few hours of NIV initiation [26].

According to the most recent Pediatric Acute Lung Injury Conference Consensus (PALICC) recommendations, pediatric patients with ARF receiving nasal CPAP and requiring ≥40% FiO_2 are considered "at risk of PARDS," while ARF patients receiving full face-mask CPAP≥5 cm H_2O with PaO_2/FiO_2 ratio (PF ratio) ≤300, or oxygen saturation/FiO_2 ratio (SF ratio) ≤264, meet PARDS criteria.

CPAP refers to the application of a constant flow with resultant constant positive pressure throughout the respiratory cycle while the patient is spontaneously breathing. The use of CPAP to support children with ARF has been mainly described in patients with bronchiolitis and asthma [34, 41, 67, 68]. In a randomized controlled study including 142 infants with severe viral bronchiolitis, Milési et al. showed that CPAP is superior to HFNC with a relative risk of success of 1.63 (95% CI 1.02–2.63), higher with CPAP compared with HFNC. Failure occurred in 31% in the CPAP group and 50.7% in the HFNC group [34]. These results were similar to a previous single-center randomized trial in a similar patient population [67].

There are different types of interface used in NPPV: Nasal prongs, oronasal (full-face) mask, nasal mask, helmet, total face mask, and mouth piece. Oronasal is the most commonly used interface in acute settings. This can be effective in improving gas exchange and lung recruitment in PARDS. Gastric distention can be problomatic, so special attention should be taken while caring for these patients to avoid vomiting and minimize risk of aspiration [18, 39, 61, 69, 70].

CPAP of 6–12 cmH_2O with FiO_2 0.4–0.6 would be acceptable initial settings. FiO_2 should be titrated to achieve SpO_2 88 to ≤97%. Weaning of CPAP may be attempted once underlying pathology is resolving. CPAP can be trialed off when the patient has been stable at a level of 5–6 cm H_2O with an $FiO_2 < 0.40$.

CPAP mode is usually well tolerated in children [34, 48, 71], but it is not unusual that patients need sedation at initiation or throughout the implementation to facilitate patient-interface tolerance [72].

Bi-Level Positive Airway Pressure (BiPAP)

Among children with acute hypoxemic respiratory failure treated with NIV, only those receiving oronasal (full-face) mask CPAP or BiPAP are classified as meeting PARDS criteria [26]. Despite the PALICC recommending clinicians not use BiPAP in children with moderate and severe PARDS, the use of this mode of NIV continues to gain popularity [28, 29]. In a multicenter, prospective study including over 15,000 pediatric admissions, use of NIV, including BiPAP, was associated with decreased hospital length of stay and decreased mortality [6].

A well-fitted facial mask is essential for effective BiPAP use. Air-leaks around an ill-fitting mask will prevent generation of adequate mean airway pressure. Masks that are too tight, however, can lead to skin breakdown and pressure ulcers that preclude continued use. There are multiple patient interfaces available, with the oronasal (full-face) masks being most commonly used in the PICU. For most ventilators, the clinician will set up PEEP, inspiratory time, pressure support above the PEEP, a back-up mandatory respiratory rate, and FiO_2.

With an appropriately fitting mask and patient-ventilator synchrony, BiPAP can effectively pro-

vide airway pressure, improve oxygenation, and unload fatigued respiratory muscles in children with acute respiratory failure. BiPAP is generally well tolerated, and its low-risk profile makes it an attractive first-line support therapy. Care should be taken, however, in patients with persistently low PF ratio, low SF ratio, and elevated respiratory rates, as these have all been associated with BiPAP failure [73–75].

Neurally Adjusted Ventilatory Assist (NAVA)

Neurally adjusted ventilatory assist (NAVA) is a relatively recent modality of mechanical ventilation. It is a pressure-assisted mode that utilizes the electrical activity of the diaphragm (EAdi) to trigger a spontaneous assisted breath and deliver inspiratory pressure in response to that activity. NAVA detects this electrical activity through eight electromyogram detectors located at the end of special nasogastric or orogastric tube. The distal end of this tube is usually placed at the end of the esophagus near the gastroesophageal junction where the trunk of the phrenic nerve meets the diaphragmatic muscle.

NAVA has been successfully used in acute respiratory failure in intubated children and adults on mechanical ventilation. NAVA has been shown to improve patient synchrony with the ventilator, decrease need for sedation, and possibly reduce PICU length of stay [76–83].

In a prospective randomized cross-over study, Vignaux et al. [84] reported improved patient-ventilator synchrony in infants and children with ARF receiving NIV while on NAVA. In a more recent prospective study, Baudin et al. [77] described the use of NIV-NAVA in 11 infants less than 6 months of age with ARF. The study showed that the asynchrony index was significantly lower in NAVA mode compared to pressure-assist control mode (3 ± 3% and 38 ± 21% respectively $P < 0.0001$). There were more ineffective breathing efforts in pressure control mode than NAVA as well (21.8 ± 16.5 vs. 0.54 ± 1.5 events/minute, respectively). More studies are needed to evaluate the use on NIV-NAVA in PARDS.

Negative Pressure Ventilation (NPV)

NPV was the first form of ventilator used to treat respiratory failure using the "iron lung." Recently, there has been a renewed interest in the use of NPV in children with ARF. To date, there are few reports, mostly case series and case reports, describing the use of NPV in pediatric population with acute respiratory failure due to different etiologies [22, 85–93].

NPV using a cuirass works by exposing the surface of the chest wall to subatmospheric (negative) pressures resulting in recruitment of the alveoli and expansion of the lungs (Figs. 9.1, 9.2, and 9.3). The negative pressure can be maintained at a constant level throughout the respiratory cycle, resulting in Continuous NEgative extra thoracic Pressure – CNEP mode, or the inspiratory and expiratory phases can be fully controlled with biphasic cuirass ventilation at a mandatory rate by modifying the negativity of the air pressure – Control mode [22, 90].

In an animal study comparing NPV and PPV using surfactant-depleted rabbits, Grasso et al. [87] showed that NPV was associated with better gas exchange, greater lung perfusion, better lung expansion, and less lung injury.

Shah et al. and colleagues [85] studied the effectiveness of NPV or CPAP compared to conventional mechanical ventilation in children with acute respiratory failure. In this Cochrane review, there was some evidence of lower need for intubation, and shorter hospital stay with the use of

Fig. 9.1 NPV cuirass ventilator

Fig. 9.2 NPV cuirass ventilator

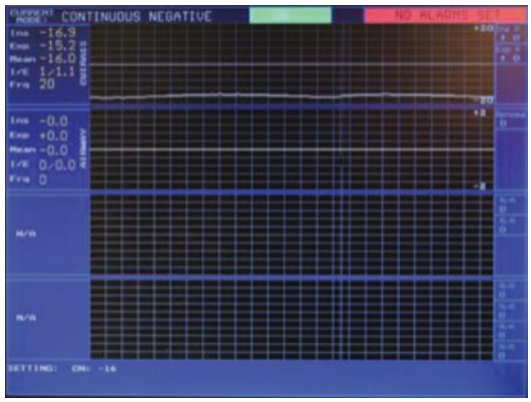

Fig. 9.3 NPV cuirass ventilator: Screen shot, Continuous NEgative Pressure (CNEP) mode

NPV. The study concluded that there is a need for well-designed, controlled randomized trials to assess the NPV safety, role in acute respiratory failure, and outcomes. In 2017, a large retrospective chart review study described the single-center use of NPV in pediatric patients 2 month to 22 years of age with ARF [22]. Out of 233 patients who were supported with NPV, 163 (70%) had resolution of ARF while receiving NPV, and 63 subjects (nonresponders) required change to PPV modalities including intubation. NPV cuirass was removed from five patients due to complications (gastroesophageal reflux, hypothermia, and skin bruising; no sequalae) and from two other patients for transport purposes. Viral bronchiolitis was the most common diagnosis (70% of the cases). There was 28% reduction of intubation rate during the study period compared to the prior 3 years, but did not reach statistical significance. NPV use via cuirass may be suitable for children with facial deformities, facial burns, claustrophobia, severe agitation, and those with oronasal secretion burden (Table 9.4).

Table 9.4 Advantages, disadvantages, and complications of NPV

Advantages
Avoidance of risks of positive pressure ventilation (e.g., barotrauma, decreased venous return)
Comfort
Ability to speak
Access to oral and nasal secretions
Less need for sedation
Suitable for patients with facial trauma/burns
Reduced risk of aspiration
Disadvantages
Cannot be used in patients over 170 kg
Cuirass fitting can be a challenge in patients under 4 kg
Requires a patent/viable airway
Contraindications
Burns on the chest wall or abdominal wall
Thoracic and abdominal surgery
Chest and abdominal trauma – flail chest
Respiratory arrest
Cardiac arrest
Hemodynamic instability (shock)
Severe PARDS
Need for immediate intubation
Rapid progression of neuromuscular illness
Rapid worsening of neurological illness
Inability to clear oropharyngeal secretions
Impaired gag and cough reflex

Similar to other modalities of NIV, NPV can be considered for "at risk for PARDS" patients as well as patients with mild PARDS. Further studies are needed to compare NIV and NPPV, to evaluate the role of NIV in mild-to-moderate PARDS, and to assess outcomes (e.g., rate of intubation, complications).

Patient Monitoring While Receiving NIV

Pediatric patients requiring NIV for acute respiratory failure should be admitted to the PICU. However, there is some evidence to suggest that HFNC, and possibly nasal CPAP, are safely delivered on a general inpatient ward, primarily in patients with viral bronchiolitis. Monitoring of heart

rate, respiratory rate, continuous pulse oximetry (SpO_2), and noninvasive blood pressure is necessary. Although the optimal fluid management strategy in these patients is yet to be defined, current consensus guidelines recommend judicious use of fluids to maintain appropriate intravascular volume. Hemodynamic monitoring during NIV in PARDS is important to appropriately guide the fluid management therapy and avoid fluid overload. Monitoring urine output, capillary refill, and peripheral pulses is recommended [26].

The Pediatric Acute Lung Injury Consensus Conference (PALICC) recommended that Oxygenation index (OI = FiO_2 × Mean Airway Pressure × 100)/PaO_2) is the preferred metric to define PARDS in patients supported by IMV, while PaO_2/FiO_2 ratio (PF ratio) is the primary metric to define PARDS in patients with NIV receiving CPAP or BiPAP with a minimal CPAP level of 5 cmH_2O.

Oxygen Saturation Index (OSI = FiO_2 × Mean Airway Pressure × 100)/SpO_2) and Oxygen saturation/FiO_2 ratio (SF ratio) are recommended to use for monitoring in cases where PaO_2 value cannot be obtained. Oxygen supplementation must be titrated to achieve SpO_2 88 to ≤97%. Children requiring full mask CPAP or BiPAP ≥5 cmH_2O meet PALICC PARDS criteria when PF ratio ≤ 300, or Oxygen saturation/FiO_2 ratio ≤ 264 [26]. There is no severity stratification of OI and OSI during noninvasive mechanical ventilation, but OI > 4 and OSI > 5 are considered abnormal.

Blood gas measurements (arterial, venous, capillary) add further information on gas exchange, help the critical care providers to better assess the clinical status, and provide guidance to escalate therapy as needed. There is no consistency in the literature to support the timing and frequency of sampling, but oxygenation indices and other gas exchange metrics should be evaluated at onset of PARDS, initiation of NIV support, within 24 hours of initiation, and serially at the discretion of the critical care providers determined by the patient's clinical progression.

Special attention should be given to avoid nasal and facial pressure sores [94, 95]. Initially by avoiding fitting the interface too tightly, followed by implementing safety practices with frequent checking of the pressure areas, adjusting the interface accordingly, and by judicious use of gel pads and cushions to protect the skin.

Need for Sedation During NIV

To be physiologically beneficial, all forms of NIV require patient-interface tolerance and synchrony. While most patients tolerate treatment with nasal CPAP and HFNC, many younger children and infants may have difficulties in enduring face mask positive pressure [4] and NPV [22]. Agitation can precipitate patient-ventilator asynchrony, diminishing its effectiveness and leading to barotrauma. Pharmacologic sedatives and anxiolytics can be safe and effective, provided the patient anxiety is not due to impending respiratory failure requiring immediate invasive mechanical ventilation.

The ideal sedative should provide appropriate anxiolysis without affecting respiratory drive, airway tone, or hemodynamics. Midazolam has been used successfully in children with status asthmaticus [96], and infants with hypoxemic respiratory failure [97], although concerns regarding hemodynamic stability, airway tone, respiratory drive, and long-term neurologic morbidity may limit use.

Dexmedetomidine use has experienced an increase in popularity. A recent single-center study described 202 children with acute respiratory failure due predominantly to status asthmaticus and bronchiolitis treated with NIV (defined as CPAP, BiPAP, HFNC) and concurrent dexmedetomidine infusion. Most received dexmedetomidine as a single agent, with 83% of included patients achieving adequate sedation. The majority of patients did well, with 98% successfully weaned off NIV without need for intubation. However, clinically significant events included bradycardia (13%), hypotension (20%), and hypopnea (5%), while a one-month-old infant with bronchiolitis required CPR and vasoactive medications following apnea and bradycardic arrest during dexmedetomidine infusion. Dexmedetomidine is an alpha-2 adrenergic agonist with minimal effects on respiratory

drive, thus making it an attractive sedative agent [98], but the negative effects on hemodynamics, including decreased catecholamine release [99], decreased cardiac index, bradycardia, and hypotension, should be carefully considered when initiating this medication. Risk of withdrawal must also be considered with dexmedetomidine use, [100, 101] although this is generally only of consequence following prolonged infusions [102].

Failure of Noninvasive Ventilation

Some children clearly require immediate intubation and IMV, and for these, NIV is contraindicated. Many children benefit from NIV and recover from their acute lung injury. There are concerns, however, that application of NIV may mask progressive worsening of respiratory failure, delay the timing of intubation, and increase the risk of associated complications, including death [103, 104]. Furthermore, the failure rate for NIV is variable, and likely dependent upon the underlying disease process and the chosen mode of ventilation.

Evidence in support of NIV, including reduced intubation rates, is best established in infants receiving CPAP or HFNC with bronchiolitis [33, 34, 105, 106]. Studies demonstrating successful treatment of bronchiolitis with either modality show improvements in respiratory effort as measured by vital signs, clinical respiratory scores, and gas exchange [34, 107–109]. Clear recommendations for use of NIV in other forms of pediatric acute hypoxemic respiratory embarrassment, including PARDS, are lacking [110]. For infants with bronchiolitis, failure rate with use of CPAP and HFNC can be as low as <3%, [34], but for children with PARDS, it is as high as 50% [2]. Understanding which patients are unlikely to be successful NIV candidates, and indicators of failure, are especially important as use of NIV in the pediatric population continues to increase [5, 28].

Many children with PARDS, those at risk for PARDS, or those with acute lung injury/acute hypoxemic respiratory failure ultimately require IMV despite initial treatment with NIV [17]. A recent international, multicenter, prospective observational study including pediatric patients with PARDS found that of the 708 included patients, 22.6% received NIV as first-line respiratory support, and half of these patients (n = 80) ultimately required IMV. These children who failed first-line therapy with NIV had higher rates of PICU mortality and 90-day mortality compared to those children successfully managed with NIV [2]. In this cohort, more severe hypoxemia at PARDS diagnosis was strongly associated with subsequent intubation.

In several single-center studies, NIV failure was associated with higher severity of illness at admission, number of organ failures, nonrespiratory primary diagnosis, higher oxygen requirement, and higher respiratory rate [73, 74, 111, 112].

Summary

With appropriate patient selection, NIV is a viable alternative to IMV in children with acute respiratory failure and mild PARDS. Despite the scarce data to support NIV use in moderate to severe PARDS, clinical evidence of its usefulness has led to its increasing use in critical care units over the last two decades. Close monitoring is important to assess disease progression, avoid delaying appropriate therapy, and reduce potential complications. Intubation should be considered in patients receiving NIV who fail to show clinical improvement or have signs and symptoms of worsening disease process within few hours of NIV implementation.

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10 Ancillary Pulmonary Treatments for Pediatric Acute Respiratory Distress Syndrome

Andrew L. Beardsley

Prone Position

The acute respiratory distress syndrome (ARDS) is characterized by heterogeneous lung disease with extensive dependent atelectasis (Fig. 10.1). Gas exchange may be improved by several potential mechanisms while in the prone position. Patients in the prone position have altered distribution of alveolar ventilation and redistribution of pulmonary blood flow. The net effect of these changes is an improved matching of local ventilation and perfusion and reduction in regions with a low ventilation/perfusion ratio. In addition, compression of the lungs by the heart and by the abdominal contents is lowered in the prone position. Homogenization of intrathoracic pressure, in part due to the compliant anterior ribs being compressed by the somewhat rigid patient bed, also improves lung mechanics. Apart from physiologic changes in gas exchange, another potential therapeutic benefit is enhanced secretion clearance by alteration of the orientation of the large airways [1].

Placing adults with acute hypoxemic respiratory failure in the prone position has been reported to improve oxygenation as early as 1976 [2]. Since then, many studies have confirmed improved oxygenation, but meaningful outcomes such as improved survival and ventilator-free days have been inconsistently reported. The prone position was first reported to improve oxygenation in a case series of children with pediatric ARDS (PARDS) in 1994. Children in this report had improved oxygenation after spending only 30 minutes in the prone position.

In the early 2000s, prone positioning became widely studied as a potential therapy for PARDS. Curley, Kornecki, Bruno, and Casado-Flores all published studies of children with PARDS [3–6]. These studies were all small, single-center trials with various study designs, including differing inclusion criteria and protocols for use of prone position. In all of them, children served as their own controls, comparing oxygenation markers between prone and supine positions. They all showed consistent findings of improved oxygenation with the use of the prone position. Children in these studies who were maintained in the prone position for 8–12 hour cycles had a response rate ranging from 78% to 90% [3, 4, 6]. Another consistent finding in these studies was the safety of prone positioning, demonstrating extremely low rates of adverse events in placing patients in the prone position. Additionally, no specialized equipment or drug is required, making the cost-benefit ratio in the use of prone position highly favorable.

Because of this, a large multicenter randomized controlled trial was undertaken by Curley

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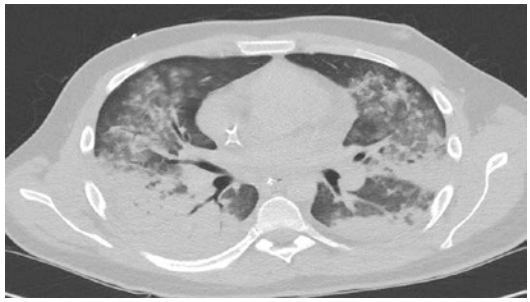

Fig. 10.1 Computed tomography image of a patient with pediatric acute respiratory distress syndrome, demonstrating heterogeneous lung disease with dependent atelectasis

et al. [7]. In this study, patients with acute lung injury, defined by PaO2/FiO2 ratio less than 300 mm Hg, were randomized within 48 hours to standard supine positioning or prone positioning for 20 hours daily. Similar to the previous smaller trials, 90% of prone patients in this trial responded with improved oxygenation. Despite this, the study was stopped on interim analysis due to finding that outcomes did not differ between study groups. Ventilator-free days, mortality, and cognitive function, among other outcomes assessed, were not improved by use of the prone position despite its apparent effect on improved oxygenation. Of note, use of the prone position was demonstrated to be generally safe in this relatively large trial [8].

In contrast to studies of pediatric patients, some trials of adult patients have demonstrated improved outcomes in addition to improved oxygenation. A 2008 meta-analysis of 1559 patients with acute hypoxemic respiratory failure again showed that prone position is associated with improved oxygenation, but not with improved outcomes such as improved survival [9]. However, in a follow-up subanalysis of 555 patients with severe hypoxemia, defined as a PaO2/FiO2 ratio less than 100 mm Hg, a survival benefit was demonstrated [10].

In 2013, Guérin et al. reported the results of the largest multicenter randomized controlled trial of prone positioning in adults with severe ARDS, known as the PROning SEVere ARDS patients (PROSEVA) trial [11]. Severe disease was defined by PaO2/FiO2 ratio less than 150 mm Hg with an FiO2 of at least 0.60 and a PEEP greater than or equal to 5 cm H2O. Four hundred sixty-six patients were randomized to standard supine position or prone position for 16 hours daily. All-cause 28-day mortality in patients randomized to the prone arm was 16%, compared to 33% in patients randomized to the supine arm (hazard ratio, 0.39; 95% CI, 0.25–0.63; $p < 0.001$). This 50% relative risk reduction in mortality suggests a massive potential benefit in adults with the most severe disease. Extrapolation of this result to pediatric patients is questionable and may be answered by the ongoing PROSPECT study. Even without such data, experts from the Pediatric Acute Lung Injury Consensus Conference (PALICC) stated that, while prone positioning "cannot be recommended as routine therapy in PARDS…it should be considered an option in cases of severe PARDS" [19].

The optimal protocol for prone positioning to maximize its benefit is unknown. Improvements in oxygenation are seen quickly. However, a retrospective analysis in 2003 showed oxygenation was improved more in patients who were kept in the prone position for a prolonged period of 18–24 hours compared to a short period of 6–10 hours. Additionally, the improvement in oxygenation was more stable after 12 hours in the prone position [12]. The PROSEVA trial demonstrated improved outcomes with 16 hours per day in the prone position, while the study in pediatric patients by Curley et al. showed improved oxygenation but not improved outcomes using 20 hours per day in the prone position. The difference in the results of these studies is likely due to differences in inclusion criteria (only severe patients in the PROSEVA trial), or differences between adult and pediatric patients, and/or differences in concurrent therapies, but duration of the use of prone positioning is theoretically a factor.

Another consideration in use of the prone position is the way in which the patient is turned. Specialized beds are available for use in adults that can be used in larger pediatric patients. These beds use continuous rotation of the prone patient from side to side up to 60° in either direction,

termed continuous rotational therapy. While not extensively studied, this method shows comparable improvements in oxygenation to prone positioning in a standard bed, but may have adverse hemodynamic effects [13]. Care of larger patients in these beds may be perceived to be easier; however, they may substantially increase cost and expertise required in order to utilize the prone position. Of note, patients in the PROSEVA trial were placed in the prone position in their standard ICU bed.

In summary, prone positioning clearly can improve oxygenation in a vast majority of patients with acute hypoxemic respiratory failure. Improvements in other outcomes, such as improved survival, are questionable in pediatric patients. Patients with severe PARDS may have improved benefits compared to those with less severe disease, and further study is warranted (and ongoing) in this population. Due to the highly favorable safety record of prone position in prior trials, fear for patient safety or patient care limitations should not limit its use. While prone positioning cannot be recommended as standard of care, its use should be considered in cases of severe PARDS, especially given the low cost and potential improvements in patients with severe disease.

Pulmonary Vasodilators

The vascular endothelium synthesizes nitric oxide (NO) by the action of NO synthase on the precursor L-arginine. NO diffuses into an adjacent vascular smooth muscle cell, where it directly stimulates soluble guanylate cyclase (sGC). NO has local action only, as it undergoes rapid oxidative inactivation in the serum. Guanylate triphosphate is converted to cyclic guanylate monophosphate (cGMP) by sGC, which exerts a vasodilatory effect by indirectly blocking calcium influx into the smooth muscle cytoplasm. cGMP is inactivated by phosphodiesterase-5 (PDE5).

Prostaglandin I2 (PGI2) is also synthesized in the vascular endothelium, via the arachidonic acid – cyclooxygenase pathway. It then activates adenylate cyclase on the smooth muscle cell membrane, converting adenylate triphosphate to cyclic adenylate monophosphate (cAMP). cAMP acts through protein kinase A to lead to smooth muscle relaxation. cAMP is inactivated by phosphodiesterase-3 (PDE3).

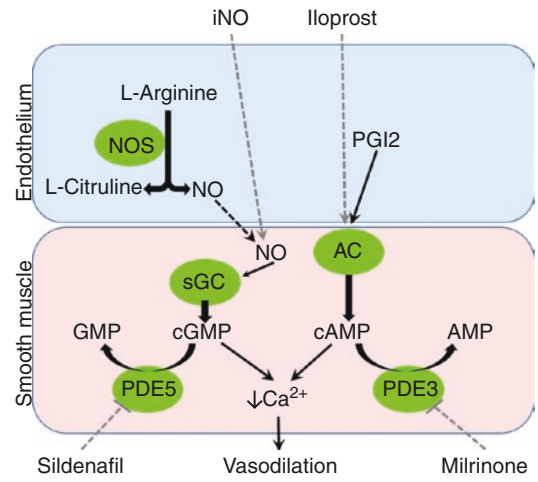

Fig. 10.2 Physiology and pharmacology of pulmonary vasodilation. *iNO* inhaled nitric oxide, *NO* nitric oxide, *NOS* nitric oxide synthase, *PGI2* prostaglandin I2, *AC* adenylate cyclase, *sGC* soluble guanylate cyclase, *cGMP* cyclic guanylate monophosphate, *cAMP* cyclic adenosine monophosphate, *PDE5* phosphodiesterase 5, *PDE3* phosphodiesterase 3

Various drugs are available to influence pulmonary smooth muscle relaxation (Fig. 10.2). Inhaled nitric oxide (iNO) directly supplies NO to the vascular endothelium. Similarly, inhaled prostaglandin I2 (Iloprost) supplies PGI2. Sildenafil, tadalafil, and vardenafil inhibit PDE5, while milrinone, among others, inhibits PDE3. The use of some of these drugs has been applied to the treatment of acute respiratory distress syndrome.

Inhaled Nitric Oxide

Inhaled nitric oxide (iNO) has been considered a potentially ideal pulmonary vasodilator in use for PARDS due to its local action in well-ventilated portions of the lung. Since it is inhaled, it will exert maximal effect in the best ventilated regions of the lung, and little-to-no effect in poorly venti-

lated regions. This will cause blood to shunt away from poorly ventilation regions to well-ventilated regions, and ultimately improve ventilation-perfusion matching. The net effect of this is overall improved gas exchange, leading to improved oxygenation. Therefore, iNO has been used in PARDS to improve oxygenation, with the hope of ultimately having a favorable affect on the outcome of the disease. Standard dosing for iNO is up to 20 parts per million (ppm), although doses as low as 1 ppm may be effective in improving oxygenation [13, 14].

After several case series reported rapid improvements in oxygenation with the use of iNO in patients with PARDS, three randomized controlled trials were performed. In 1997, Day et al. demonstrated improvements in oxygenation compared to control in a small study, which was not designed to assess mortality [15]. Then, in 1999, Dobyns et al. reported a larger, multicenter randomized controlled trial of children with severe acute hypoxemic respiratory failure (with oxygenation index >15) [16]. One hundred eight children were randomized to iNO at 10 ppm or a placebo-control. This trial confirmed the beneficial effect of iNO on oxygenation, but survival did not differ between groups. Finally, Ibrahim et al. reported in 2007 a smaller trial of 32 patients with severe PARDS randomized to iNO in prone position, iNO in supine position, or without iNO in prone position. This again confirmed a benefit on oxygenation but not in other outcomes such as mortality. More recently, Bronicki et al. reported on 55 children from 9 centers with PARDS and showed that ECMO-free survival was more common in the treated group (92% vs. 52%, $p < 0.01$), though overall survival was not.

A Cochrane meta-analysis was published in 2011 including pediatric and adult patients [17]. Improved oxygenation was confirmed, with no improvement in survival, duration of mechanical ventilation, length of ICU stay, or any other outcome. A concerning finding of increased incidence of renal impairment was found in patients treated with iNO.

Despite the improvement in oxygenation, there is no conclusive evidence to support the use of iNO for patients with PARDS given the lack of consistent improvement in patient outcomes. However, as indicated in a consensus statement from the European Society for Pediatric and Neonatal Intensive Care, its use can be considered in patients with pulmonary hypertension or severe right ventricular dysfunction [18]. iNO use may be beneficial in this population not solely due to its effect on oxygenation, but rather its effect on decreasing pulmonary vascular resistance and therefore improving cardiac output and/or decreasing right ventricular strain. The benefit of iNO on mortality remains unproven in this scenario; however, there is sufficient theoretical benefit to consider its use. More research is needed to further guide therapy decisions in patients with PARDS and pulmonary hypertension or severe right ventricular dysfunction.

As extracorporeal membrane oxygenation (ECMO) increases in use in severe PARDS, the role of iNO to rescue from ECMO or bridge to ECMO remains unstudied. Because of the lack of evidence, experts from PALICC concluded that iNO could be considered in severe PARDS as a rescue from or bridge to ECMO [19].

Because of the considerable cost and potential toxicities associated with iNO use, a cost-benefit analysis should be carefully considered before initiating therapy. Once used, an assessment of clinical benefit should be undertaken, and steps should be made to wean and discontinue it as soon as possible [19]. Renal function should be carefully monitored especially with concurrent use of nephrotoxins. While methemoglobinemia is a potential concern at very high doses of iNO, at standard doses of iNO less than or equal to 20 ppm, it is a rare occurrence and routine lab monitoring for this toxicity with co-oxymetry may not be necessary [20].

Inhaled Prostaglandin Therapy

Inhaled PGI2 can be considered similarly to iNO [21]. As stated above, PGI2 causes pulmonary vasodilation, although via a different pathway from iNO. Since it is inhaled, it has many of the same potential benefits of improving ventilation-perfusion matching in patients with PARDS. It

has not been studied sufficiently to make claims on outcomes, but there is no reason to believe it would differ substantially from iNO. While the cost of its use may be favorable to the cost of using iNO, there is much less experience with its use. At this time, its use in the management of PARDS is not recommended [19]. Until further evidence is available, inhaled PGI2 could be considered to likely have similar effects to iNO.

Systemic Pulmonary Vasodilators

Systemic medications such as PGE5 inhibitors, PGE3 inhibitors, and intravenous prostaglandins can be used as pulmonary vasodilators, but should not be considered specifically to treat PARDS. Their use for pulmonary hypertension or severe right ventricular dysfunction may be warranted based on the management strategies for those conditions. However, in PARDS, the widespread pulmonary vasodilation in the setting of heterogeneous ventilation has the potential to worsen ventilation-perfusion matching and worsen, or at least not improve, oxygenation [22].

Inflammatory Modulation

Glucocorticoids

Glucocorticoids are drugs which exert various actions through binding with the glucocorticoid receptor, having a similar effect to the naturally occurring hormone cortisol. Commonly used glucocorticoids include hydrocortisone, prednisone, methylprednisolone, and dexamethasone, among others. They are commonly used in many aspects in medical care as broad-spectrum anti-inflammatory drugs. Their use in PARDS has been considered because of the tremendous inflammation present in the disease.

The systemic use of glucocorticoids has been studied more in adults with ARDS than in children. Two meta-analyses have been published using different methodologies to evaluate the current available evidence in trials of glucocorticoids for adults with ARDS [23, 24]. In the first, no definitive role of glucocorticoids for ARDS was established [23]. In the second, an association between glucocorticoid use and improved survival was only found when combining randomized controlled trials (four trials, $n = 341$) with cohort studies (five studies, $n = 307$). With this full analysis, glucocorticoid use had a relative risk of mortality of 0.62 (95% CI, 0.43–0.91) [24]. However, combining the various study types into one analysis introduces more risk for confounding or bias in the results. Therefore, there is still no clear determination of the role of glucocorticoids for adults with ARDS. Evidence quality for glucocorticoid use in pediatric patients is poor, consisting only of case reports and case series [19].

Treatment protocols studied have varied by the drug used, the dose, the duration, the use of dose tapering, and the timing during the disease process. This variation further complicates the analysis of the efficacy of glucocorticoids for ARDS [24]. While meta-regression analysis of these types of variations in treatment strategy did not detect differing efficacy, power was insufficient to detect small or even modest effects in many of the variables.

Further study is certainly needed to determine the treatment effect as well as optimal dosing strategies and patient selection for glucocorticoid use in PARDS, and their routine use is not recommended [19]. If used, a low dose (equivalent of methylprednisolone 2 mg/kg/day) and short duration (total 7 days of therapy with or without a dose taper) may be sufficient to achieve the potential benefit while minimizing potential adverse effects.

Etanercept

Tumor necrosis factor-α (TNF-α) is an important pro-inflammatory mediator in many diseases, including PARDS. The idiopathic pulmonary syndrome (IPS) in patients following hematopoietic stem cell transplant is one disease in which high levels of TNF-α are found in the serum and broncho-alveolar lavage fluid. Because of this finding, interest was generated for the potential use of etan-

ercept (a soluble TNF-α-binding protein, which inactivates TNF-α) in IPS. In uncontrolled trials, a combination of etanercept and corticosteroids has been associated with improved survival in patients with IPS compared to historic controls [25, 26]. Response rates were highest when the therapy was initiated before mechanical ventilation was initiated, indicating that timing of inflammatory mediation has an important role in its efficacy. A randomized controlled trial of this therapy in adults with IPS showed a 17% absolute increase in survival, but this did not reach statistical significance as the trial was unfortunately stopped early due to slow subject accrual [27]. The available evidence suggests etanercept is a promising therapy for this specific syndrome. This and other methods of specific immunomodulation could potentially impact the course of PARDS in other patient populations as well, but the utility remains to be determined and this use should currently be reserved for the research setting.

Exogenous Surfactant

The use of exogenous surfactant in the neonatal respiratory distress syndrome has revolutionized the care of babies born extremely prematurely. As its use has become standard of care in this population, outcomes for these patients have dramatically improved. Because of this observation, it is tempting to try to extrapolate this strategy to older children with severe hypoxic respiratory failure.

While neonatal respiratory distress syndrome is characterized by surfactant deficiency due to immature type 2 alveolar cells not producing it, the acute respiratory distress syndrome may have qualitative defects of surfactant due to the inflammatory pathophysiology [28–30]. After case reports and case series of surfactant use in PARDS showed promise for the benefit of this therapy, surfactant use was studied extensively in clinical trials. An early open-label, uncontrolled observational trial of calf lung surfactant extract (calfactant) conducted by Willson et al. in 1996 demonstrated a dramatic improvement in oxygenation in children with acute hypoxemic respiratory failure [31]. While this was an uncontrolled trial, the mortality among the 29 subjects was only 14%, which was better than survival estimates.

Subsequently, several small randomized controlled trials were conducted on children with respiratory failure. In two trials of surfactant use in children with bronchiolitis requiring invasive mechanical ventilation, Luchetti et all showed that porcine surfactant (curosurf) use improved oxygenation and ventilator parameters, and shortened ventilator durations and PICU stays [32, 33]. All patients in both of these trials survived their illness. In a more severely ill cohort of patients with acute hypoxemic respiratory failure, Willson conducted a prospective randomized controlled trial of 42 subjects, also showing improved oxygenation and shortened ventilator duration and PICU length of stay [34]. Finally, a multicenter trial of 35 children conducted by Möller et al. again showed improvement in oxygenation with surfactant use, along with a non-significant trend toward decreased mortality [35].

The promising findings in small randomized controlled trials led to the largest multicenter randomized placebo-controlled trial on surfactant use for PARDS to date [36]. For this trial, 153 pediatric patients with acute hypoxic respiratory failure were randomized to receive calfactant versus air placebo. As in previous studies, patients in the experimental surfactant arm demonstrated a significant improvement in oxygenation after treatment. However, this study revealed no difference in the primary outcome, ventilator-free days. Mortality was lower in surfactant-treated children (19% vs. 36%, $p = 0.03$), but the difference was not significant (OR for survival, 2.11; 95% CI, 0.93–4.79) after adjusting for immunocompromised state, which was unequally distributed between groups.

This led to the hypothesis that surfactant use in the immunocompromised patient would have an improvement in mortality. Unfortunately, a study to address this question suffered from poor enrollment [37]. In this study of children and young adults (aged 18 months to 25 years) with leukemia or lymphoma having undergone hematopoietic stem cell transplantation, and now suffering from severe acute hypoxic respiratory failure, 43 subjects were enrolled from 17 PICUs. There were no differences in PICU survival, oxy-

genation, ventilator-free days, or functional outcomes between treatment arms.

Additionally, another study was conducted including both adult and pediatric patients with acute respiratory distress syndrome [38]. In this trial, a different, double-concentrated formulation of calf's lung surfactant was used. In this trial, only patients with direct lung injury were included (i.e., lung injury originating on the alveolar side of the alveolar-capillary membrane). Both adult and pediatric arms of this study were terminated after interim analysis demonstrated no effect on mortality. Also, this study failed to show an improvement in oxygenation, as had been shown in prior trials.

This result calls to question the potential importance of the surfactant formulation on its efficacy. While the double concentration of surfactant was chosen to decrease the volume necessary to instill into the lungs of larger pediatric and adult patients, this may have had an unintended adverse effect on the effective distribution of surfactant throughout the extremely large surface area of the mature lung.

Although surfactant is perhaps the most extensively studied specific ancillary pulmonary treatment for PARDS, its role is still unclear. Early successes have been frustrated by more recent failures of clinical trials to show a benefit of surfactant use. It is quite possible that specific patient populations would benefit from the right formulation of exogenous surfactant, delivered in the appropriate way. Further study is warranted to evaluate specific populations, dosing forms, and delivery regimens. For now, exogenous surfactant use is not recommended for routine use in PARDS [19].

Pulmonary Hygiene

Endotracheal Suctioning

Maintenance of a patent endotracheal tube is of obvious importance in the care of patients with PARDS requiring invasive mechanical ventilation. However, methods to clear pulmonary secretions from the airway are variable and likely based more on institutional culture and routine practice than on medical evidence.

While clearance of the airway is crucial, care must be taken to avoid the unintended consequence of alveolar derecruitment caused from application of highly negative pressures within the airway or from disruption of continuous positive pressure ventilation. Because of the lung volume loss associated with ventilator circuit disruption, closed suctioning systems should be used [39]. Also, deep suctioning with uncontrolled pressures should be avoided, as this is associated with significant risk for lung collapse [40].

The utility and risks of lavage to aid in secretion clearance are also undetermined. Saline lavage may at times be necessary for removal of thick secretions, but its routine use is not recommended [41]. Additionally, routine periodic suctioning of the endotracheal tube may cause more harm than benefit, and suctioning should be performed only when secretions are present at the most shallow depth necessary [19]. Attention to avoid excessive trauma and bleeding is also recommended.

Chest Physiotherapy

There are a myriad of mechanisms available that have the goal of aiding in pulmonary secretion clearance to maintain patent lower airways and improve alveolar recruitment. These include hand percussion and various devises that provide vibration, intrapulmonary percussive ventilation, chest wall oscillation, and rapidly alternating pressures, among other mechanisms. There are no trials evaluating these various mechanisms in PARDS. Decisions to apply chest physiotherapy in the presence of atelectasis must be made after weighing the potential benefit against the risks and significant costs. Routine prophylactic use against the development of atelectasis in the PARDS patient is not warranted.

Nebulized Therapies

The nebulization of medications to aid in pulmonary secretion clearance is common practice in the PICU, but is not supported by medical evidence. The use of N-acetylcysteine, dornase alfa,

and hypertonic 3% saline lacks sufficient evidence to promote routine use in PARDS. The prophylactic use of 3% saline in mechanically ventilated children was associated with no difference in duration of ventilation or mechanical ventilation parameters taken before and after treatment, compared to placebo [42]. As with chest physiotherapy techniques, nebulization of medications to aid in secretion clearance and to prevent lower airway obstruction and atelectasis is not routinely warranted in PARDS. Individual use must weigh the potential benefit with the risks and costs of these therapies.

β-agonist therapy has also not been studied specifically in PARDS, but studies are available in adult patients with acute lung injury. A meta-analysis of these studies showed an association with β-agonist treatment and increased morbidities such as reduced mechanical ventilation-free days and organ failure-free days [43]. Therefore, β-agonist therapy is not recommended for use in PARDS outside of a specific alternative indication.

Bronchoscopy

The diagnostic and therapeutic application of bronchoscopy in PARDS is also not well defined in the medical literature. It may be considered in a case-by-case basis to obtain bronchoscopic broncho-alveolar lavage samples for their diagnostic utility. The therapeutic application for clearance of secretions from large airways (with or without lavage) may also be considered. In cases of persistent lobar atelectasis, this method to clear potential mucus plugs of the large airways may be warranted after consideration of risks and benefits. Further evidence is needed to determine the optimal utility of bronchoscopy for both diagnostic and therapeutic reasons.

Bronchoscopy has also been used to instill various medications, such as dornase alfa, directly to the airways. Again, evidence is limited to few case reports, and routine use of this treatment strategy is not recommended. Finally, bronchoscopy has also been reported as a modality to deliver surfactant [44, 45]. Further study is warranted to investigate this strategy, which may improve the distribution of surfactant in larger patients.

Stem Cell Therapy

Endothelial cell damage of the pulmonary capillaries is one of the inflammatory hallmarks of ARDS. The recruitment of circulating endothelial progenitor cells, which leave the bone marrow into the blood stream and can reconstitute the endothelium, may be one important step in recovery from ARDS. Because of this, cell-based therapies have become a novel area of research in developing new treatments for ARDS [46]. Currently, animal studies are showing the utility of both intravenous and endotracheal administration of mesenchymal stem cells or endothelial progenitor cells in animal models of ARDS [47–49]. The future development of these therapies may be an exciting new frontier in the treatment of PARDS.

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11 Analgesia, Sedation, and Neuromuscular Blockade in PARDS

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Introduction

The use of sedation is a very important component in the treatment of pediatric acute respiratory distress syndrome (PARDS) in the PICU. The child with ARDS is usually intubated, sedated, and ventilated for a period that may extend for several weeks. As the child is supported during this acute phase of respiratory failure, the child should receive hypnosis and analgesia. There are several reasons a child may benefit from sedation and analgesia. Use of these medications allows for the invasive instruments (endotracheal tube, lines, etc.) that are required, both during their initial placement and continued use, both of which are noxious stimuli. The child may be critically dependent on this instrumentation and any untoward excessive movement could cause a loss or dysfunction of these life-sustaining supports [1]. Limiting the child's work of breathing may optimize oxygen delivery to other tissues, and limiting ventilator asynchrony can improve gas exchange. Other benefits include the prevention of unpleasant ICU memories and the control of the neuroendocrine stress response.

It is also important to avoid oversedation, which may result in cardiovascular compromise and has been associated with a prolonged ICU stay. As such, sedation assessment and possibly sedation protocols may have an important place in the management of children with ARDS. After the sedation is no longer required, it is important to consider the risk of drug withdrawal, whose management is also vitally important for patient comfort and safety as they are weaning from ventilation support. Delirium and post-ICU psychological disorders are also appreciated as a potential serious cause of morbidity to these patients.

There are several classes of sedation agents and analgesics available for the intensivist to use in the PICU. It is important to note that the majority of these drugs are not actually FDA approved for prolonged pediatric sedation. The majority of these drugs come from the anesthesia world, where their use is most often for short periods only; so, data pertaining to efficacy and complications may not perfectly transfer to the ICU. The recent concerns for anesthesia adversely affecting the brain development of young children should also be a concern for the pediatric intensivist.

The recent PALICC consensus statement for PARDS [2] included several important "strong agreement" recommendations concerning sedation. These included (1) analgesia and sedation should be targeted but minimal, using

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validated sedation and pain scores and goal-directed protocols, and (2) individualized weaning plans should be guided by objective assessments and scores.

Ventilator Strategies and Sedation

Several different respiratory support strategies are used in PARDS and this can have effects on the type of sedation required. Permissive hypercapnia is often used and may increase ventilator asynchrony and patient discomfort [3]. The use of opiates or deep sedation to reduce the respiratory drive may ameliorate this risk. Inverse ratio ventilation strategies may be uncomfortable and require a deeper level of sedation [4]. However, opiate and benzodiazepine requirements have been reported as less in APRV patients compared to a conventional low-volume ventilation strategy [5]. Patients on HFOV often have an increased need for deep sedation or even paralysis, though some patients (especially neonates) may not [6, 7]. It may be more difficult to manage sedation on ECMO patients due to a variety of factors, including the catastrophic consequences of cannula dislodgement, increased volume of distribution, and decreased renal/hepatic function. Adsorption of the medications to circuit components can reach up to 50% for some sedative agents, and dose requirements increase by about 50% during the initial 2 days of ECMO [8]. On the other end of the spectrum, patients managed using noninvasive ventilation strategy may require the use of adjunct sedation to facilitate mask tolerance and dexmedetomidine would appear to be a suitable choice [9].

Pertinent Pharmacology

There is a significant risk of altered drug half-lives in the ICU setting [10]. This may be particularly important when weaning from ventilator support. The duration of infusion can impact the half-life, as the clinical effects of many agents wear off mostly due to redistribution rather than elimination, leading to longer half-lives with prolonged administrations. This time to recovery period is known as the context-sensitive half-life. This is usually related to a complex multicompartment kinetic model. In addition to this model, there are the effects of altered metabolism and excretion as well as the effects of altered volume of distribution. The published kinetic data for most sedatives used in the ICU does not represent these complicated scenarios and as such the sedation agents' clinical effect can be much longer than anticipated in some patients. Children requiring sedation for intubation may be lively while the endotracheal tube is in place, but then become sedated when the stimulation ceases after extubation. In the face of an unknown and unpredictable prolonged sedative effect, this can cause extubation to fail. The use of bridge sedation agents for extubation may prevent this complication. Over-night propofol or remifentanil has been shown to be effective in this scenario. Remifentanil when compared to fentanyl for extubation in young children showed a much quicker time to extubation [11].

Types of Sedatives and Analgesic Agents

Patients with PARDS often require prolonged ventilation and as such prolonged sedation management. Reviewing every pertinent aspect of all agents used to provide sedation and/or analgesia is beyond the scope of this book, but the following section highlights facts regarding selected agents that the practicing intensivist may find particularly useful.

Opiates

Opioids are used commonly to provide analgesia for children with PARDS. Fentanyl and morphine are frequently used agents. The mu (μ) receptor accounts for the majority of therapeutic and adverse effects seen in the ICU, including analgesia, blunting of the stress response, sedation,

anxiolysis, euphoria, respiratory depression, urinary retention, and constipation.

Morphine may cause histamine release [12] and vasodilation, so may be inappropriate for patients with hemodynamic instability. Morphine is metabolized by gluconuridation in the liver. The clearance is substantially decreased in term and preterm neonates, resulting in a half-life up to 9 hours [13]. Dosing recommendations in the ICU include a bolus dose of 0.05–0.1 mg/kg and a starting infusion of 10–30 μg/kg/h. These doses should be reduced in neonates. Opioid tolerance is mainly limited to the depressant actions such as analgesia, respiratory depression, anxiolysis, and drowsiness, but not constipation. The tolerance appears more rapidly with infusions and is not common with opioid dosing for less than 3 days. With prolonged administration, tolerance levels as high as 20× normal dosing can occur.

Fentanyl is a synthetic opiate. Due to its lipid solubility, its onset is very rapid, and clinical effects of a single bolus are short due to rapid redistribution. With long-term infusion, fentanyl accumulates in fat, and its elimination half-life is about 4 hours [6]. It is metabolized in the liver to nor-fentanyl and hydroxy fentanyl derivatives, both of which are inactive. Fentanyl bolus doses of ≥5 μg/kg may be associated with chest wall rigidity, which can be treated with neuromuscular blockade or naloxone. Fentanyl has minimal hemodynamic effects. Dosing in the ICU is by bolus (1 μg/kg) and/or infusion (1–3 μg/kg/h) with higher doses as tolerance develops.

Meperidine has one-tenth the potency of morphine and has a more rapid onset due to increased lipid solubility. Its use has decreased significantly due to the potential for accumulation of its main metabolite nor-meperidine [14], which can cause tremors, myoclonus, psychiatric changes, or seizures.

Remifentanil is a newer synthetic opiate metabolized by plasma esterases. Because it has a short half-life, the depth of sedation is rapidly reflected by changes in the infusion rate without the need for bolus administration. It is substantially more potent than fentanyl. For sedation, 0.1–0.4 mcg/kg/minutes are similar in effect to 1–4 mcg/kg/hour fentanyl. It has a stable cardiovascular profile similar to fentanyl, and may be appropriate for PICU patients with severe renal/hepatic disease or who may require a rapid awakening for neurologic assessment [15].

Benzodiazepines

Benzodiazepines are commonly used to provide sedation in the ICU. They bind to benzodiazepines receptors in the brain, which are part of the $GABA_A$ receptor. This opening of the chloride channel hyperpolarizes the neuron [16], resulting in anxiolysis, sedation, amnesia, euphoria, muscle relaxation, and anticonvulsant effects, but no analgesia. They have negative inotropic and chronotropic effects, especially when the sympathetic response has been abolished [17], so caution should be observed in critically ill patients to avoid hypotension.

Midazolam is an imidazobenzodiazepine with a short elimination half-life of about 2 hours. Infusion starting dose is usually about 0.03–0.05 mg/kg/hour. It is metabolized in the liver. Due to its extensive protein binding, hepatic or renal failure can have a significant effect on the free midazolam levels as well as the excretion of the active metabolite hydroxymidazolam. This can result in a significant prolongation of the half-life in critically ill patients.

Lorazepam has a slow onset and a long half-life (14 hours). Metabolism is via gluconuridation pathways without active metabolites and is less impacted by hepatic dysfunction than midazolam [6]. It is typically used as an intermittent medication at doses of 0.05–0.10 mg/kg, as infusions may cause propylene glycol toxicity [12].

Diazepam has a long half-life (24 hours) and is metabolized to several long-acting active metabolites (12–90 hours). These properties have resulted in its rare use in the ICU. It is fast acting when given orally for indications such as anxiolysis and is effective when given rectally for seizure management (Diastat).

Other Sedative Agents

Propofol is a rapid-onset, short-acting, highly lipid-soluble IV anesthetic agent. Propofol has a rapid redistribution phase (half-life ~3 minutes) and is rapidly cleared by the liver; however, its half-life after prolonged infusion is context-sensitive and may be greater than 6 hours. Propofol can cause severe hypotension, especially when given by bolus and if the child is critically ill and dependent on sympathetic tone for blood pressure stability. Use as a prolonged infusion, especially at higher doses (>4 mg/kg/hour), is associated with the often-fatal propofol infusion syndrome (PRIS) and is avoided by many pediatric intensivists [18–20]. PRIS consists of refractory metabolic acidosis with fatal myocardial failure, bradycardia, lipemia, and rhabdomyolysis, potentially related to mitochondrial dysfunction.

Dexmedetomidine is a selective α_2 adrenergic agonist that causes sedation, analgesia, and an inhibition of sympathetic activity. Its elimination half-life in children is about 2 hours but is prolonged with hepatic failure [21]. Advantages of dexmedetomidine include minimal respiratory depressant effect and less hypotension (in some instances, mild hypertension has been reported). Bradycardia is a common side effect, especially if a loading dose is given. The sedation from dexmedetomidine can result in a sleeping patient who is easily aroused when stimulated. This may be desirable in some settings such as use of noninvasive ventilation, periextubation, and following cardiac surgery. Adults with sepsis randomized to dexmedetomidine had improved ventilation days and mortality compared to lorazepam [22]. In a more recent study, mechanically ventilated adults had shorter duration of ventilation and improved interaction with their environment when randomized to dexmedetomidine versus midazolam, though they also had more hypotension and bradycardia. In children, dexmedetomidine may reduce opiate requirements, improve time within targeted sedation ranges, and reduce delirium [23–25].

Ketamine is a phencyclidine derivative that provides a dissociative sedation. Ketamine is metabolized by the liver and excreted renally with an elimination half-life of about 3 hours. Ketamine is a direct myocardial depressant, but usually leads to tachycardia and hypertension by increasing sympathetic tone. It also is a bronchodilator. Possible side effects include increased intracranial pressure and sialorrhea.

Etomidate is a rapidly acting IV anesthetic agent that causes minimal cardiac or respiratory depression. Use as continuous infusion is avoided because it is formulated in 30% propylene glycol, but it is frequently used for rapid sequence intubation where the cardiac stability is especially beneficial. The elimination half-life is about 3 hours. The main disadvantage of etomidate is adrenocortical suppression due to inhibition of 11-β-hydroxylase [26]. This inhibition can occur after a single dose [27] and outcomes are not improved with prophylactic hydrocortisone replacement [28].

Neuromuscular-Blocking Agents

In various clinical scenarios in the PICU setting, the total prevention of skeletal muscle movement is necessary, thereby mandating the use of neuromuscular-blocking agents (NMBAs) (Table 11.1) [29, 30]. These agents may be administered as a single dose to facilitate procedures such as endotracheal intubation or by a continuous infusion when more prolonged immobilization is needed. Overall there has been a decrease in the use of NMBAs in the PICU setting, likely related to improved techniques for providing sedation and analgesia in the PICU setting and data demonstrating NMBA's adverse-effect profile and questioning their therapeutic benefit in specific clinical scenarios.

To maintain the balance benefits between risk and benefit, NMBAs should be used only when absolutely indicated and with appropriate knowledge of and training in their pharmacology, metabolism, and adverse-effect profile. Use of the term "muscle relaxant" should be avoided. Rather, these agents should be thought of as NMBAs, thereby identifying their mechanism of action in their name. With interruption or

Table 11.1 Indications for neuromuscular blockade in the pediatric ICU

1. Facilitation of procedures or diagnostic studies
(a) Endotracheal intubation
(b) Central line placement
(c) Radiological imaging (MRI, CT scanning)
2. Immobilization during interhospital or intrahospital transport
3. Intensive care indications
(a) To facilitate mechanical ventilation (especially high-frequency techniques)
(b) Control increased intracranial pressure
(c) Eliminate shivering (therapeutic hypothermia)
(d) Decrease peripheral oxygen utilization
(e) Control severe agitation unresponsive to adequate sedation
(f) Maintain immobilization after surgical procedures
(g) Decrease the risk of pulmonary vasospasm in patients with pulmonary hypertension
(h) Management of tetanus

Table 11.2 Classification of nondepolarizing neuromuscular-blocking agents

Aminosteroid compounds
Pancuronium
Rocuronium
Vecuronium
Pipecuronium
Rapacuronium (no longer available)
Benzylisoquinolinium compounds
Mivacurium
Atracurium
Cisatracurium
Doxacurium

blockade of skeletal muscle function, these agents cause cessation of respiratory function, mandating the need to provide effective airway control and mechanical ventilation. These agents should not be administered if there is any question as to the normalcy of the airway or the ability to successfully accomplish bag-mask ventilation and endotracheal intubation [31]. The inability to manage the airway including the provision of bag-mask ventilation and/or endotracheal intubation will result in hypoxia and death. These agents provide no amnestic, analgesic, or sedative properties, and should not be used without the coadministration of an amnestic agent (i.e., benzodiazepine, propofol, ketamine, inhalational anesthetic agent). Depth of neuromuscular blockade can be objectively measured using train of four (TOF) monitoring.

Two general classes of NMBAs (depolarizing and nondepolarizing agents) are available for clinical use. Depolarizing agents, such as succinylcholine, mimic acetylcholine. They bind to the acetylcholine receptor at the neuromuscular junction and activate it. As succinylcholine is used only for rapid neuromuscular blockade during endotracheal intubation, further discussion will not be included in this chapter. The nondepolarizing NMBAs act as competitive antagonists, competing with and blocking the effects of acetylcholine at the receptor; however, these agents do not activate the acetylcholine receptor. The nondepolarizing agents may be divided into two groups based on their basic chemical structure: aminosteroid and benzylisoquinolinium compounds (Table 11.2). The basic differences in their chemical structure may impact their clinical differences including onset of action, duration of action, cardiovascular effects, metabolism, and metabolic products. The first nondepolarizing NMBAs (curare, gallamine, metocurine) have been replaced by the newest generation of NMBAs, which have more favorable profiles (cardiovascular effects, onset times, recovery times, and metabolic fate).

Vecuronium is an aminosteroid NMBA that was released for clinical use in the 1980s. In doses of 0.1–0.15 mg/kg, complete neuromuscular blockade with conditions adequate for endotracheal intubation is provided in 90 seconds with a clinical duration of action of 30–40 minutes (intermediate-acting agent) [32]. The onset of complete neuromuscular blockade can be achieved more rapidly by increasing the dose to 0.3 mg/kg. With the larger dose, the onset time is approximately 60–75 seconds, but the duration of neuromuscular blockade is prolonged to 60–90 minutes. Even at these higher doses, vecuronium is devoid of cardiovascular effects. Metabolism is both hepatic (70–80%) and renal (20–30%), so the duration of action is prolonged with hepatic or renal insufficiency.

Rocuronium is a desacetoxy analog of vecuronium. It remains one of the newer aminosteroid NMBAs, having been released for clinical use in the early 1990s. Following a dose of 0.6 mg/kg, the duration of action is 20–40 minutes. Larger doses (1–1.2 mg/kg) are frequently used during rapid sequence intubation as the onset time with these doses has been shown to approximately parallel those of succinylcholine. Clinical studies have demonstrated acceptable conditions for endotracheal intubation in the majority of older children and adolescents within 60 seconds following a dose of 1.0 mg/kg [33–35]. Given its rapid onset of action, rocuronium has been accepted as the agent of choice for endotracheal intubation and RSI by many practitioners. As with other agents, the duration of action increases when larger doses are administered so that 60–90 minutes of neuromuscular blockade occurs following a dose of 1.0 mg/kg. A mild vagolytic effect, less in intensity than that seen with pancuronium, may increase heart rate in the range of 10–20 beats per minute and mean arterial pressure following bolus dosing [36]. Rocuronium undergoes primarily hepatic metabolism, so clinical effects last longer in children with hepatic insufficiency and in infants with immature hepatic microsomal enzymes [37]. There is also a mild prolongation of the clinical effect when rocuronium is administered to patients with renal failure [38, 39].

Cisatracurium is a stereoisomer of atracurium, which itself is uncommonly used because it causes histamine release [40]. Both agents are nondepolarizing NMBA of the benzylisoquinolinium class. Acceptable conditions for endotracheal intubation are provided in approximately 2 minutes with cisatracurium [41]. Hemodynamic effects are minimal. Metabolism of cisatracurium occurs via Hofmann degradation, a pH- and temperature-dependent chemical process, to form laudanosine and the monoquaternary acrylate metabolite. The metabolic pathway is not affected by renal or hepatic function, thereby providing stable pharmacokinetics even in the setting of multisystem organ failure. Laudanosine crosses the blood-brain barrier and animal data have shown that it may cause CNS excitement and seizure activity [42]. The risk of post-ICU weakness is also less with cisatracurium than with aminosteroid agents [43].

Reversal of Neuromuscular Blockade

In the PICU setting, when there is no longer a need for neuromuscular blockade, the agent is discontinued and spontaneous recovery allowed. In certain circumstances, a clinician may desire to reverse the effects of nondepolarizing NMBAs, as is more commonly done in the operating room, with a medication that inhibits acetylcholinesterase. For these medications to effectively reverse neuromuscular blockade, some degree of residual neuromuscular function must be present such as 1–2 twitches on the TOF. Inhibition of acetylcholinesterase results in the accumulation of more acetylcholine to compete with the NMBA at the nicotinic receptor of the neuromuscular junction. The commonly used acetylcholinesterase inhibitors or "reversal agents" include neostigmine, pyridostigmine, and edrophonium. Adverse effects related to the use of reversal agents generally relate to their inhibition of acetylcholinesterase at sites away from the neuromuscular junction. These agents should always be preceded by an anticholinergic agent such as atropine or glycopyrrolate, since the inhibition of acetylcholinesterase at muscarinic receptors leads to symptoms like bradycardia and even asystole. Other adverse effects related to the reversal agents included augmentation of cholinergic function in the gastrointestinal tract (salivation, diarrhea, nausea, and vomiting) and the respiratory tract (bronchospasm). A newer agent, sugammadex, does not inhibit acetylcholinesterase, but rather encapsulates aminosteroid NMBAs (e.g., rocuronium and vecuronium), removing these agents from the plasma and thereby reversing neuromuscular blockade [44, 45].

Adverse Effects of Neuromuscular Blockade

The most devastating adverse effect is the inability to provide adequate oxygenation and ventilation. Therefore, these medications should never be used if there is any suspicion that the airway cannot be controlled. NMBAs will also eliminate routine physiologic functions such as blinking and routine self-repositioning to avoid pressure points. Eye care with the application of artificial teas at fixed intervals is necessary to avoid drying of or damage to the cornea [46, 47]. Adjunctive care includes repositioning of the patient at fixed intervals, early involvement of physical/occupational therapy, use of special mattresses, deep vein thrombosis prophylaxis, and placement of splints to avoid contractures. Ineffective coughing and clearance of secretions mandates the implication of suctioning protocols to limit the risk of nosocomial pneumonias and worsened lung mechanics [48].

Perhaps of greatest concern during the administration of NMBAs is the potential for long-term sequelae with muscle atrophy and weakness. These issues generally resolve spontaneously over time with no longer-term impairment of neuromuscular function. Of more concern, is what is now termed the acute quadriplegic myopathy syndrome (AQMS) [49]. Clinical signs and symptoms include weakness or even flaccid paralysis, relative preservation of extraocular movements, decreased deep tendon reflexes, respiratory insufficiency, intact sensory function, and normal findings in the cerebrospinal fluid. Recovery may be prolonged, requiring weeks to months, with the need for prolonged rehabilitation care, and tracheostomy with chronic ventilatory support. AQMS is associated with the coadministration of NMBAs and corticosteroids, thereby suggesting a heightened awareness in such patients [50, 51]. Critical illness polyneuropathy may be confused with AQMS. It is a combined motor and sensory neuropathy that results from ischemia of the microvasculature of the nerves, which is seen most commonly in patients with multisystem organ failure. The EMG demonstrates a pattern different from that seen in AQMS.

Neuromuscular Blockade and Acute Lung Injury

Despite the potential for adverse effects, recent work has demonstrated the potential for improved outcomes including a survival benefit when NMBAs are administered early in the course of adult patients with ARDS. Three multicenter randomized trials of cisatracurium for neuromuscular blockade in patients with ARDS [52–54] demonstrated a clinical advantage of early neuromuscular blockade manifested as improved oxygenation. A subsequent pooled analysis demonstrated reduced mortality at 28 days and at hospital discharge and a decreased incidence barotrauma [55]. A fourth study from the Chinese literature demonstrated a similar reduction in mortality in adults with ARDS with the use of a vecuronium infusion [56] Despite these findings, the mechanisms remain speculative perhaps relating to promotion of patient-ventilator synchrony, decreased barotrauma/volutrauma, and reduced shearing injury to the lung with reduction of the generation of inflammatory mediators. Based on these findings, the recent Society for Critical Care Medicine guidelines for the use of neuromuscular-blocking agents in adults suggest that "an NMBA be administered by continuous intravenous infusion early in the course of ARDS for patients with a PaO_2/FiO_2 less than 150." This was listed as a weak recommendation with moderate quality of evidence. The PALICC guidelines recommend that "if sedation alone is inadequate to achieve effective mechanical ventilation, neuromuscular blockade should be considered" with a daily NMBA holiday.

Iatrogenic Withdrawal Syndrome

PICU patients may develop tolerance, increased dosing required for a consistent clinical effect, to all the commonly used sedatives and analgesics. Tolerance can be due to receptor desensitization or upregulation of the postreceptor pathways, and often results in a physiological dependency state. When the offending medica-

tion is stopped, the signs and symptoms of the iatrogenic withdrawal syndrome (IWS) can be present, including agitation, grimacing, abnormal movements, diarrhea, tachypnea, tachycardia, fever, sweating, and hypertension [57]. Risk factors for IWS include longer duration of therapy and higher dosages [58]. Infusions for more than 5 days or doses of >5 mcg/kg/hour fentanyl appear to be risk factors [59]. As children with ARDS often undergo a prolonged period of ventilation and sedation, the risk for IWS is high. IWS has been shown to delay patient recovery and prolong hospitalization [58].

To facilitate appropriate management, the clinician requires a withdrawal assessment tool to determine the presence and treatment efficacy of the IWS. The Withdrawal Assessment Tool-1 (WAT-1) was developed and validated in a PICU population based upon a population of children who received mechanical ventilation for >5 days [60]. The score is quick and easy to perform, and is often performed once a shift. A WAT-1 score of 3 or greater (maximum 12) may be considered to reflect IWS. The score has features that reflect opiate withdrawal (sweating, yawning, loose stools) as well as benzodiazepine withdrawal (agitation, tremor, uncoordinated movements). The Sophia Observational Score (SOS) has also been validated for use in the PICU [61]. It has many similarities to the WAT-1, but includes more signs of high sympathetic tone and benzodiazepine withdrawal. The intra- and interrater analyses of both scores are good and both scores appear to be useful tools.

The simplest way to prevent IWS is to slowly taper the drug over a period of days to weeks depending on the duration of the infusion. For opiates, this is usually managed by replacing the infusion with an equivalent methadone dose started initially IV, then converting to oral dosing and weaning. The duration of weaning using methadone is usually between 5 and10 days unless very high doses or prolonged infusions are used [62]. Methadone has a high oral bioavailability (80%), a long half-life (24 hours), and has less sedating effect than morphine or fentanyl. Using about three times the total fentanyl daily dose (mcg) divided in three doses per day has been shown to be effective [63]. Dexmedetomidine can also control the signs and symptoms of opiate withdrawal in PICU patients [64]. When discontinuing midazolam, the conversion to a long-acting and effective oral benzodiazepine would be attractive as with using methadone for fentanyl withdrawal. Methadone conversion rates have been well studied; however, the conversion from midazolam to long-acting benzodiazepines has been studied much less so. The total daily midazolam dose (mg) divided by 12 has been used to convert to oral lorazepam, which has a high oral bioavailability (90%) [65], which can then be weaned off.

The incidence of IWS has been reported at 35% for dexmedetomidine infusions greater than 48 hours in the PICU [66]. The more frequent signs and symptoms were agitation, fever, loose stools, vomiting and sleep disturbance, as well as tachycardia and hypertension [67]. These symptoms appear to reflect sympathetic hyperactivity, akin to those experienced during opiate withdrawal. The use of clonidine to treat dexmedetomidine withdrawal has been reported in several small series [66, 67].

Delirium in the PICU

Delirium is characterized by acute and fluctuating disturbances of consciousness and cognition, with inattention and impaired information processing and memory [68]. Children with delirium can have hypoactive, hyperactive, or mixed symptoms. The reported incidence of delirium in the PICU is 25–40% [69, 70]. Risk factors include younger age, developmental delay, and benzodiazepine usage [71, 72]. Recognizing delirium in the PICU is often best aided by the use of scoring systems as the signs and symptoms are multiple and nonspecific for delirium. The pediatric Confusion Assessment Method for Intensive Care Unit (pCAM-ICU) [73] and Pediatric Confusion Assessment Method [70] are two validated tools to assess delirium in the PICU.

Rather than treating delirium, it would be better if we could avoid, or at least minimize, the problem. Adoption of a benzodiazepine-sparing approach may reduce delirium. Dexmedetomidine in adults has been shown to reduce the incidence of ICU-related delirium [74], but the evidence supporting this in children is not as robust. Early mobilization has been reported as a strategy to reduce the incidence of delirium in a PICU [75]. Pharmacologic treatment options for delirium in the ICU include antipsychotic agents such as haloperidol [76]. However, the newer atypical antipsychotics have generally replaced haloperidol due to fewer side effects. Olanzapine and respiridone have been reported as effective in the PICU setting [77], and both are available as a tablet or an orally disintegrating tablet. Olanzapine tends to be more sedating, which may be an added benefit. Results of randomized trials of treatment of ICU delirium in adults with antipsychotic agents have been generally disappointing [78].

Immunomodulatory Effects of Sedation

It has been well documented in both *in vitro* and *in vivo* studies that sedation agents have immunomodulating properties [79]. This has been mostly demonstrated in the case of sepsis; however, ARDS and sepsis share significant immune activation pathways and there may be a significant immune effect of sedation in the PARDS setting as well. PARDS patients are frequently receiving other immune-modulating therapies and how these all interact is unknown. As such, the predicted beneficial or detrimental effect from a sedative agent alone may be unclear. Propofol has been shown to have anti-inflammatory effects possibly related to its antioxidant properties [80]. Its immune-suppressive effects stem in part from inhibition of macrophage and neutrophil function. Benzodiazepines exhibit a similar immune-suppressant profile [81]. However, a short-term, low-dose infusion of midazolam in burn patients was found to enhance the immune response and tissue-protective/tissue-repair mediators [82]. Different opioids show different effects on the immune system with both immunosuppressive and immune-stimulatory effects being reported [83]. This may reflect a direct effect on immune cells, and interaction with the hypothalamic-pituitary-adrenal axis, glucocorticoid effect, or modulation of sympathetic activity and catecholamine release. The interaction within these sites is complex and varies between agents as well as between species. Morphine demonstrates anti-inflammatory effects *in vitro* and increases mortality *in vivo* in animal models of infection. The effect on lymphocyte function may be associated with late secondary infections. Opioid administration may therefore contribute to the immunosuppression observed in the critically ill. Ketamine [84] has also demonstrated a decrease in cytokine production in experimental septic shock. Dexmedetomidine also appears to have anti-inflammatory effects [85].

Sedation Assessment

As part of the sedation management in the PICU, the depth of sedation should be evaluated on a regular basis. There are many PICU-validated scoring systems available, which can be used by the bedside caregiver to adjust the sedation dosing to the needs of the child. The use of a sedation-scoring system [86] has been shown to reduce the incidence of oversedation- as well as undersedation-related complications. However, the use of nurse-driven protocol did not reduce the number of ventilator days in the RESTORE study [87]. Children in the protocol group had more days when they were awake or only lightly sedated; however, they also had more days when they experienced high pain scores or episodes of agitation, possibly reflecting undersedation.

The Richmond Agitation-Sedation Scale (RASS) [88] and State Behavioral Scale (SBS) [89] are two commonly used tools. Older children may be calm and comfortable with either mild (RASS-1 or − 2) or moderate sedation (RASS-3), but younger children do not under-

stand the need for the uncomfortable "lines and tubes" and deeper sedation may be required. The bispectral index (BIS) monitor may remove the subjectivity from sedation assessment. The BIS monitor measures the level of hypnosis using analysis of the EEG waveform components referenced to a proprietary waveform database, and it has been validated in the PICU [90]. It does not reflect the drug concentration of any particular drug, but the overall sedative effect. The BIS score can be helpful in paralyzed patients [91] as most of the scoring systems are unable to be performed due to a lack of movement response to stimulus. Nurses have been shown to significantly overestimate a paralyzed child's sedation [91].

Serially assessing sedation with these tools may reduce the overall exposure to these drugs. Another potential strategy to reduce sedation is the use of sedation interruption. Although there are limited studies evaluating this strategy in children, one demonstrated no benefit with respect to ventilator days or dosing of sedation [92]. The cycling of sedation has also been evaluated; however, switching between different sedatives has of yet not be shown to reduce sedation-related complications [92]. The pattern of sedation weaning may also affect the child's care and outcome. It appears that a continuous wean rather than an interrupted wean was associated with a quicker wean with less withdrawal [93]. This may be more related to the dosing and sedation needs rather than actual sedation weaning. Weaning of opiates or benzodiazepines may be more likely to be successful if the sedatives are weaned using appropriate doses of replacement drugs such as methadone [91]. If the wrong dose is used, then oversedation may occur and delay the weaning process, but underreplacement will result in increased withdrawal symptoms.

Apoptosis and Sedation in the PICU

There is evidence from many rodent and primate studies [94] that suggests most of the general anesthetic agents and sedatives, which are either *N*-methyl-d-aspartate receptor antagonists or $GABA_A$ agonists, can trigger neuronal apoptosis [95]. In 2017, the FDA issued a warning that the following agents could negatively affect brain development in children under the age of 3: fluorinated inhalational agents, midazolam, lorazepam, propofol, etomidate, and ketamine. While retrospective studies suggested that anesthesia early in life was associated with unfavorable neurocognitive outcomes, more recent prospective studies which compared general anesthesia to regional anesthesia for elective hernia repair in infancy did not demonstrate any delirious effect from the anesthesia agents at 2 years [96] and 5 years post anesthesia [97]. However, it is still unknown if exposure to GABA agonist or NMDA antagonists for prolonged periods lasting days to weeks, as is often needed in PARDS, influences neurocognitive outcomes [98].

Conclusion

Sedation for ventilated children with ARDS is required for patient's comfort, amnesia, safety, and ventilator synchrony. Multiple agents are available, each with unique strengths and weaknesses. Though no specific strategy has been proven to improve outcomes in children with ARDS, it is recommended to use serial objective assessments to provide the lowest possible dose needed to achieve individualized goals for that patient. Considering these risks of delirium, IWS, and altered neuronal development, a combination of opiates and dexmedetomidine may appear to be the best choice. Extrapolating from adult data, use of an NMBA early in the course of severe PARDS may improve outcomes. Cisatracurium offers the advantage of no dependence on end-organ-dependent elimination and may be a more appropriate choice in patients with hepatic or renal failure, since such problems do not alter dosing requirements of this agent. Specific protocols should be in place to ensure appropriate care of the patient who is receiving neuromuscular blockade with attention toward the provision of adequate sedation and

analgesia, eye care, prevention of pressure sores, and pulmonary toilet. Overall, more studies are needed to identify the optimal way to provide sedation, analgesia, and neuromuscular blockade in children with ARDS.

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12 Fluids, Nutrition, and Acute Kidney Injury in Pediatric Acute Respiratory Distress Syndrome

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Introduction

Fluid and nutrition support play an essential role in the care of pediatric patients with pediatric acute respiratory distress syndrome (PARDS). Adequate fluid resuscitation preserves organ perfusion, while excess fluid is associated with worse patient outcome. Similarly, adequate enteral nutrition (EN) preserves lean body mass, provides substrate for the production of acute-phase proteins, and is associated with improved 60-day mortality in mechanically ventilated children [1–3]. Adequate protein delivery prevents loss of respiratory and cardiac muscle functions and is associated with increased ventilator-free days, and is independently associated with improved mortality in PARDS [4]. Children have ongoing growth and neurological development, making them uniquely sensitive to even brief periods of starvation. Several barriers exist to provision of goal enteral nutrition (EN), and as a result, median delivery of EN remains 40–75% of goal over the first week of PICU hospitalization [3, 5–10]. Barriers to provision of EN include delayed initiation, perceived feed intolerance, prolonged fasting for procedures, and withholding or limiting EN to avoid or manage fluid overload. In the setting of fluid overload and/or acute kidney injury (AKI) in PARDS, nutrition support is often sacrificed to limit further fluid overload, with unknown consequences to patient outcome. AKI is very common in the critically ill patients, impacting 1 in 3 of all PICU patients [11, 12]. Management of fluid overload includes limiting total fluids, diuretic therapy and mechanical fluid removal via renal replacement therapy (RRT), frequently extracorporeal and continuous. Continuous renal replacement therapy (CRRT) is the standard of care for managing AKI in resource-replete environments. RRT is required in 10% of severe AKI patients. A lung-kidney crosstalk has long been proposed. In fact, AKI incidence rises to over 80% in children who are ventilated [13]. While nonoliguric AKI management is relatively easier, conservative management of oliguric AKI requires significant fluid restriction, with only repletion of insensible and measured losses, and creates a barrier to adequate nutrition delivery. In fact, an RRT indication unique to pediatrics is to "make room for" nutrition; by preventing and treating fluid accumulation through mechanical fluid removal, unrestricted fluid administration is permitted to facilitate optimal nutrition delivery.

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Fluid Management in ARDS

Conservative and Liberal Fluid Strategies

Insufficient evidence exists to guide fluid management in the general pediatric ICU patient after the resuscitation period. Fluid administration remains the cornerstone of medical therapy to restore effective circulatory volume and maintain end-organ perfusion in critically ill patients. However, the currently used maintenance fluid calculations were derived in healthy children, and likely do not apply to the critically ill. Many intensivists have adopted a moderate fluid restriction strategy: by only prescribing 75% of "regular" maintenance fluid volume (i.e., 1200 ml/m^2/day as opposed to 1600 ml/m^2/day) with the reasoning that intubated patients on humidified circuits do not have transpulmonary losses. It is well recognized that the bulk of the fluid accumulation occurs in the first week of ICU admission. In fact, Abulebda et al, showed that in a risk-stratified heterogeneous pediatric septic shock cohort, a positive fluid balance – both in the first 24 hours and cumulative during ICU stay – was associated with mortality only in low-risk patients but not in the moderate- to high-risk group, introducing the possibility of overtreatment in the low-risk group [14]. A recent meta-analysis evaluating the association between adverse outcomes and fluid overload demonstrated that fluid overload was associated with increased in-hospital mortality with 6% increased odds of mortality with every 1% increase in percent fluid overload [15]. Daily positive fluid balance in patients with respiratory failure requiring mechanical ventilation has adverse effects with increased morbidity and fewer ventilator-free days. Additionally, cumulative fluid balance has been associated with worse oxygenation, impaired pulmonary mechanics, and higher mortality in pediatric patients with Acute Lung Injury [16, 17] (see Table 12.1). Additionally, in data from critically ill patients requiring RRT, survivors with fluid overload (FO) <20% had shorter time to renal recovery versus those with fluid overload greater than 20% (8 vs. 26 days) [21]. In a prospective cohort of critically ill pediatric patients, Li et al, noted that early fluid overload in the first 24 hours after ICU admission was associated with AKI, including a higher fluid balance in nonsurvivors versus survivors in their study cohort [25]. In addition, studies on critically ill children convalescing from cardiac surgery have shown a significant association between peak cumulative percent fluid overload and higher peak oxygenation index [26]. However, it is unclear whether it is the initial resuscitation or the ongoing administration of fluids that is responsible for this cumulative fluid accumulation. The negative associative relationship of fluid accumulation with end-organ dysfunction and global outcomes does not prove causality and needs further prospective study.

In PARDS, positive fluid balance is associated with a decrease in oxygenation and ventilator-free

Table 12.1 Reported association of fluid balance with respiratory and global outcomes

Author	Cohort	FO threshold	Outcome
Gillespie et al. [18]	CRRT	10%	OR death 3.02 > 10% FO
Foland et al. [19]	CRRT	10% increment	1.78 OR death for each 10% FO increase
Goldstein et al. [20]	CRRT	20%	<20% FO: 58% survival >20% FO: 40% survival
Hayes et al. [21]	CRRT	20%	OR death 6.1 > 20% FO
Akcan-Arikan et al. [16]	PICU	15%	Longer duration of mechanical ventilation Worse oxygenation
Valentine et al. [22]	PICU	10% on day 3	Longer duration of mechanical ventilation
Sinitsky et al. [23]	PICU	<5,<10, <15,>15 at 48 hour	Higher OI, longer duration of mechanical ventilation
Ingelse et al. [24]	PICU	N/A	Longer duration of mechanical ventilation

CRRT continuous renal replacement therapy, *PICU* pediatric intensive care unit, *FO* fluid overload, *OI* oxygenation index, *OR* odds ratio

days [17]. Increased lung water retention is likely an explanation of worsening in oxygenation by causing pulmonary edema, which, in turn, may result in worsening compliance as well as predisposing to ventilator-associated conditions, such as infections. As liberal administration of fluid to patients with respiratory failure could lead to fluid accumulation with deleterious consequences on oxygenation, length of ventilation, and ICU stay, an enhanced awareness of fluid exposure is needed. Unfortunately, despite recommendations for conservative fluid strategy, intensivists still administer large amounts of fluid in pediatric acute lung injury [17]. It is not uncommon for fluid orders to be written without dedicated attention to other fluid intake driven by the obligate administration of medications, especially in the form of drips. Conversely, indiscriminate fluid restriction could also be detrimental, as it could lead to hypoglycemia, especially in younger patients with limited endogenous stores and gluconeogenesis capacity, which renders them more dependent on exogenous glucose infusion rates [27]. Strategies to better manage fluid delivery include implementation of a preemptive fluid treatment bundle to prevent fluid overload in children with PARDS and sepsis [27]. Recently, there has been a practice drift to only use isotonic fluid for maintenance fluid administration in the PICU due to observational studies reporting high prevalence of hyponatremia with hypotonic fluid use [28]. Since the most frequently used isotonic fluid, 0.9 N sodium chloride ("normal saline"), includes supraphysiological quantities of sodium and chloride, sodium overload could have unintended consequences of worsening fluid accumulation. Moreover, high chloride levels have been associated with worse AKI and worse outcomes in sepsis as well as CRRT patients, and may increase minute ventilation to compensate for nonanion gap metabolic acidoses [29, 30].

Critically ill adults with Acute Lung Injury randomized to conservative fluid strategy had better oxygenation, shorter length of mechanical ventilation, and shorter ICU stay in the National Heart, Lung, and Blood Institute (NHLBI) ARDS Network's FACTT (Fluid and Catheter Treatment Trial) trial [31]. However, conservative fluid management may not be appropriate for all patients. The conservative strategy was associated with long-term neurologic morbidity [32]. Furthermore, two subphenotypes with treatment response to fluid restrictive fluid strategy in opposite directions are recognized in adult patients with ARDS, which suggests differing underlying pathophysiology between the subphenotype groups [33]. Subphenotype 2 was characterized by higher inflammatory biomarkers and hypotension, and a fluid-conservative strategy was associated with 40% mortality, whereas a fluid-liberal strategy was associated with 50% mortality. Subphenotype 1 was a less "inflammatory" biomarker phenotype and had 26% mortality with fluid-conservative management and 18% mortality with a fluid-liberal strategy. While it is plausible to propose that there could be similar subphenotypes in children with PARDS, there is no evidence as to which fluid administration protocol would be beneficial in a more or less "inflamed" subphenotype in pediatrics.

In the absence of clear subphenotype data or classification, Pediatric Acute Lung Injury Consensus Conference (PALICC) recommendations include administering sufficient volume to ensure adequate intravascular volume while avoiding positive fluid balance by using a goal-directed approach (see Table 12.2) [34, 35]. Unfortunately, objective reliable metrics to guide fluid administration do not exist in pediatrics. Inferior vena cava (IVC) diameter, optimal central venous pressure (CVP) goal, pulse wave variability, stroke volume variation, and assessment of extravascular lung water by invasive and noninvasive monitors have all been studied with varying outcomes in adults but pediatric data are insufficient to guide clinical practice. Several investigators have reported varying success with bioimpedance measurements, and while this tool is used in the chronic pediatric dialysis population, it is yet to be validated in critically ill children. Titration of fluid intake to maintain adequate perfusion and urine output with constant awareness of total fluid exposure

Table 12.2 Pediatric acute lung injury consensus conference recommendations for fluid management in PARDS

PALICC fluid recommendations [34]	
Total fluid goal	We recommend that pediatric patients with PARDS should receive total fluids to maintain adequate intravascular volume, end-organ perfusion, and optimal delivery of oxygen
Goal-directed fluid management	After initial fluid resuscitation and stabilization, we recommend goal-directed fluid management. Fluid balance should be monitored and titrated to maintain adequate intravascular volume while aiming to prevent positive fluid balance
Fluid titration	We recommend that fluid titration be managed by a goal-directed protocol that includes total fluid intake, output, and net balance

Text in tables adapted from: Valentine et al. [34]
PARDS pediatric acute respiratory distress syndrome

remains the foundational basis of fluid management in PARDS. Given the lack of pediatric literature for an optimal fluid management approach, it may be best to recommend minimizing inadvertent fluid intake with meticulous attention to total fluid intake, while prioritizing the nutritional demands in the catabolic patient. If severe AKI is hindering nutrition due to the need for fluid restriction, early utilization of CRRT for fluid and metabolic management should be considered. Contrary to common beliefs, protein restriction is not required in AKI management. Children with AKI are already at high risk of undernutrition due to both inadequate prescription and inadequate delivery [36]. Protein administration, especially in the form of intravenous supplementation, increases glomerular filtration rate, and might hasten renal recovery [37]. The use of an institutional nutritional guideline improved protein delivery to patients with AKI, and patients who met >80% of their protein needs were more likely to recover renal function [36].

Diuresis and Mechanical Fluid Removal

Careful attention to fluid accumulation and early intervention with goal-directed use of diuretics may be beneficial in adults with ARDS. Diuresis can be augmented with albumin in patients with hypoalbuminemia [38, 39]. However, diuretics as currently used in the PICU might not be adequate to achieve fluid balance goals; despite considerable doses of diuretics, pediatric acute lung injury patients often fail to achieve negative fluid balance by PICU day 3 [22]. Management of hypoxemia in severe PARDS with early institution of CRRT should be considered in order to prevent fluid overload, especially in cases where there is relative oliguria, or when fluid intake (due to ongoing resuscitation, need for blood products, or large number of medications) far exceeds urine output. Unfortunately, restitution of euvolemia has not been shown to negate the negative outcome associations with fluid accumulation, suggesting that it is not the edema per se that leads to adverse outcomes but possibly a hidden confounder – such as severity of illness not captured by the scores used currently – that is responsible for the outcomes in observational studies. For instance, in pediatric Extracorporeal Membrane Oxygenation (ECMO) patients on RRT or mechanical fluid removal, reversal of fluid overload by fluid removal did not improve outcomes [40]. Alternatively, this observation might also suggest that interventions aimed at prevention of fluid accumulation may be more effective compared to fluid removal. Perhaps even basic measures such as using maximally concentrated feeds and medications early on, in addition to being mindful of the free water content of IV fluids and parenteral nutrition compared to enteral feeds, may have a greater impact on preventing fluid accumulation.

Acute Kidney Injury in PARDS

The association between AKI and lung dysfunction has been extensively reported in adults and recently in children [41–45]. Patients with AKI

have longer duration of ventilation, and patients with acute respiratory failure have high rates of AKI. Organ crosstalk between kidney and lung, with spillover of cytokines and damage-associated molecular patterns into the circulation mediating inflammation in the distal organ, has been proposed as the link between AKI and propagation of lung injury. More importantly, this relationship seems bidirectional in nature. Established AKI could lead to increased pulmonary vascular permeability and leukocyte trafficking, promoting lung injury. A high incidence of AKI has been reported in adult patients with ventilator-associated pneumonia. High mean airway pressures can cause proximal tubular apoptosis under experimental conditions. Fluid overload, which frequently accompanies oliguric AKI, can lead to increased venous pressures, which in turn can lead to elevated renal venous pressure, compromising renal perfusion. This mechanism is likely to be augmented in invasively ventilated patients who are on higher mean airway pressures, such as those with severe PARDS. Prudent attention to the management of mechanical ventilation and lung-kidney interactions is required to address this deleterious organ crosstalk. What is still not clear and requires further study is whether oliguria associated with AKI leads to pulmonary fluid accumulation and hence worsening lung injury or whether prevention of AKI could modulate the inflammatory profile and prevent distant organ injury. In a prospective multicenter study, one in four ARDS patients had severe AKI on days 1–3 of PARDS. The prevalence of AKI increased when creatinine was adjusted for fluid accumulation. ICU mortality increased 8% for each 20 ml/kg increase in cumulative fluid balance in children with PARDS if they also had coexisting AKI. Interestingly, on day 3, patients with AKI had slightly higher fluid intake compared to those without AKI despite having similar output [46]. Evaluation for drivers of fluid intake could allow identification of modifiable causes – such as inadvertent liberal fluid prescription – and, thus, opportunities for improvement in management. What is more, neither AKI in its modern definition nor degrees of fluid overload are components of illness severity in currently used organ dysfunction systems. Data from ventilated critically ill adults suggest pulmonary edema/fluid accumulation contributes to up to 50% of ventilator-associated events [47]. The association among fluid overload, AKI, and pulmonary morbidity can easily be overlooked unless they are transformed into objective, quantifiable, and trackable metrics that also incorporate visual cues [48].

AKI typically occurs early in the PICU stay, with most cases developing in the first 3 days and more than 80% happening in the first week of ICU admission. Positive fluid balance also maps to this period, usually peaking around PICU day 5. Both early fluid overload and net positive fluid balance for each day are associated with increased respiratory and global morbidity [16, 22, 23]. Serum creatinine, the current functional marker of AKI, changes with the total body water in which it is dissolved, such that rapid fluid accumulation can lead to a dilutional effect on serum creatinine levels and mask AKI [49]. A recent international multicenter study of pediatric AKI has demonstrated that over 2/3rd of cases diagnosed utilizing oliguria criteria of the current consensus criteria would have been missed if only elevations in serum creatinine were taken into consideration [12]. Adding to the complexity of exploring this relationship is the lack of consensus approach to quantify fluid balance. Weights are difficult to obtain reliably in the critically ill, and as patients often lose weight during their PICU stay due to catabolism and loss of lean body mass, the degree of fluid accumulation is often underestimated.

It is well recognized that the bulk of the fluid accumulation occurs in the first week of ICU admission. The preponderance of pediatric AKI during the initial phase of the PICU course suggests that fluid overload and AKI are closely related. In fact, the timeline of fluid overload occurrence directly overlaps with critical illness–associated pediatric AKI, which also largely happens in the first week of ICU admission. This temporal relationship has led many to surmise fluid overload to be an excretory problem and a surrogate indicator for oliguric AKI (at least relative oliguria). It is quite possible that fluid

overload is a natural consequence of AKI, particularly oliguric AKI, that might be undetected, especially if urine output is not taken into consideration.

Nutrition in PARDS

Improved energy and protein adequacy, when administered via the enteral route, are associated with lower ICU mortality in PARDS [4]. Mechanisms for improved patient outcome with improved EN adequacy relate to both nutritive and non-nutritive effects of adequate EN. Direct nutritive consequences of inadequate nutrition are due to insufficient protein substrate for production of acute-phase and immune proteins, and loss of lean body mass. Utilization of lean muscle mass to recruit amino acids pool for synthesis of acute-phase and immune proteins results in loss of respiratory and cardiac muscles and difficulty with ventilator weaning. Non-nutritive benefits of EN include improved intestinal barrier function, improved immune function, and maintenance of intestinal microbiome diversity. Therefore, "optimal" nutrition can be defined differently based on the specific outcome or target. Optimal nutrition can be defined as: sufficient EN to meet metabolic demands, sufficient EN to maintain lean body mass and functional recovery, sufficient EN to maintain neurocognitive development, sufficient EN to maintain intestinal barrier functions, or adequate enteral composition to maintain microbiome diversity.

Shifts in Metabolism During Pediatric Critical Illness

An understanding of normal nutritional needs of children and the metabolic response to critical illness helps guide nutritional support recommendations in critically ill children. Critical illness induces a catabolic state with cessation of normal growth [1, 50]. Systemic metabolism shifts away from growth to production of acute-phase proteins, enzymes, and glucose [50, 51]. If this process is prolonged, there is progressive depletion of nutritional resources, which leads to muscle wasting, diminished immune function, and poor wound healing. Pediatric patients with pre-existing chronic illnesses or pre-existing malnutrition are particularly susceptible to adverse sequelae of inadequate nutrition delivery due to their limited macronutrient and micronutrient reserves [52]. In addition, many children develop undernutrition during their PICU stay. While up to 30% have pre-existing acute or chronic malnutrition at PICU admission, up to 58% are malnourished at PICU discharge [3, 6, 53]. When mechanically ventilated, both obese and underweight children are at increased risk compared to normal weight children for worse outcomes [54]. Therefore, comprehensive nutritional support strategies should include early screening and diagnosis of malnutrition (undernutrition and obesity) [55]. In the setting of PARDS, loss of lean body mass may impact respiratory muscle function and prolong ventilator dependence. In addition, therapies commonly used in PARDS patients, such as ECMO and CRRT, may increase nutrition needs or increase risk for specific nutrient deficiencies.

Nutrient Needs During Pediatric ARDS

Protein

Increased early protein delivery is independently associated with decreased mortality in PARDS [4]. Despite cessation of normal growth, protein requirements during pediatric critical illness are increased due to production of acute-phase and immune proteins, and for tissue repair, and may be further increased in the setting of CRRT or ECMO [1]. Increased protein turnover is a hallmark of the metabolic stress response in critical illness and in PARDS. Adequate protein delivery is most important in younger children and patients who are malnourished, as they have limited protein reserves and may quickly develop severe muscle wasting. Children receiving ECMO and CRRT have increased protein turnover, and therefore increased protein needs [56].

The goal of early protein delivery is to limit the impact of protein catabolism on lean body mass and prevent severe muscle wasting. Relevant to patients with PARDS, patients with a prolonged catabolic state may experience decreased cardiopulmonary function secondary to breakdown of cardiac and respiratory muscle masses. Early delivery of protein prevents recruitment of lean muscle mass as the major source of amino acids to acute-phase and immune protein production [56, 57]. Current protein recommendations in critically ill children range from 1.5–3 gm/kg/day, and guideline-recommended minimum protein delivery is 1.5 gm/kg/day for all age groups (see Table 12.3) [58, 59]. Patients with burn injuries present a unique category of PARDS with regard to protein supplementation. In the acute phase of burn injury, and in convalescence, protein supplementation may be insufficient to prevent muscle wasting and require treatment with anabolic steroids or other adjuvant metabolic medications [60]. While extracorporeal support with CRRT allows more liberal fluid administration during preventing fluid accumulation, there are nutritional consequences of dialysis and ultrafiltration. Up to 20% of delivered amino acids are removed in the CRRT effluent; these losses would be expected to be augmented in patients who are on higher clearances [61]. Other specific nutritional deficiencies induced by CRRT caused by loss of water-soluble vitamins and carnitine removal in CRRT effluent need to be taken into account while prescribing nutrition [62]. Monitoring for tolerance of protein is necessary as excess protein delivery is associated with metabolic acidosis, azotemia, and neurologic dysfunction [63, 64]. Advances in body composition assessment that may be informative during PARDS include ultrasound, bioelectrical impedance, CT imaging, and functional outcomes assessments to monitor lean body mass. Close monitoring of lean body mass during PARDS is a possibility, but requires further study [65–68]. New technologies may offer the advantage of monitoring nutritional adequacy based on maintenance of lean body mass as a surrogate to direct measurement of protein requirements.

Table 12.3 Pediatric Acute Lung Injury Consensus Conference and Society of Critical Care Medicine/American Society for Parenteral and Enteral Nutrition recommendations for nutrition risk screening and nutrition management

Directive	PALICC [34]	SCCM/ASPEN [58]
Nutrition screening	No recommendation	Early screening of nutritional status to identify patients at high nutritional risk
Nutrition management		
Nutrition plan	We recommend that pediatric patients with PARDS should receive a nutrition plan to facilitate their recovery, maintain their growth, and meet their metabolic needs	Use of predictive equations to determine energy requirements without the addition of stress factors when indirect calorimetry is not available Target energy for the first week of critical illness should be at least 2/3 of total energy requirements Minimum protein delivery is 1.5 g/kg/day
Enteral nutrition	We recommend that EN, when tolerated, should be used in preference to parenteral nutrition	EN is the preferred route of nutrition delivery
Goal-directed nutrition management	We recommend that EN monitoring, advancement, and maintenance should be managed by a goal-directed protocol that is collaboratively established by the interprofessional team	EN should be initiated within 24–48 hours of ICU admission, and advanced by a stepwise institutional algorithm

Text in this table adapted from: Valentine et al. [34] and Mehta et al. [58]
PALICC pediatric acute lung injury consensus conference, *ASPEN* American society for parental and enteral nutrition, *ARDS* acute respiratory distress syndrome, *EN* enteral nutrition, *ICU* intensive care unit

Energy

Multiple retrospective studies report an association between early energy adequacy and reduced mortality in pediatric critical illness [3, 69]. However, calculation of energy requirements during pediatric critical illness is challenging. The influence of critical illness on metabolism in children is unpredictable, and energy requirements change over the course of the ICU stay [70–72]. And yet, an accurate and precise energy prescription is important because both underfeeding and overfeeding are associated with worse clinical outcomes [3, 58, 72]. Complications associated with underfeeding included delayed ventilator weaning, impaired protein synthesis, organ failure, and an increased risk of sepsis [7, 10, 73, 74]. Overfeeding is associated with delayed ventilator weaning, lipogenesis, hepatic dysfunction, hyperglycemia, increased mortality, and prolonged hospitalization. Several potential mechanisms exist for the negative impact of overfeeding on patient outcome, such as increase in carbon dioxide production, increased intolerance of EN and PN, refeeding syndrome, azotemia and metabolic acidosis from excess protein administration, hepatic steatosis from excess glucose delivery, hyperglycemia, hypertriglyceridemia, and (on the cellular level) the suppression of autophagy [72, 75–77]. Common factors, which may raise or lower total energy expenditure in PARDS, include fever, sedation, temperature support, paralytics, renal replacement therapies, ventilator support, and ECMO. The inter- and intra-individual variation in energy expenditure over the course of the ICU stay necessitates frequent reassessment and adjustment of nutritional support to avoid both under- and overfeeding.

Predictive equations to determine energy needs were developed in populations of patients and are inaccurate when applied to individual patients as they do not sufficiently account for individual variation in energy expenditure. Methods to correctly determine daily energy requirements such as indirect calorimetry (IC) are labor intensive and not available at all institutions [78]. Nor do clinical exams correctly identify patients who are hypometabolic, normometabolic, or hypermetabolic [72]. When available, IC should be used to determine energy expenditure and guide energy prescription, especially in patients at nutritional risk [58]. According to current U.S. guideline recommendations, indirect calorimetry is specifically recommended in the setting of BMI <5th percentile or > 85th percentile, a > 10% change in weight, prolonged ventilation, prolonged muscle relaxation, thermal injuries, oncologic diagnosis, or neurologic injury with dysautonomia [58, 59]. When IC is not available or impractical to perform, predictive equations such as Schofield or World Health Organization should be use without the addition of stress factors to avoid the risks of overfeeding (see Table 12.3) [58]. As most CRRT solutions contain bicarbonate, the impact of bicarbonate flux needs to be taken into consideration if IC will be used in patients on CRRT.

Energy should be provided as a mixture of carbohydrates and lipids with provision of adequate protein to preserve lean body mass. A balanced prescription of carbohydrates and lipids to provide energy in addition to appropriate protein provides sufficient macronutrients while avoiding the potential complications of excess protein, carbohydrates, or lipids. Excess carbohydrates should be avoided as they are converted to lipids with the byproduct of carbon dioxide formation, potentially prolonging mechanical ventilation [79]. Lipid turnover is increased in pediatric critical illness, and lipids are generally limited to 30–40% of calories. An inadequate lipid prescription may lead to rapid development of fatty acid deficiencies in infants and children who at baseline have limited fat stores.

Early Nutrition Support

Delivery of early EN within 48 hours of ICU admission is associated with improved tolerance of future EN and lower 90-day mortality in general critical illness, mechanically ventilated children, and in PARDS [3, 69]. Multiple retrospective studies in critically ill children demonstrate associations between reduced mortality with improved energy and protein adequacy [2, 3, 69]. In a prospective, international study of nutritional practices in 500

mechanically ventilated children, Mehta et al. found decreased odds of mortality for every tertile of increased energy delivered. This relationship was observed when increased energy was enterally, but not parenterally delivered [3]. Wong et al. examined 107 children with PARDS and identified that earlier energy and protein intake were associated with reduced ICU mortality, while protein adequacy was also associated with increased ventilator-free days [4]. Optimizing early, safe EN, rather than delivery of energy or protein via other routes, is important for improving outcomes of PARDS, and is consistent with both the 2015 PALICC Guidelines and the 2017 ASPEN/SCCM Nutrition Support Guidelines [34, 58].

Route of Enteral Nutrition

There are limited data to guide decisions regarding gastric versus postpyloric feeding route. In a study of 74 critically ill children randomly assigned to gastric or postpyloric feeds, no difference in complications was found between study groups. Patients receiving postpyloric feeds did receive more of their daily prescribed calories [80]. Nonetheless, it is not clear if this benefit outweighs the delays to EN initiation to place and confirm position of postpyloric tubes, or interruptions to EN to replace a dislodged or occluded postpyloric tube. Nasogastric tubes are invariably more rapidly placed, and easier to replace. Data in adult ICU patients are also inconclusive regarding benefits of postpyloric tubes. A large meta-analysis of adult patients with severe traumatic brain injury demonstrated a decreased risk of pneumonitis with postpyloric feeds [81]. Other researchers found an increased risk of gastrointestinal complications when postpyloric feeds were used in septic patients or patients on epinephrine [82, 83]. No studies so far have specifically evaluated gastric versus postpyloric feeds in the setting of PARDS.

Parenteral Nutrition in PARDS

Current standard practice in the USA is to reserve PN for situations in which EN fails or is not possible. The Pediatric Early versus Late Parenteral Nutrition in Intensive Care Unit (PEPaNIC) study was an international, multicenter, randomized controlled trial comparing early versus late initiation of PN in critically ill children [84]. The PEPaNIC Trial randomized 1440 children from newborn to 17 years of age to early versus later PN supplementation. They found no difference in mortality between the study allocation groups, but an increase in hospital-acquired infections in the early PN group [85]. This study was not limited to children with PARDS, but supports recommendations that PN should only be used in PARDS patients who fail to tolerate EN or cannot be enterally fed in the first week of ICU stay. Research from neonatal intensive care supports the early use of trophic EN with PN supplementation to support bowel health and meet metabolic needs [86]. The use of combined EN and PN nutrition support, beginning with the first hours to days of life in preterm infants, has been associated with improved growth, improved neurodevelopment, improved EN tolerance, and decreased morbidity at both intermediate- (18 months) and long-term (5 year) follow-up [87–90]. It remains unclear if older or term infants with PARDS might benefit from a similar early PN strategy with regard to long-term neurocognitive outcomes. Despite the results of the PEPaNIC study, equipoise remains pertaining to the PARDS population. The optimal macronutrient dose, timing, and formulation of EN and PN support are yet to be elucidated as increasing evidence demonstrates links among the immune system, homeostasis, and nutritional intake [81, 91–94]. Questions remain whether early PN is of benefit or harm in PARDS, or if various IV lipid formulations or supplements could be of benefit. The current clinical focus is to provide sufficient energy and protein preferentially by the enteral route when safe to do so, until further studies are completed.

Failure to Receive Enteral Nutrition

Median delivery of enteral nutrition is 40–75% of goal during the first week of critical illness

[3, 5–10]. Reasons for failure to receive EN are broadly categorized as medical contraindication, prescriber discomfort, and frequent interruption [7, 9, 95, 96]. Noninvasive ventilation (NIV) is increasingly used as a first-line respiratory support modality in PARDS, and is associated with worse nutritional adequacy [97]. We do not know if perceived potential benefits to NIV, used to avoid invasive mechanical ventilation, are outweighed by risks of underfeeding. Cited relative contraindications to EN often include a need for volume restriction, hemodynamic instability, and ill-defined feeding intolerance. Hemodynamically unstable adults requiring vasopressors have lower mortality when receiving early EN [98]. Large database studies do not demonstrate increased adverse outcomes in children fed enterally while on vasoactive infusions; however, in small studies, children with hemodynamic instability who develop complications of EN have worse outcomes than children who were never enterally fed [82, 99]. Therefore, provider reluctance to initiate or advance EN in the setting of hemodynamic instability may be justified [82]. Research is needed to better identify patients who will and will not develop complications from EN when on vasoactive infusions.

Feeding intolerance is the most frequent cause of interruption to EN and occurs in 45–57% of critically ill children [9, 100]. There is immense variability in clinician assessment of feeding intolerance and frequently used clinical criteria such as emesis, bowel sounds, abdominal exam, gastric residual volumes, diarrhea, and lactate levels are either imprecise, subjective, or have poor interrater reliability [9, 95, 101, 102]. The definition of feeding intolerance is widely variable between providers and centers, and no standardized definition or "score" is validated. Delayed gastric emptying occurs in up to 50% of critically ill children, yet remains underrecognized as a clinical concern in the PICU [103]. Poor intestinal motility is often multifactorial in nature, due to opioid drips and other elements of critical illness. Only erythromycin and metoclopramide are FDA-approved as promotility agents to treat gastric and intestinal dysmotility during pediatric critical illness and have variable success at improving poor motility in the PICU. Newer promotility agents such as cholecystokinin receptor antagonists, ghrelin, and methylnaltrexone, in the setting of opioid-induced dysmotility, are under evaluation in pediatric critical illness [104, 105]. Early initiation of a bowel regimen to prevent constipation and subsequent feeding intolerance should be prescribed and the patient monitored for diarrhea and constipation, especially for children on opioid drips. Poor intestinal motility, delayed gastric emptying, and lack of an appropriate bowel regimen may delay achievement of goal EN.

Objective biomarker-based tools for the safe initiation and advancement of EN would decrease barriers to nutritional support and improve delivery of EN, but no such tools currently exist. Ideally, biomarkers to guide EN advancement would predict which patients would experience complications of EN in the first week of ICU stay, and identify patients who might benefit from PN to achieve macronutrient goals. Procedures are also a frequent cause of interruption of nutritional support [9]. Noninvasive ventilation and intensive therapies such as ECMO are associated with failure to achieve goal EN [106, 107]. One strategy successfully employed in adult ICUs to improve nutritional adequacy is a strategy of volume-based daily enteral feed goals rather than an hourly feed goal [108]. Volume-based orders prescribe a daily volume goal for EN, typically delivered over 18–20 hours rather than the traditional 24-hour delivery. This strategy automatically accommodates usual feed interruptions for procedures, so that total volume of prescribed EN is delivered when possible throughout the day. No matter the method, presence of a multidisciplinary team focused on nutrition support in the PICU is an important part of a successful nutrition program. Implementation of an early EN guideline improved percent of goal energy and protein achieved in multiple retrospective studies, likely due to perceived emphasis on nutrition in a particular PICU and change in clinician behaviors for prescribing nutrition [109, 110].

The Gut as the Motor for ARDS

Gastrointestinal Tract and Microbiome Influences Immune and Lung Function in ARDS

The gastrointestinal tract is a primary lymphoid organ, housing 70% of all of the body's immune cells [111–114]. The intestinal microbiota plays an important role not only in the development of the immune system in infancy, but also in shaping systemic and pulmonary immune responses during critical illness [115, 116]. Diet is a potent determinant of intestinal microbiome diversity and of intestinal barrier function, and in murine models is more important than genetic background in predicting microbial community composition [117]. Carmody et al. found that rapid changes in diet resulted in rapid shifts in microbial composition [117]. In health, the gut microbiome helps to regulate lung immunity and host defenses through several mechanisms. Intestinal commensal (beneficial) bacteria act to directly counteract proinflammatory bacteria, decrease the overall inflammatory "tone," and preserve intestinal epithelial barrier function, preventing the translocation of inflammation-inducing bacterial components [115, 116, 118, 119]. Dysbiosis, the imbalance in the gut microbiome characterized by increased relative abundance of pathobionts and decreased relative abundance of commensal bacteria, occurs in ARDS, and is further exacerbated by treatment factors such as antibiotic use, altered intestinal pH, and prolonged critical illness [115, 120, 121]. In pediatric critical illness, this dysbiosis is characterized by increased relative abundance of pathobionts such as *Enterococcus* and *Staphylococcus,* and decreased relative abundance of beneficial commensal organisms such as *Ruminococcus* and *Faecalibacterium* [120, 122]. In addition, virulence of Gram-negative pathobionts is enhanced when nutrient deprivation occurs during systemic stress or opioid exposure, a common clinical scenario in PARDS patients [123]. Through effects on the intestinal microbiome and the intestinal epithelial barrier, specific nutrients and pre- or probiotics may impact lung and systemic proinflammatory tone and neutrophil accumulation in the setting of PARDS [124–126]. Nonnutritive benefits of enteral feeding include reduction in proinflammatory signaling to the lung, an important potential therapeutic target in PARDS [111, 127, 128]. An area of emerging research surrounds the role of nutritional support and the intestinal microbiota in shaping systemic and pulmonary inflammation and immune responses in ARDS.

Immunonutrition

Despite initial encouraging results from small single-center studies of individual pharmaconutrients, multiple larger trials of combination pharmaconutrients designed to modulate the inflammatory response in critically ill adults have not shown benefits or have shown harm [129, 130]. Combination therapies have included: various antioxidants, arginine, glutamine, metoclopramide, ω-3 polyunsaturated fatty acids (PUFA's), zinc, and selenium [131–137]. The Randomized Comparative Effectiveness Pediatric Critical Illness Stress-Induced Immune Suppression (CRISIS) Prevention Trial evaluated daily enteral zinc, selenium, glutamine, and IV metoclopramide in critically ill children. The primary outcome was the incidence of nosocomial infections. The trial was stopped early due to futility, although secondary analysis of the dataset does suggests further research is needed in patients with baseline immune dysfunction [134].

Research continues to evaluate ω-3 PUFAs and their downstream mediators as potential pharmaconutrient targets in PARDS. Rationale behind ω-3 PUFAs is that they would directly compete with ω-6 PUFAs, and act to decrease the synthesis of proinflammatory eicosanoids, increase production of anti-inflammatory lipid mediators such as resolvins and protectins, decrease chemotaxis, decrease Reactive Oxygen Species (ROS) and proinflammatory cytokines, and decrease leukocyte binding and activation through decreased expression of adhesion molecules [138]. It is not clear if improving these intermediate biochemical targets would result in

improved clinical outcomes, and this would possibly depend on appropriate identification of PARDS subphenotypes that were more proinflammatory and therefore more likely to benefit from an anti-inflammatory treatment strategy.

Multiple studies identify an association between decreased vitamin D levels and increased risk of ARDS, although the mechanistic underpinnings of this association are not currently understood [139–141]. Vitamin D deficiency is associated with impaired pulmonary function and increased incidence of viral and bacterial infections, relevant to ARDS [142–144]. Vitamin D deficiency status may prove to be an important element of a PARDS subphenotype that predicts treatment responses. Vitamin D is known to modulate macrophage, lymphocyte, and epithelial cell functions and is therefore a rational target for further study in ARDS pathophysiology [140, 145]. It unknown if treatment with vitamin D supplementation has any role in PARDS management. Multiple nutrient deficiencies are known to occur during critical illness, but it is unclear if these truly reflect deficiency states, or reflect adaptation or redistribution as a response to critical illness. Further clinical trials are needed to assess the individual contributions of specific micronutrient replacement and nutritional modulation of the immune system to understand if there is a role for these therapies in PARDS.

Summary

The balanced management of nutritional status, fluid overload, and AKI presents unique challenges when caring for children with PARDS. Careful multidisciplinary team-based care is necessary to prescribe guideline-recommended minimum macronutrient needs to preserve lean body mass and respiratory muscle function, to avoid fluid overload, and coordinate care for AKI. As we improve our understanding of patient phenotypes and crosstalk among the lung, kidney, and gastrointestinal tract, highly personalized nutritional and fluid management strategies will likely emerge based on patient severity of illness, premorbid nutritional risk, the inflammatory phenotype in ARDS, measured energy expenditure, active monitoring of lean body mass, and the composition of patient intestinal microbiome. A select group of high-risk patients are likely to especially benefit from a tightly titrated nutritional, fluid, and kidney resuscitation plan, which may include early mechanical fluid removal. Long-stay patients; patients with PARDS, sepsis, or burns; and children with pre-existing severe malnutrition are most likely to benefit from a personalized nutrition and fluid approach, which takes into consideration the interrelatedness of these organ systems.

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Heart–Lung Interactions and Cardiovascular Support in Pediatric Acute Respiratory Distress Syndrome

Saul Flores, Rohit S. Loomba, and Ronald A. Bronicki

Introduction

ARDS is characterized by bilateral diffuse alveolar disease on radiograph, restrictive lung physiology, a decrease in FRC, intrapulmonary shunt, and arterial hypoxemia. In ARDS, significant positive airway pressure is often needed in order to recruit collapsed alveoli and maintain alveolar patency. Despite improving oxygenation, the use of PPV may lead to a decrement in CO, negating the increase in oxygen content, or in more severe cases a decrease in systemic DO_2. In this chapter, we will discuss the physiologic underpinnings of heart–lung interactions, with an emphasis on the impact of PPV on RV loading conditions and output and the salient aspects of the pathophysiology of ARDS in order to discuss the impact, assessment, and treatment of PPV-induced cardiovascular dysfunction in pediatric ARDS.

While there are similarities in pediatric and adult ARDS, there are several factors that are unique to children that may influence the pathophysiological process and disease progression [1]. The lung parenchyma undergoes significant structural remodeling and growth during childhood; the innate and adaptive immunological response to infection and injury differs between children and adults; and there are differences in the underlying condition (e.g., pneumonia vs. sepsis and type of organism) and comorbidities. These age-related differences, and the fact that our understanding of the disease process and treatment strategies are primarily derived from adult studies, should be kept in mind as we discuss pediatric ARDS.

The Effects of Respiration on Cardiovascular Function

The Effects of Respiration on Right Ventricular Preload

Respiration has a significant impact on systemic venous return; thus, a review of the determinants of systemic venous return is germane to any discussion of cardiopulmonary interactions. The force responsible for driving systemic venous return from the periphery to the central venous structures is the pressure gradient that exists between the systemic venous reservoirs and the right atrium (RA) [2]. The resistance to venous return remains remarkably constant under a

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number of conditions, including large adrenergic stimulation.

The pressure within the systemic venous reservoirs is equal to the mean systemic pressure (P_{ms}). The P_{ms} is a function of intravascular volume and vascular capacitance, the vast majority of which reside within and with the systemic venous reservoirs, respectively. These venous reservoirs, the most important of which are located within the splanchnic and cutaneous circulations, are much more compliant than, and have 18 times the capacitance of, the systemic arterial resistance vessels and thus contain the majority of intravascular volume (upward of 70% of total). For these reasons, the function of the venous reservoirs is an important determinant of systemic venous return and therefore CO. Guyton and colleagues found the P_{ms} to be 7 mmHg in dogs and the normal mean RA pressure is 2 mmHg, producing a driving pressure for systemic venous return under normal conditions of 5 mmHg [3]. Based on this conceptual framework, the pressure generated by the heart has no direct influence on systemic venous return, and the flow into the systemic arterial circuit is only relevant insofar as it is responsible for maintaining the volume of the venous reservoirs [4].

The P_{ms} increases as intravascular volume expands, which occurs over hours with stimulation of neurohormonal pathways, or acutely with the administration of volume. Intravascular volume expansion produces a linear increase in the P_{ms}. An immediate compensatory increase in the P_{ms} occurs with vasoconstriction of the venous capacitance vessels. An increase in venomotor tone reduces the compliance and therefore capacity of the venous reservoirs, increasing the pressure within. Venoconstriction increases the P_{ms} and then plateaus, with the most pronounced increase in vasomotor tone occurring with the Cushing reflex. Endogenous catecholamines, angiotensin, and vasopressin are the primary mediators of this acute compensatory circulatory mechanism for maintaining an adequate P_{ms} and systemic venous return. Pharmacologic agents, such as furosemide, nitric oxide donors such as nitroprusside and nitroglycerin, and combined inodilators such as milrinone and dobutamine, vasodilate venous reservoirs, increasing their capacitance, and decreasing the P_{ms} and systemic venous return. Pathophysiologic states such as sepsis may induce vasomotor paresis increasing venous capacitance while decreasing intravascular volume as a result of an increase in microvascular permeability. The net effect is a marked reduction in the P_{ms} and systemic venous return.

The downstream pressure for systemic venous return is the RA pressure, which is affected by a number of factors including cardiac function and the cardiac cycle (so-called cardiac suction factors) and most importantly respiration. For example, during spontaneous respiration, intrathoracic pressure (ITP) decreases, the transmural pressure (P_{tm}; P_{tm} = inside – surrounding pressure]) for intrathoracic structures increases, which when positive distends a structure in proportion to its compliance (P_{tm} = volume/compliance). Thus, as ITP decreases, the RA P_{tm} and chamber volume increase and the pressure within falls, driving systemic venous return.

With PPV the opposite occurs. During PPV, the ITP throughout the respiratory cycle is above atmospheric pressure, which decreases the RA P_{tm} and its pressure rises. For a given P_{ms} an increase of only 1 mmHg in RA pressure decreases systemic venous return by 14%. As RA pressure approaches P_{ms}, systemic venous return ceases unless circulatory reflexes compensate by increasing P_{ms} [2]. As described above, this is accomplished acutely with adrenergic stimulation and over time with retention of intravascular volume.

It is important to recognize that the increase in RA pressure that occurs during PPV results from an increase in ITP and decrease in the RA P_{tm} and not from an increase in systemic venous return and RA filling. It may seem counterintuitive that an increase in RA pressure may be associated with a decrease in systemic venous return, RA filling, and, ultimately, RV stroke volume because RA pressure is used as an indicator of RV preload. However, the increase in RA pressure is due to a decrease in its effective compliance, which results from an increase in surrounding pressure/decrease in P_{tm}. Pinsky and colleagues demonstrated that it is the effect of interventions such as

changes in ITP or intravascular volume on the RA P_{tm} and not the RA pressure per se that correlates with RV stroke volume [5].

The extent to which systemic venous return is affected by PPV depends on several factors, including the extent to which positive airway pressure is transmitted to the intrathoracic vascular structures (discussed under respiratory mechanics below) and the adequacy of circulatory reflexes to maintain an adequate P_{ms}. Another important related factor is where the RV resides on its pressure stroke volume curve (Fig. 13.1). A congested RV will tolerate a decrease in systemic venous return (i.e., stroke volume will be unchanged) so long as it remains operating on the flat portion of its pressure stroke volume curve. However, if the decrease in systemic venous return causes the RV to fall onto the ascending portion of its pressure stroke volume curve, stroke volume will decrease. Ultimately, RV end-diastolic volume is a function of its diastolic P_{tm} and compliance and, as is the case for the RA, for a given RV filling pressure, as the surrounding pressure increases, its effective compliance, and the extent to which it fills, decreases.

The Effects of Respiration on Right Ventricular Afterload

Respiration affects pulmonary vascular resistance (PVR) by altering blood pH, alveolar oxygen tension, and lung volumes. Respiratory and metabolic alkalosis induces pulmonary vascular vasodilation, whereas acidosis causes vasoconstriction.

Respiration also affects PVR by altering lung volumes. This cardiopulmonary interaction is not mediated by changes in ITP per se, but rather is a function of the alveolar P_{tm}, regardless of the mode of ventilation, and respiratory system compliance. Alveolar vessels lie within the septa, which separate adjacent alveoli. Alveolar pressure is the surrounding pressure for these vessels. Extra-alveolar vessels are located in the interstitium and are exposed to intrapleural or

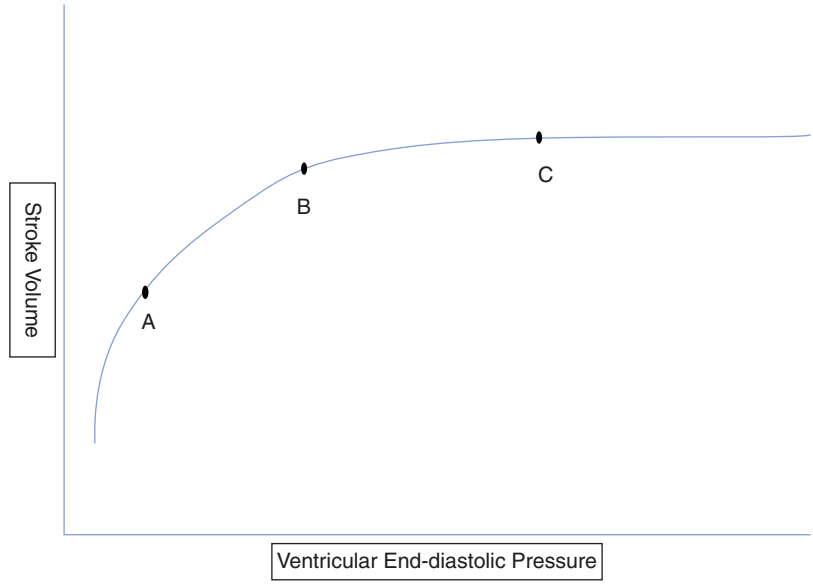


Fig. 13.1 Ventricular pressure stroke volume curve. With a decrease in systemic venous return, the ventricle moves from position C to B, diastolic volume and therefore pressure decrease while stroke volume remains unchanged. With a further decrease in systemic venous return (B to A), ventricular diastolic volume and pressure fall further and stroke volume decreases. Conversely, moving from position A to B with volume administration for example increases stroke volume; however, additional volume (B to C) increases diastolic volume and pressure but stroke volume does not increase

ITP. Because alveolar and extra-alveolar vessels are in series, the resistance provided by each are additive. FRC is the lung volume from which normal tidal volume breathing occurs. PVR is lowest near the FRC and increases at both high- and low-lung volumes albeit for different reasons.

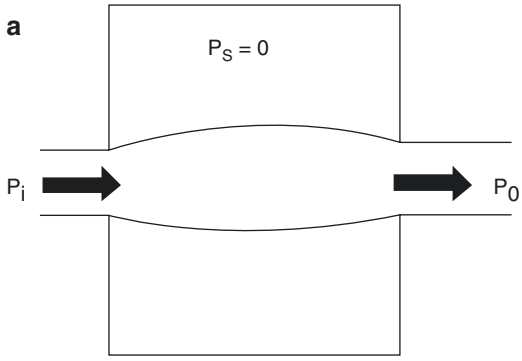
At low-lung volumes, the radial traction provided by the pulmonary interstitium diminishes, leading to a decrease in the cross-sectional area of the extra-alveolar vessel. In addition, low end-expiratory lung volumes and alveoli collapse lead to hypoxic pulmonary vasoconstriction, and the resistance of extra-alveolar vessels increases further. Meanwhile, the P_{tm} of alveolar vessels increases, the vessels distend, and resistance falls because the alveolar P_{tm} has decreased. Nonetheless, the net effect is for PVR to increase at low-lung volumes.

As lung volumes rise well above FRC, PVR increases. Large tidal volumes or tidal volumes superimposed on an elevated FRC significantly increase PVR. With large lung volumes, overdistended alveoli compress interalveolar vessels, decreasing the P_{tm} for the interalveolar vessel and increasing PVR. With PPV, the interstitial pressure is positive, decreasing the P_{tm} for the extra-alveolar vessels as well, contributing to PPV-induced increases in PVR. In other words, during PPV, alveolar and intrapleural pressures are positive during inspiration and expiration and resistance is elevated in both alveolar and extra-alveolar vessels throughout the respiratory cycle. This is in contrast to an increase in lung volume due to negative pressure ventilation where interstitial pressure is negative. Despite the fact that alveolar recruitment improves oxygenation thereby releasing hypoxic pulmonary vasoconstriction of extra-alveolar vessels, and an increase in lung volume increases the radial traction and cross-sectional area of the extra-alveolar vessels, the net effect of large lung volumes is to increase PVR.

The extent to which lung volume affects PVR also depends importantly on pulmonary vascular hydrostatic pressures (Fig. 13.2). In the lung, pulmonary arterial pressure is the inflow pressure (P_i), pulmonary venous pressure is the outflow downstream pressure (P_o), and alveolar pressure is the surrounding pressure (P_s). In addition, there is a vertical hydrostatic pressure gradient from the most dependent to the most superior portions of the lung. Because the weight of air is negligible, there is no measurable vertical gradient for alveolar pressure. In the gravity-dependent portions of the lung, P_i and P_o are greater than P_s and the P_{tm} for the alveolar vessel is positive throughout and the vessels is widely patent (zone III conditions) (Fig. 13.2). With progression to the non-gravity-dependent regions of the lung, PVR begins to increase as P_s becomes greater than P_o but remains less than P_i (zone II conditions) (Fig. 13.2). In the event that P_s becomes greater (as with PPV) than P_i and the P_{tm} for the alveolar vessel becomes negative, the vessel collapses and flow ceases (zone I conditions) (Fig. 13.2). In the absence of cardiopulmonary disease, zone I conditions do not exist. *However, the proportion of lung units under zone I and II conditions increase in a variety of clinical settings, such as when alveoli becomes overdistended and or when pulmonary perfusion decreases*. In contrast, conditions such as left-sided heart disease significantly mitigate if not eliminate the propensity to develop lung regions under zone I and II conditions because pulmonary venous hypertension causes P_o and P_i to exceed P_s throughout the lung.

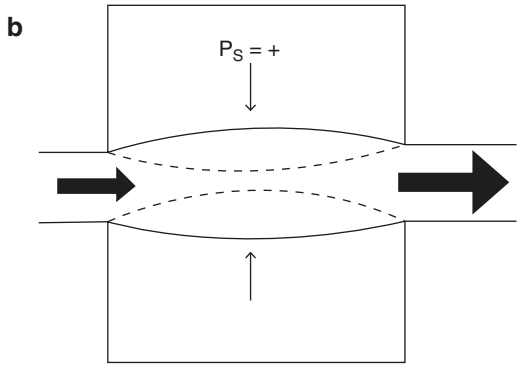
RV Performance and Ventricular Interaction

An important determinant of the impact of PPV-induced increases in RV afterload on cardiopulmonary function is RV systolic function. The RV contracts by 3 mechanisms: inward movement of the free wall, which produces a bellow-like effect; contraction of the longitudinal fibers, which shortens the long axis and draws the tricuspid annulus toward the apex; and traction on the free wall at the points of attachment secondary to left ventricular (LV) contraction (i.e., systolic ventricular interaction – discussed below) [6]. With a progressive increase in RV afterload, compensatory ventricular hypertrophy maintains ventricular arterial coupling and stroke volume is



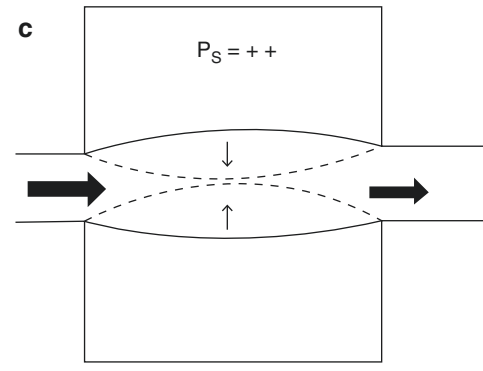
Baseline (Zone III)

- $P_i > P_0 > P_S$
- $Q = P_i - P_0$



P_S increases (Zone II)

- $P_i > P_S > P_0$
- $Q = P_i - P_S$
- Resistance to inflow increases
- $P_{TM}\downarrow$, the volume of the tube $\downarrow$ / pressure $\uparrow$ and outflow increases transiently



P_S increases further (Zone I)

- $P_S > P_i$
- Resistance to Q increases further
- P_{TM} becomes negative, the tube collapses and flow may cease

Fig. 13.2 The relationship between lung volume, pulmonary vascular hydrostatic pressure, and pulmonary vascular resistance in a patient receiving positive pressure ventilation for acute respiratory distress syndrome. P_s, surrounding (alveolar) pressure for the interalveolar vessel; P_i and P_o, inlet and outlet pressure for the interalveolar vessel; Q, flow; P_{tm}, transmural pressure. *Condition A*: Base of the lung where hydrostatic pressure is at its greatest and P_s is at its lowest (collapsed lung): P_i and P_o are greater than P_s, and the alveolar vessel is widely patent; zone III conditions; $Q = P_i - P_o$. *Condition B*: Proceeding from the base to the apex of the lung. Vascular hydrostatic pressure has fallen due to the effects of gravity, and P_s has increased as airway pressure distends alveoli to a greater extent in the less gravity-dependent portions of the lung. $P_i > P_s > P_o$, resistance to flow has increased as the P_{tm} for the alveolar vessel has decreased and the vessel is partially compressed; $Q = P_i - P_s$; zone II conditions. *Condition C*: Apex of the lung where vascular hydrostatic pressures are at their minimum and alveoli are over distended. $P_s > P_i$, the P_{tm} for the alveolar vessel becomes negative, the vessel collapses, and Q ceases; Zone I conditions

preserved [7]. However, even a *modest acute* increase in afterload causes stroke volume from the unprimed RV to decrease, which is much less responsive to increases in preload and much more sensitive to increases in afterload than the LV.

RV systolic dysfunction (primary or secondary to an acute increase in afterload) decreases LV filling and CO by three mechanisms. In addition to a decrease in RV stroke volume and output, RV dysfunction compromises LV filling as a result of ventricular interdependence [6]. Ventricular interdependence describes how a change in volume and pressure in one ventricle affects the pressure–volume relationship for the other, and how LV contraction contributes to RV systolic pressure and ejection (Fig. 13.3). The substrate for this phenomenon is the intimate anatomic relationship of the right and left ventricles, which includes interlacing muscle bundles, the atrial and ventricular septum, and the pericardium.

RV afterload-induced systolic dysfunction causes ventricular volume and therefore pressure to be elevated throughout the cardiac cycle, decreasing if not eliminating the normal transseptal pressure gradient (Fig. 13.3). Under normal conditions, LV diastolic pressure is greater than right causing the interventricular septum (IVS) to bow into the RV (Fig. 13.3). With RV diastolic hypertension, the IVS occupies a more neutral position between the two ventricles (Fig. 13.3). If RV diastolic pressures were to rise above left, the septum would actually bow into the LV. In either case, the LV becomes restrained not only by RV pressure and the deviated septum but also its free wall becomes constrained by the pericardium and potentially lung. These factors decrease the effective compliance of the LV. Even though LV diastolic pressure is elevated, intrapericardial pressure has risen to a greater extent, and the net effect is a reduced LV diastolic P_{tm} and LV filling. This phenomenon is known as *diastolic ventricular interdependence.*

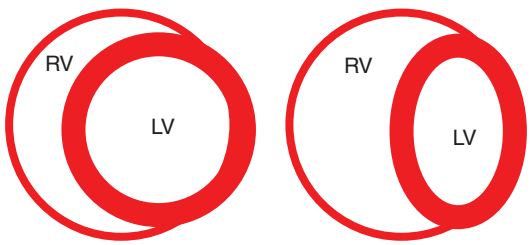
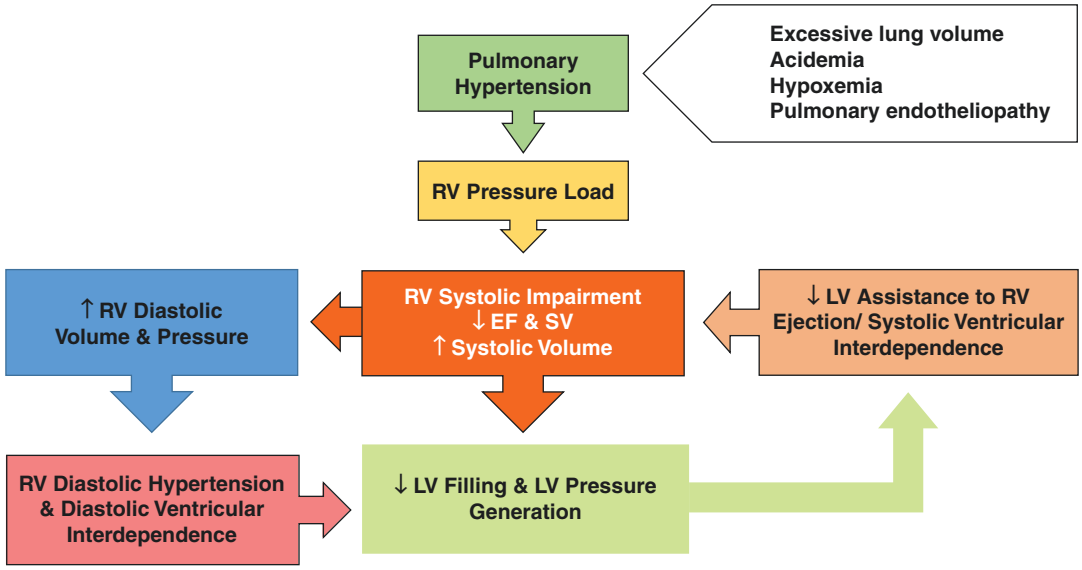


Fig. 13.3 Ventricular interdependence. Cartoon of a parasternal short-axis view of the left and right ventricles (LV, RV). Under normal conditions, the interventricular septum is oriented such that in the short axis the LV is circular. Under conditions when the pressure in the RV is elevated, the interventricular septum is displaced to the left, decreasing the effective compliance of the LV. Without an increase in the LV diastolic transmural pressure, LV filling decreases

As LV filling decreases, the LV is less able to generate tension and pressure. The significance of this as it relates to the circulation with pulmonary hypertension and RV systolic dysfunction is that the LV is responsible for generating upward of 40% of RV systolic pressure. This phenomenon appears to be mediated by the IVS. The greater the displacement of the IVS by the contracting LV into the RV cavity, the greater is the contribution to RV systolic pressure generation. This decrease in LV assistance to RV ejection leads to further increases in RV volume and pressure, which further impairs LV filling and pressure generation, and a vicious cycle ensues (Fig. 13.4). This phenomenon is known as *systolic ventricular interdependence*. Adverse diastolic and systolic ventricular interactions are an integral part of the pathophysiology of several diseases, including RV afterload-induced RV systolic failure. An assessment of ventricular interaction and therapeutic strategies that address these adverse interactions is essential to optimizing the management of patients with PPV-induced RV systolic impairment.

Respiratory Mechanics

Most commonly the decrease in compliance, or increase in elastance, of the respiratory system in ARDS has been attributed to changes in lung compliance. However, it is important to consider changes in chest wall compliance when implementing PPV to improve oxygenation and just as importantly when considering and discussing the impact of PPV on RV loading conditions and output.



RV, right ventricle; LV, left ventricle; EF, ejection fraction; SV, stroke volume

Fig. 13.4 Pathophysiology of low cardiac output in pulmonary arterial hypertension. *RV* right ventricle, *LV* left ventricle, *EF* ejection fraction, *SV* stroke volume

The respiratory system includes the lung and chest wall and the overall mechanical behavior depends on the mechanical characteristics of its components and their interactions. The chest wall, consisting of the thoracic cage and diaphragm (the latter mechanically links the abdominal cavity to the thorax), and lungs are in series and may be expressed as follows when airway resistance is minimal: $P_{aw} = P_{tp} + P_{pl}$ and $E_{tot} = E_L + E_{cw}$, where P_{aw} is static airway pressure, P_{tp} is transpulmonary pressure, P_{pl} is pleural pressure, E_{tot} is total respiratory system elastance (elastance is inversely related to compliance), E_L is lung elastance, and E_{cw} is chest wall elastance [8]. By rearranging this equation, it follows that: $P_{pl} = P_{aw} \times E_{cw}/E_{tot}$, which enables us to consider the impact of changes in lung and chest wall elastance on P_{pl} (ITP) and therefore the impact of P_{aw} on RV loading conditions under a variety of conditions.

For a given P_{aw}, as *E_{cw} rises P_{pl} increases*, increasing ITP and RA pressure and potentially decreasing systemic venous return, while decreasing the RV diastolic P_{tm}, contributing to a decrease in RV filling. For the same P_{aw}, as P_{pl} rises the P_{tp} decreases, decreasing end-expiratory lung volume and tidal volume, with an indeterminate effect on RV afterload (derecruitment and hypoxic pulmonary vasoconstriction versus decreasing the extent of alveolar overdistension and the proportion of lung regions under zone I and II conditions). Conversely, for a given P_{aw}, as E_L increases, the transmission of airway pressure and thus P_{pl} decreases.

Chest wall elastance may be elevated due to a number of factors, including chest wall edema and pleural effusions, as well as factors responsible for increasing abdominal pressure, such as obesity, ascites, and visceromegaly. The importance of considering E_{cw} in the management of ARDS cannot be overstated, as it has a profound impact on respiratory and cardiovascular function and at least in adults may impact outcomes [8].

The Effects of Respiration on Left Ventricular Afterload

While the primary impact of PPV on cardiovascular function in patients with ARDS is on RV loading conditions, other factors may come into play that adversely impact LV function (e.g., underlying LV dysfunction, sepsis-mediated ventricular dysfunction). Thus, an understanding of

the impact of respiration on LV function is relevant to the management of the critically ill patient with ARDS [2]. Just as changes in ITP affect the return of blood from the periphery to the heart, so too does it affect the egress of blood from the thoracic to extrathoracic arterial system.

During spontaneous respiration, the fall in ITP increases the P_{tm} and therefore volume for the thoracic arterial system. As a result, the pressure within these structures decreases relative to the extrathoracic arterial system and LV afterload increases. If the fall in ITP occurs during ventricular diastole, antegrade flow runoff decreases, resulting in an increase in thoracic arterial blood volume and an increase in the inertial forces opposing ejection during the following systole. A fall in ITP during ventricular systole decreases LV ejection and stroke volume and the egress of blood from the thorax. As LV systolic function wanes or as ITP becomes more negative, the adverse impact of respiration on LV afterload increases. With PPV, the decrease in P_{tm} for the thoracic arterial system increases the pressure within these structures ("reverse pulsus paradoxus") creating a waterfall-like effect, driving blood into the extrathoracic compartment.

With impaired LV systolic function, the rise in pulmonary venous pressure will markedly enhance the rate and extent of extravascular lung water (EVLW) formation, necessitating even greater positive airway pressure. However, the elevation in pulmonary venous pressure significantly reduces the propensity to develop lung regions under zone I and II conditions. Meanwhile, because the afterload for the RV is elevated, it should be operating on the flat portion of its pressure stroke volume curve, rendering it less sensitive to decreases in systemic venous return. Therefore, PPV should have a significant beneficial impact on cardiopulmonary function in these circumstances.

The Acute Respiratory Distress Syndrome

Pathophysiological Processes

ARDS results from inflammation caused by pulmonary and/or extrapulmonary insults, most commonly pneumonia and sepsis, respectively, which transforms the pulmonary endothelial cell phenotype into a prothrombotic and proinflammatory state. Activated neutrophils are sequestered within the pulmonary vasculature, where they cause endothelial and alveolar epithelial damage, leading to a marked increase in vascular permeability and the development of interstitial and alveolar edema, as well as allowing for the extravasation of plasma proteins and the formation of alveolar hyaline membranes. Injury to type II alveolar epithelial cells type decreases surfactant production, which is compounded by surfactant inactivation by extravasated plasma proteins. The decrease in surfactant activity increases alveolar surface tension forces, promoting alveolar collapse.

While the increase in air–blood barrier permeability is evenly distributed, and EVLW is diffusely increased, a vertical, gravitational gradient exists for lung densities and EVLW formation [9]. The increase in lung weight exaggerates the normal compressive gravitational forces present in lung parenchyma, leading to the formation of nonaerated tissue in gravity-dependent regions of the lung. Lung tissues in nondependent regions of the lung are well aerated with near-normal mechanical characteristics [9].

Pulmonary hypertension is invariably present to a varying degree in patients with ARDS [10]. The are several factors responsible for the development of pulmonary hypertension including those related to lung volume described previously and include a shift in the pulmonary endothelial cell phenotype to a prothrombotic and proinflammatory state, leading to microvascular occlusion by thrombi and cells (neutrophils and platelets) and endothelial injury and dysfunction, leading to an imbalance between vasodilating and vasoconstricting mediators.

The primary gas exchange abnormality in ARDS is impaired oxygenation due to alveolar collapse. Studies of adult patients with ARDS have demonstrated that the primary abnormality responsible for arterial hypoxemia is pulmonary shunt, with only a small portion of lung units demonstrating low ventilation to perfusion (V/Q) ratios [11]. As with other lines of investigation, diffusion abnormalities do not contribute to

impaired oxygenation [12]. Hypoxic pulmonary vasoconstriction limits perfusion to non- or poorly ventilated alveoli, improving the relationship between ventilation and perfusion and oxygenation. An additional factor that may contribute to arterial hypoxemia is the presence of a patent foramen ovale and right-to-left atrial shunting**.** Areas of high ventilation to perfusion ratios contribute to impaired gas exchange in ARDS by wasting ventilation and impairing CO_2 clearance, and result from those factors that lead to alveolar overdistension and a decrease in pulmonary perfusion. The presence of right-to-left atrial shunting and dead-space ventilation not only impact the acute management of but have been shown to be of prognostic significance in adult patients with ARDS [13–15].

PPV-Induced Cardiovascular Dysfunction in ARDS

Despite the use of lung-protective ventilation for ARDS, PPV may induce significant heart–lung interactions that adversely impact gas exchange, RV loading conditions, CO and ultimately systemic DO_2 [16]. PPV may compromise RV output predominantly as a result of an increase in ITP and decrease in systemic venous return and RV filling, increase in PVR and impaired RV systolic performance, or a combination of both [16].

More than 60% of adult patients with ARDS experience hemodynamic failure, necessitating vasoactive support [17, 18]. ARDS is frequently associated with RV dysfunction, the most severe form of which is acute cor pulmonale, which occurs in 25–30% of adult patients with ARDS [19, 20]. Further, RV dysfunction has been shown to be independently associated with a higher risk of death in these patients [21, 22].

PPV may decrease RV filling by increasing RA pressure and decreasing the pressure gradient for systemic venous return. The extent to which this occurs depends on the adequacy of circulatory reflexes to elevate the P_{ms}, where the RV is positioned on its pressure stroke volume curve and the degree to which airway pressure is transmitted to intrathoracic structures, the latter of which is a function of respiratory system elastance. In any case, a greater RV diastolic P_{tm} is needed to maintain RV filling, as PPV reduces the effective compliance of the RV.

RV output may be decreased due to primarily an increase in afterload, resulting from PPV-induced alveolar overdistension. As discussed, during PPV the *non-gravity-dependent region* of the lung is well aerated and possesses near-normal compliance and thus receives a disproportionate amount of the airway pressure, resulting in alveolar overdistension (Fig. 13.2) [9]. Blood flow in this region is limited due to the effects of gravity on pulmonary perfusion, which is compounded by the factors that limit RV output such as decrease in RV preload reserve, pulmonary endothelial dysfunction, and, in severe sepsis, cytokine-mediated cardiomyocyte dysfunction (Fig. 13.2) [23, 24]. Pulmonary vascular resistance increases to the extent that zone I and II conditions are created in the lung, which depends on alveolar and interalveolar vessel pressures.

A limitation of preload and increase in afterload may combine to decrease RV output. With an increase in afterload, a compensatory increase in preload is needed to maintain stroke volume, which may be limited for the reasons discussed [25]. Vieillard-Baron and colleagues described this finding in their study of adult patients with ARDS using echocardiography with Doppler to evaluate beat-to-beat inflow and outflow and ventricular dimensions throughout the respiratory cycle [25]. They demonstrated inspiratory reductions in RV fractional area contraction associated with a significant increase in RV end-systolic dimensions, while RV end-diastolic area remained unchanged. They concluded that this likely reflects a relative decrease in RV preload because an increase in afterload and end-systolic volume should produce a corresponding (compensatory) increase in preload.

The incidence and severity of PPV-induced cardiovascular dysfunction in pediatric ARDS are unknown. A timely and objective assessment of cardiovascular function is essential for optimizing the management of the pediatric patient with ARDS.

Assessment of Cardiovascular Function and Tissue Oxygenation

Standard hemodynamic monitoring (blood pressure, central venous/RA pressure, heart rate) as well as adjunctive monitoring modalities are indicated in patients with ARDS in order to determine if and to what extent and by which mechanism(s) PPV has compromised cardiovascular function (Table 13.1). The proceedings of the Pediatric Acute Lung Injury Consensus Conference recommend that with increasing end-expiratory pressure and with arterial oxygen saturations (SaO_2) of less than 92%, markers of DO_2 (O_2ER) and hemodynamics should be closely monitored [26].

Table 13.1 Hemodynamic insufficiency: assessment and treatment strategies

Objectively determined limited cardiac output state
Elevated O_2ER
Lactic acidosis due to inadequate DO_2 and not impaired clearance, the latter producing a normal or decreased O_2ER
Themodilution-derived measurement of cardiac output
Preload deficient state
Nondilated RV
"Low" RA pressure
Arterial pressure variation (does not distinguish between preload and afterload effect)
Therapy
Intravascular volume
Consider reducing airway pressure
Afterload induced RV systolic dysfunction
Dilated RV; increase RV/LV diameter or area
Pulmonary hypertension
Based on velocity of tricuspid regurgitant jet
Deviated ventricular septum
Decreased RV systolic function
Right-to-left atrial shunting through a patent foramen ovale
"High" RA pressure
Arterial pressure variation (does not distinguish between preload and afterload effect)
Therapy
Avoid intravascular volume
Inotropic agents
Selective pulmonary vasodilators
Consider reducing lung volume, avoid acidemia
Consider vasopressor therapy if LV systolic function is normal in order to reposition the interventricular septum

O_2ER oxygen extraction ratio, *DO_2* oxygen delivery, *RA* right atrium, *RV and LV* right and left ventricles

Continuous blood pressure monitoring allows for the assessment of gas exchange but does not provide an indication of CO and tissue oxygenation. However, the variation in arterial blood pressure that occurs during PPV has been shown to be highly predictive of a decrease in RV output in critically ill adult patients [27]. From an apneic baseline, PPV causes the arterial pressure to increase ("reverse pulsus paradoxus") due to the effects of an increase in ITP on the thoracic arterial vessels. After a cardiac cycle or two, the arterial pressure decreases due to the adverse effect of PPV on the RV loading conditions. It is important to appreciate that arterial pressure variation during PPV is due to a decrease in RV output, which may be due to a decrease in RV filling or impaired systolic performance [16, 25]. The parameters most commonly evaluated in adults are the pulse pressure variation, which is defined as the maximal pulse pressure less the minimum pulse pressure divided by the average of these two pressures, and the systolic pressure variation, which is the difference between the maximal and minimal systolic pressures. A favorable response to therapy (increase in RV output) is indicated by a decrease in the degree of arterial pressure variation. While arterial pressure variation has been shown to be predictive of fluid responsiveness in adults, its utility in managing critically ill children remains to be determined [28].

The central venous or RA pressure is used as a surrogate for RV end-diastolic volume; however, no correlation is found between CVP and RV end-diastolic volume in normal subjects or in critically ill patients because ventricular compliance (for each ventricle) is invariably affected by disease and changes in ITP, and varies considerably between patients, overtime, and with interventions, as described above [5, 29, 30]. Further, in the setting of cardiopulmonary disease, no correlation is found between the central venous/RA pressure and left atrial and LV end-diastolic pressure [31]. And, as is the case for the RV, it is the LV diastolic P_{tm} and compliance that determine LV end-diastolic volume and stroke volume. For these reasons, what constitutes an adequate central venous pressure and, in certain circumstances, and adequate left

atrial/LV end-diastolic pressure may need to be determined.

Venous oximetry is readily available and provides objective information on the relationship between global oxygen supply and demand [32]. A central venous oxygen saturation ($ScvO_2$) is a very good surrogate for a mixed venous oxygen saturation and is obtained from the jugular vein or superior vena cava, or from the RA if there is no atrial level shunt. A $Scvo_2$ obtained from the inferior vena cava is subject to the effects of vascular streaming and may provide misleading information. An oxygen extraction ratio (O_2ER; $O_2ER = SaO_2 - ScvO_2/SaO_2$) of 25–30% is normal, and an O_2ER of 30–50% is consistent with a limitation of DO_2 and a commensurate increase in tissue extraction of oxygen. The critical O_2ER, which is defined by the onset of anaerobic metabolism, is 60%. It is important to appreciate that it is not until the critical O_2ER has been reached and lactate production exceeds its clearance that serum lactate levels begin to increase.

An indispensable monitoring modality in patients with ARDS is echocardiography, as the technologies discussed provide little information as to the extent to and mechanisms by which PPV has adversely impacted RV loading conditions and output [16, 25, 33–35]. The assessment involves a determination of RV function and dimensions. The RV fractional area of change is an index of global RV systolic function and is obtained by tracing the RV endocardium in systole and diastole from the apical 4-chamber view. This parameter provides information about longitudinal and radial components of RV contraction. The challenge and limitation of this method is the difficulty in clearly defining the endocardial border, which may lead to significant interobserver variability. Tricuspid annular plane systolic excursion (TAPSE) assesses RV longitudinal function by measuring the displacement of the tricuspid annulus toward the RV apex during systole measured by M-mode from the apical 4-chamber view. TAPSE appears to be a good indicator of global RV function; however, it does not assess regional areas of hypokinesia.

Because methods for assessing RV systolic function have limitations, additional parameters such as RV dimensions should be assessed and are essential in determining the extent to which PPV has altered RV loading conditions [16, 25, 33–38]. Because ventricular interdependence causes LV constraint as the RV dilates, the best way to assess RV dilation is to evaluate the ratio of ventricular volumes. This approach also circumvents individual variations in cardiac size [16, 25, 33–38]. PPV-induced RV systolic dysfunction results in elevated RV volumes and pressure throughout the cardiac cycle. Ventricular end-diastolic and end-systolic dimensions (area or diameter) can be obtained from the apical 4-chamber or parasternal short-axis views. A value of 0.5 or so is normal, with a ratio approaching 1 consistent with mild-to-moderate RV dilation, and a ratio greater than 1 consistent with severe dilation [16, 33–38].

The pulmonary artery systolic pressure may be estimated by measuring the velocity of the tricuspid regurgitant jet ($4[\text{velocity}]^2$ plus RA pressure). In the absence of tricuspid regurgitation, the orientation and position of the IVS during ventricular systole may be used to approximate RV systolic pressure. A flattened IVS during systole has been shown to be consistent with RV systolic pressure being at least half the LV, and approaching if not exceeding LV with bowing of the IVS into the LV at end-systole [39]. Echocardiography is also essential for determining the presence and significance of cardiac shunting through a patent foramen ovale.

In severe cases of ARDS and certainly in those patients with an unfavorable clinical trajectory, consideration should be given to the use of a pulmonary artery or transpulmonary artery thermodilution catheter in order to establish an objective comprehensive hemodynamic profile. CO is measured and PVR and systemic vascular resistance (SVR) may be derived. With a pulmonary artery catheter, pulmonary arterial and pulmonary artery occlusion pressures are measured, the latter establishing the extent to which permeability and hydrostatic factors are responsible for the increase in EVLW.

Treatment

Utilizing the monitoring strategies discussed above enables one to make a timely and accurate assessment of the extent to which and mechanisms responsible for impaired cardiovascular function and to tailor therapies accordingly (Table 13.1). If RV output is decreased, *optimization of airway pressure* (i.e., manipulation of end-expiratory pressure and FRC, or ventilatory pressure [static pressure – end-expiratory pressure] and tidal volume, or both) may be indicated. Decreasing airway pressure should improve venous return; however, the impact on afterload is indeterminate as it is a battle between lung recruitment and alveolar overdistension and lung derecruitment and hypoxic pulmonary vasoconstriction. The converse is true when increasing airway pressure. Not only may increasing airway pressure adversely affect RV loading conditions and CO, but the expected improvement in gas exchange may be offset by these same interactions. Increasing airway pressure may increase pulmonary venous saturations; however, the increase in RV afterload and decrease in RV ejection fraction increases RV and RA volumes and pressures, creating or increasing the extent of cardiac right-to-left shunting [13]. Similarly, increasing ventilatory support may have an indeterminate effect on CO_2 clearance, as it may further increase ventilation to perfusion ratios, increasing the extent of wasted ventilation [11, 40, 41].

A *preload deficient state* should respond robustly to volume expansion (Table 13.1). On the other hand, if *afterload-induced RV systolic impairment* is primarily responsible for a decrease in CO volume, expansion will not improve CO and may, due to a worsening of adverse ventricular interaction, further decrease LV compliance and CO (Fig. 13.1, Table 13.1). Inotropy, optimization of airway pressure, and selective pulmonary vasodilators are indicated. Permissive hypercapnia and the resulting increase in PVR will not be tolerated (Table 13.1). Afterload-induced RV impairment and a limitation of systemic venous return may both be responsible for a decrease in CO. If the constellation of hemodynamic and echocardiographic findings does not clearly indicate RV dysfunction, then an assessment of volume responsiveness is reasonable.

An additional strategy to consider in the patient with intact LV systolic function is to increase SVR and systemic arterial blood pressure [42–44]. An increase in LV afterload causes a compensatory increase in LV end-diastolic volume, and therefore pressure, as its pressure–volume loop shifts to the right, altering the diastolic transseptal pressure gradient and driving the IVS back toward the RV. As a result, LV end-diastolic volume and stroke volume increase (heterometric autoregulation). Separate from an increase in LV end-diastolic volume, as LV afterload increases so too does its inotropic state (homeometric autoregulation). Both factors contribute to an increase in LV systolic pressure, enhancing the contribution of the LV to RV systolic pressure generation and output through systolic ventricular interdependence. Vasoconstrictors such as vasopressin and norepinephrine are ideal for this strategy. Decreasing the systemic arterial blood pressure will promote further deviation of the IVS into the LV, worsening LV compliance, filling, and output. This may occur, for example, with the use of a nonselective vasodilator that has minimal impact on PVR while decreasing SVR and the systemic arterial pressure [45].

Summary

The goal of therapies for patients with ARDS is to restore and maintain adequate respiratory function, allowing time for resolution of the underlying process. The judicious use of PPV improves oxygenation while minimizing ventilator-induced lung injury; however, despite these efforts, PPV may have an adverse effect on RV loading conditions and output. Timely, objective, and accurate assessments of cardiovascular function should be made and the appropriate therapies initiated in order to generate adequate gas exchange and CO and to accomplish the overarching goal of delivering adequate DO_2.

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14 Red Blood Cell Transfusion in Pediatric Acute Respiratory Distress Syndrome

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Abbreviations

ALI	Acute lung injury
ARDS	Acute respiratory distress syndrome
CFH	Cell-free hemoglobin
NO	Nitric oxide
RBC	Red blood cell
TACO	Transfusion-associated circulatory overload
TLR-4	Toll-like receptor-4
TRALI	Transfusion-related acute lung injury
TRIM	Transfusion-related immunomodulation

Introduction

The pathogenesis of the acute respiratory distress syndrome (ARDS) involves activation and injury of pulmonary endothelial and epithelial cells, diffuse inflammation and coagulation, and increased alveolar capillary barrier permeability, leading to alveolar edema and the accumulation of cellular debris, including RBCs, within alveolar spaces. While alveolar hemorrhage was noted in the initial description of ARDS, until recently, it has primarily been viewed as a marker of alveolar capillary permeability and disease severity rather than a pathologic mediator of injury [1, 2]. When considering RBC transfusion in critically ill children with pediatric ARDS (PARDS), two important issues must be addressed: (1) the use of RBC transfusions to improve oxygen delivery; and (2) the potential for RBC transfusion to exacerbate lung injury. Oxygen delivery in the setting of ARDS may be threatened due to impaired pulmonary gas exchange and/or hemodynamic instability. RBC transfusion is commonly employed with the intent to improve oxygen delivery in these settings, though few clinical data exist to guide RBC transfusion decisions in children with PARDS. Importantly, there are several mechanisms through which RBCs may contribute to the pathogenesis of ARDS, including hemolysis leading to release of cell-free hemoglobin (CFH), heme, and iron; effects on vascular endothelium; and alterations in coagulation, host defense, and inflammation. Emerging clinical data suggests RBC products may directly injure pulmonary endothelial and epithelial cells and may contribute to the pathophysiology of

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ARDS. Thus, it is of paramount importance to carefully consider potential risks and benefits of RBC transfusion in this population.

RBC Transfusion Is Common in PARDS

Hypoxemia due to impairment in gas exchange and/or ventilation/perfusion (V/Q) mismatching is a hallmark of PARDS, and the degree of hypoxemia defines PARDS severity [3]. Additionally, nearly half of the children with PARDS have concomitant shock, which may further threaten oxygen delivery to tissues above hypoxemia alone [4]. RBC transfusion is often employed in children with PARDS with the intent to improve oxygen delivery. In survey data, pediatric practitioners state that they would transfuse RBCs to achieve higher hemoglobin concentrations in the setting of hypoxemia [5, 6]. In single-center observational data, 43% of children with PARDS received an RBC transfusion during the first three days of PARDS [5].

Clinical Outcomes Associated with RBC Transfusion in PARDS

Despite how commonly children with PARDS are transfused, few data exist to guide RBC transfusion decisions. A limited number of clinical studies have evaluated relationships between RBC transfusion and respiratory-related clinical outcomes in critically ill children (Table 14.1) [5, 7–10]. In a single-center study of children with PARDS, receipt of RBC transfusion was independently associated with longer duration of mechanical ventilation (aSHR for time to successful extubation 0.65 [95% CI: 0.51, 0.83]) [5]. This relationship remained significant after accounting for important differences between transfused and nontransfused patients, and a dose–response relationship was observed. Additional observational data in critically ill children demonstrate associations between RBC transfusion and ARDS development, new or worsened respiratory dysfunction, duration of mechanical ventilation, and development of ventilator-associated pneumonia [5, 7–10]. Similarly, in observational studies of adults, RBC transfusion is an independent risk factor for the development of ARDS among perioperative and traumatically injured patients [2, 8, 11–14]. Together, these findings support the hypothesis that RBC transfusion may be injurious to the lungs and could exacerbate existing lung disease. It is important to note, however, that though these studies statistically account for differences between transfused and nontransfused subjects, the observational study design cannot exclude residual confounding by indication bias, and

Table 14.1 Observational studies demonstrate adverse respiratory effects associated with RBC transfusion in critically ill and injured children

Population	n	Design	Findings	References
Children with PARDS	357	Single-center retrospective	RBC transfusion independently associated with longer time to extubation (aSHR 0.65 [0.51, 0.83])	[5]
Traumatically injured children	488,381	Registry study (NTD)	Transfusion independently associated with ARDS development (aOR 4.7 [4.3, 5.2])	[9]
Critically ill children	842	Single-center retrospective	43% rate of new or worsened respiratory dysfunction associated with RBC transfusion; RBC transfusion independently associated with longer duration of MV (aHR 0.59 [0.45, 0.79])	[7]
Critically ill children with ALI	79	Single-center retrospective	RBC transfusion associated with increase in OI (11.7 to 18.7 vs. 12.3 to 11.1 in nontransfused) and longer duration of MV (15.2 vs. 9.5, $p < 0.001$)	[8]

PARDS pediatric acute respiratory distress syndrome, *NTD* National Trauma Database, *aSHR* adjusted subdistribution hazard ratio, *aOR* adjusted odds ratio, *ALI* acute lung injury, *OI* oxygenation index, *MV* mechanical ventilation

causal relationships between RBC transfusion and adverse clinical outcomes cannot be drawn.

A single randomized controlled trial has been performed to evaluate RBC transfusion thresholds in pediatric intensive care unit patients. The TRIPICU study randomized 637 children to receive RBC transfusion in response to hemoglobin thresholds of 7 g/dL versus 9.5 g/dL [15]. There were no significant differences in clinical outcomes between experimental groups, including the primary outcome of the development of new or progressive multiple organ dysfunction syndrome (NP-MODS) (12% in both groups, absolute risk difference 0.4%, 95% CI: −4.6 to 5.4%). Similarly, among the 48 patients with ARDS enrolled in TRIPICU, a significant difference in NP-MODS between experimental groups was not found, though the small number of ARDS patients in the cohort limits conclusive interpretation [16]. That said, based on these data, recent consensus-based recommendations for RBC transfusion in critically ill children recommend not routinely transfusing RBCs to children with respiratory failure if the hemoglobin is greater than or equal to 7 g/dL in the absence of severe hypoxemia, chronic cyanosis, hemolytic anemia, or hemodynamic compromise [16, 17]. Importantly, the TRIPICU study excluded children with severe hypoxemia, and thus, no recommendation was made to guide transfusion decisions in children with severe hypoxemia. It is also unknown whether RBC transfusion may be beneficial for selected children with PARDS and concomitant shock.

Preclinical Data Suggest that RBC Transfusion May Contribute to ARDS Pathophysiology

Understanding which patients may benefit from RBC transfusion in order to avoid unnecessary transfusion is important because RBC transfusion itself may contribute to ARDS pathophysiology. Many forms of critical illness, including ARDS, are associated with hemolysis and generation of cell-free hemoglobin (CFH). RBC transfusions may further increase CFH levels. Normally, plasma haptoglobin sequesters CFH and forms a complex for CD163-mediated uptake by macrophages and subsequent metabolism by heme-oxygenase 1 [18–21]. However, in many forms of critical illness, even moderate hemolysis may overwhelm haptoglobin-binding capacity, leading to the accumulation of CFH and the generation of its degradation products, free heme and iron, in the plasma [18, 19, 21–23]. At the biochemical level, these three distinct species elicit tissue injury through both unique and overlapping mechanisms [12].

One of the major effects of CFH is the rapid scavenging of nitric oxide (NO), resulting in rapid loss of endothelial NO availability and leading to vasoconstriction, coagulation, and the development of a proinflammatory state [12]. As it relates to ARDS, these events may be particularly problematic as they are all intricately linked to the pathogenesis of respiratory dysfunction. CFH is also capable of inducing oxidative injury and associated tissue damage [2, 14, 24]. Interestingly, in support of the hypothesis that CFH is involved in the pathogenesis of ARDS (with or without RBC transfusion), CFH levels have been shown to be elevated in adults with ARDS and correlate with the degree of alveolar capillary barrier permeability [14, 24, 25].

In an analogous process to that of CFH, free heme is sequestered by heme-binding plasma proteins including hemopexin and albumin and subsequently removed from the circulation and degraded by heme oxygenase-1, but these scavenging mechanisms can also be overwhelmed, leading to the accumulation of free heme [18, 26, 27]. Unlike hemoglobin, free heme does not interact with NO; however, it does act as a prooxidant, particularly in promoting lipid peroxidation and also resulting in inflammation and tissue damage [19, 26–30]. Of particular importance for ARDS patients receiving RBC transfusions, there are data showing that administration of heme in the setting of another hemolysis-inducing stressor (in this case ARDS itself) rapidly leads to exacerbation of this toxicity, providing a possible mechanism by which RBC transfusion may worsen the disease course of ARDS [12].

Free iron also accumulates following saturation of haptoglobin- and hemopexin-binding capacities [18, 23, 31–36]. The deleterious effects of iron are likely due to its ability to mediate pro-oxidant reactions and its role as a substrate in bacterial growth and proliferation [12]. The latter point should be underscored as sepsis is one of the most common underlying causes of ARDS in both the adult and pediatric populations, but even in ARDS due to other causes, the ability of iron to promote bacterial growth is still relevant as it likely increases the risk of nosocomial infection [12].

The biochemical consequences of hemolysis provide possible mechanisms by which the RBC, CFH, free heme, and free iron may be involved in the pathogenesis of ARDS, even in the absence of RBC transfusion, as well as the mechanism by which the transfusion of RBC in patients with ARDS may exacerbate the disease.

Immunologic Changes Following RBC Transfusion

In addition to direct cellular injury related to CFH and iron release, RBC transfusion is associated with immunologic changes that may affect the clinical course of ARDS [18, 37, 38]. Free heme itself can affect the immune response via priming, activating, and binding the lipopolysaccharide receptor, toll-like receptor-4 (TLR-4) [27, 39, 40]. The results of this interaction include both proinflammatory and immune-suppressing effects. The proinflammatory effects are due to increased activity of NF-κB and the resulting promotion of proinflammatory cytokine production [21, 27, 30, 39, 40]. Heme has also been shown to activate neutrophils and stimulate reactive oxygen species production via the respiratory burst, adding to the acute inflammation and oxidative stress seen in ARDS [41]. Conversely, the immune-suppressing effects of free heme are thought to occur through a separate pathway [27]. Additional preclinical data suggest that RBC products can interact with and impact immune cell function via a variety of potential mediators, including extracellular vesicles, bioactive lipids, cell-free nucleic acids, and residual platelets or leukocytes [18, 38]. Many of these mediators have pleotropic effects, demonstrating both proinflammatory and immune suppressive effects depending on immune cell types evaluated and experimental conditions. Whether RBC transfusion results in clinically relevant immune modulation in critically ill patients is unclear and remains an active area of ongoing investigation. Existing clinical studies of immune modulation following RBC transfusion are largely limited by small sample size and reliance on plasma protein or transcriptomic biomarkers, which may not fully reflect the complexity of the host immune response. Much work remains to be done to more fully detail potential immunologic consequences of RBC transfusion and their clinical implications.

RBC Transfusion and the Pathophysiology of TRALI/TACO

Although this chapter has mainly focused on the role of the RBC in the pathophysiology of ARDS and the potentially harmful effects of RBC transfusion, transfusion can also compromise respiratory function in patients with previously intact respiratory function. This includes two distinct posttransfusion respiratory complications: transfusion-associated acute lung injury (TRALI) and transfusion-associated circulatory overload (TACO), which account for the first and second leading causes of death from transfusion in the United States, respectively [42, 43].

The pathogenesis of TACO is believed to be similar to that of other causes of acute congestive heart failure, with increasing pulmonary capillary hydrostatic pressure leading to fluid extravasation into the alveoli [44]. The mechanism of respiratory injury in TACO is different than that of ARDS, but it is nonetheless an important respiratory complication of transfusion and could certainly complicate disease course if superimposed on a patient with ARDS. In the pediatric population, patients under the age of 3 years are at the greatest risk to develop TACO [44].

TRALI is defined as noncardiogenic pulmonary edema occurring within 6 hours of transfusion [42]. The pathophysiology of TRALI centers around a neutrophil-mediated acute inflammatory response leading to pulmonary vascular injury and, like ARDS, results in breakdown of the alveolar capillary barrier [42, 43, 45]. It is hypothesized that TRALI is the result of at least two separate clinical insults (the so-called two-hit hypothesis). The first hit is the "priming" of neutrophils, which relates to the clinical condition of the patient and may result from insults such as surgery, tissue injury, or infection and involves the upregulation of vascular adhesion molecules on the pulmonary endothelium. The second hit is the "activation" of primed neutrophils in response to proinflammatory stimuli such as antihuman leukocyte antigen (HLA) antibodies and/or bioactive lipids derived from transfused blood products [46]. Interestingly, while TRALI is a unique clinical entity, it is also one possible explanation of the observed clinical deterioration of children with PARDS receiving transfusions, with the transfusion acting as a second or additional hit leading to worsening and prolongation of the disease course [5, 8].

Future Directions

The majority of studies evaluating the roles of RBC transfusion in the pathophysiology of ARDS have been conducted on either animal models or adult patients. Given the important differences between these populations and the pediatric population, accurate conclusions cannot necessarily be drawn from this research. Thus, it is important for future studies to explore the intersection between ARDS and RBC transfusions in children. Specifically, high-quality clinical data are urgently needed to strengthen evidence-based guidelines for RBC transfusion in pediatric ARDS. Relevant studies are needed to evaluate appropriate hemoglobin and/or physiologic thresholds to prompt RBC transfusion, to evaluate transfusion efficacy, to document transfusion safety, and to evaluate potential alternatives to RBC transfusion in PARDS. Likewise, important mechanistic studies evaluating key signaling pathways from hemolytic products, such as cell-free hemoglobin, heme, and iron, are paramount to potential therapeutic potentials. These may play an integral role in the pathogenesis of ARDS, with or without transfusion, and raise the possibility of novel treatments focused at reducing the damage mediated by these products. As it is believed that haptoglobin and hemopexin become overwhelmed by increasing concentrations of hemoglobin and heme, respectively, in certain critical illnesses including ARDS, the idea of using these molecules as pharmacologic agents aimed at preventing the biochemical changes associated with hemolysis and/or to mitigate additional transfusion-related burden of hemolysis seems attractive.

Conclusion

Current consensus guidelines recommend a restrictive approach to RBC transfusion in most children with PARDS. However, high-quality pediatric data to guide RBC transfusion decisions in PARDS are few. Important questions remain regarding the management of anemic PARDS patients and how best to achieve an appropriate balance between treating the anemia to improve oxygen delivery and avoiding the deleterious effects of RBC transfusion.

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15 Pediatric Acute Respiratory Distress Syndrome in Immunocompromised Patients

Courtney M. Rowan

Introduction

The immunocompromised child presents unique considerations and challenges to the intensivist. In addition to a generally high level of acuity, these children require a specific knowledge of the underlying disease, understanding of the dynamic immune system, and a high level of multidisciplinary collaboration. They are different than the general pediatric intensive care unit (PICU) patient population. Furthermore, all immunocompromised conditions are not the same. There are multiple etiologies of immunosuppression, including malignancies, transplantation, congenital immunodeficiencies, rheumatologic, infectious, and medication-induced. The cause of the immunocompromised state frequently dictates anticipated critical care issues, underlying organ dysfunction, and prognosis. Comorbidities, preexisting lung injury, and endothelial injury precipitated by chemotherapy, conditioning regimens or radiation, may place these children at higher risk for ventilator-induced lung injury.

Despite the challenges with this population, the intensivist must be knowledgeable on these various topics, as it is a growing population. While not explicit in the pediatric literature, evidence from the adult population shows that immunocompromised patients are being admitted to the ICU with increasing frequency [1]. Advancing therapies for malignancies, improving transplantation outcomes, and overall improving mortality for the critically ill immunocompromised patient lends itself for the institution of increasingly aggressive supportive care. Even for some of our most immunocompromised patients, the hematopoietic cell transplant (HCT) recipient, outcomes have drastically improved from a near 0% survival [2] to more recent data demonstrating survival around 40% [3, 4].

It is well described that children with immunocompromised conditions are at risk for both the development of pediatric acute respiratory distress syndrome (PARDS) and PARDS-related mortality [5]. In studies of acute lung injury or PARDS, immunocompromised children routinely have worse outcomes, with mortality often more than double that of the general population [6, 7]. A multicenter study of over 200 pediatric HCT recipients receiving invasive mechanical ventilation found that 92% of these patients met PARDS criteria using the Pediatric Acute Lung Injury Consensus Conference (PALICC) definitions [8] and that the vast majority (>60%) of patients fell within the severe category [9]. Furthermore, the mortality rate for those with severe PARDS was very high at 75%. Not only does the immunocompromised state seem to independently place the patient at risk for death,

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these children are at an increased risk for multiorgan dysfunction [10, 11], which is also a well-documented risk factor for PARDS mortality.

Etiologies Leading to Acute Respiratory Failure and PARDS

Bronchoscopy with Bronchoalveolar Lavage

Immunocompromised children present to the PICU with various etiologies of respiratory failure (Fig. 15.1). They are at unique risk for infection leading to both direct PARDS secondary to a pulmonary infection, and indirect PARDS with other systemic infections resulting in multiorgan dysfunction. Further complicating the diagnostic investigation and management is that immunocompromised children are also at risk for noninfectious pulmonary complications. This is particularly evident in the children who are post-HCT. It is imperative, particularly in the initial stages of PARDS, that a thorough workup be conducted to isolate the underlying etiology. With an impaired immune response, the clinical presentation is frequently not classic [12]. Typical clinical symptoms of a pulmonary infection such as fever and chest radiographic opacities cannot be considered a reliable indication of the presence or absence of infection in these patients. Therefore, an infectious workup is most often indicated. In addition to standard cultures, immunocompromised children need extended screening for opportunistic and rare infections, including polymerase chain reaction (PCR) or antibody testing for viri and fungi, with particular consideration for pathogens that can be treated such as *Pneumocystis jiroveci* and *Mycobacterium*. A standardized, broad, diagnostic approach is need when testing for infectious pathogens.

While sending cultures, in theory, seems simple, in practice, the decision to perform a bronchoscopy with bronchoalveolar lavage (BAL) can be challenging. There is a heightened concern for the risk of complications associated with bronchoscopy including bleeding, pneumothorax, hypoxemia, and new requirement for mechanical ventilation [13].

Despite the risk of complications, establishing a diagnosis can alter therapy and potentially improve outcomes. There is a wide range of cited diagnostic yield from a BAL in the immunocompromised population, anywhere from 27% to 85% [14–16]. In a large study of children post-HCT, the diagnostic yield of BAL was as high as 67.9% [17]. The diagnostic yield is also likely to improve with time as new laboratory techniques are being investigated to identify various organisms [18]. There does seem to be an improved diagnostic

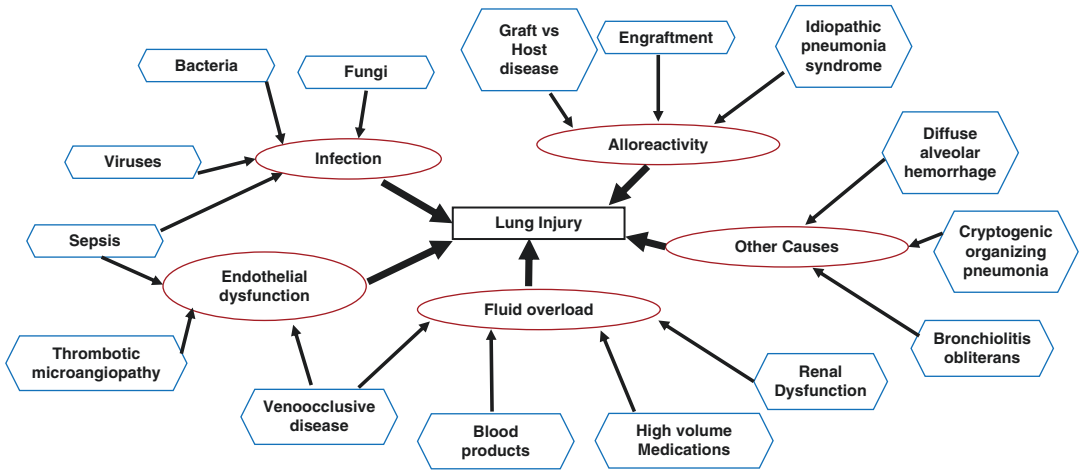

Fig. 15.1 Various etiologies of lung injury in the immunocompromised patient, all with the potential to contribute to severe PARDS

yield if the BAL is combined with transbronchial biopsy, but this technique is rarely employed in children and brings a higher risk for complications [14, 15, 19]. Studies in organ transplant recipients have found that, anywhere from 20% to 70% of the time, the results of a BAL lead to a change in therapy [20]. Even more importantly, if therapy is changed, there is the possibility to reduce mortality by 20% [21], although other studies have found no effect on mortality [16, 22]. Unfortunately, much of the data are conflicting, and the range of benefit is wide.

The risk of complications of bronchoscopy with BAL may be higher in the immunocompromised population. Complications such as bleeding in a population with low and potentially dysfunction platelets should be a concern for all clinicians and bronchoscopists involved in the care. In immunocompromised adults, the bronchoscopy complication rate is up to 21% and is even higher with transbronchial biopsy [14]. In children with cancer, the complication rate associated with bronchoscopy has been cited at 30% [23]. However, most of these complications are relatively minor and resolve without intervention. The larger concern, early in the course of respiratory distress, is the development of sustained hypoxemia and a new mechanical ventilation requirement. In various adult immunocompromised populations, there has been <1% increased risk in requiring intubation following bronchoscopy [24, 25]; however, this risk is increased in the post-HCT patient [16].

The conflicting data between benefit and the risk of complications from bronchoscopy leaves clinicians wondering if the risk is worth the benefit. There does seem to be data supporting early bronchoscopy with BAL. In a study of 501 adults post-HCT, the diagnostic yield was best if the BAL was completed within the first 24 hours of respiratory symptoms [26]. Because these patients are immunocompromised and at such high risk for infection, empiric antibiotics are frequently started. The use of antibiotics can affect the results of the BAL. Pediatric and adult studies have shown that the diagnostic yield of BAL decreases significantly following 72 hours of antibiotics [27, 28]. There is also data demonstrating a lower risk of complications when bronchoscopy is performed earlier in the course of respiratory distress [29, 30].

Chest Imaging

When considering imaging in an immunocompromised child with acute hypoxic respiratory failure, a chest radiograph (CXR) is often first in the diagnostic workup. This is especially true in the setting of fever and cough, when the clinical suspicion for pneumonia is high. If the radiograph identifies a focal infiltrate, further imaging with computerized tomography (CT) is likely not necessary. Empiric antibiotics can be started and decisions can be made about obtaining a BAL. In the setting of a normal CXR or a diffuse infiltrative process, a CT may offer useful diagnostic information. CXRs can be negative or unhelpful in the immunocompromised population despite clinical concern [31]. The CT can allow for better visualization of the lung parenchyma, offer considerations for a differential diagnosis of the underlying lung pathology, or help to identify a specific area for lung biopsy [32].

Respiratory Support for the Immunocompromised Patient

Noninvasive Respiratory Support

It is clear that the immunocompromised patient is at significant risk for PARDS; therefore, the approach to respiratory support is instrumental in their overall survival. In the immunocompromised population, many clinicians initially attempt a noninvasive respiratory support strategy, because the mortality associated with invasive mechanical ventilation is so high in these patients. However, there is little data to inform our use of noninvasive modalities, especially in children with immunocompromised conditions. Furthermore, there is a concern that these strategies may delay more definitive care. Studies investigating noninvasive respiratory support modalities in those with immunocompromised conditions are summarized

Table 15.1 Summary of studies investigating noninvasive respiratory support in immunocompromised patients

Author/Year	Study design	Study population	Main findings
Adult studies			
Antonelli et al. 2000 [37]	RCT: NIV vs. supplemental O2	40 adults post-solid organ transplant	NIV had improvement in PaO2:FiO2, had a 20% intubation rate compared to 70% for supplemental O2, a shorter length of hospital stay (5 vs. 9 days) and a lower mortality (20% vs. 50%)
Hilbert et al. 2001 [38]	RCT: Early NIV vs. supplemental O2	52 IC adults	NIV had lower intubation rate (46% vs. 77%) and lower ICU mortality (38% vs. 69%)
Squadrone et al. 2010 [40]	RCT: Early CPAP vs. Venturi mask	40 adults with hematologic malignancies	Those treated with early CPAP were less likely to be admitted to the ICU, less likely to be intubated and more likely to survive
Azoulay et al. 2014 [45]	Retrospective multicenter cohort	1004 adults with cancer and ARDS	387 patients were treated with NIV with a failure rate of 71%, and NIV failure was an independent risk factor for mortality
Lemiale et al. 2014 [46]	Post hoc of RCT	211 adults with cancer	139 patients treated with NIV, 38% failed NIV. NIV failure was not associated with higher mortality
Lemiale et al. 2015 [33]	RCT: HFNC vs. Venturi mask	100 IC adults	At 2 hours there was no difference in the rate of intubation, work of breathing, tachypnea, tachycardia, or in perceived patient comfort
Lemiale et al. 2015 [39]	RCT: NIV (BIPAP and HFNC) vs. supplemental O2	374 IC adults	There was no difference in intubation or mortality between the two groups
Harada et al. 2016 [35]	Retrospective cohort study	56 adults with hematologic disease	There was an 80% failure rate of HFNC. Those who failed required mechanical ventilation or changed to a palliative care approach. HFNC was well tolerated. Pneumonia was a risk factor for failure
Lemiale et al. 2017 [34]	Post hoc of RCT: HFNC vs. supplemental O2	127 IC adults	No difference in rate of intubation or mortality
Pediatric studies			
Pancera et al. 2008 [42]	Retrospective cohort study	120 children with cancer	There was a 26% failure rate of NIV and hemodynamic instability was a significant risk factor for NIV failure
Piastra et al. 2009 [43]	Prospective observational study	23 IC children	There was a 45% failure rate and of those that failed NIV 80% died
Murase et al. 2012 [44]	Observational study	92 children post liver transplant	NIV was used in 47 children postextubation. Those treated with NIV had a lower rate of reintubation (6.4% vs. 23.4%) and were discharged from the PICU faster
Rowan et al. 2016 [3]	Retrospective multicenter cohort	222 children post-HCT	91 children treated with NIV prior to intubation. Those treated with NIV prior to intubation had an increased risk of mortality compared to those who were intubated directly (OR: 2.1, 95% CI: 1.2–3.6)

RCT randomized controlled trial, *NIV* noninvasive ventilation, *HFNC* high flow nasal cannula, *IC* immunocompromised, *HCT* hematopoietic cell transplant

in Table 15.1. In 2015, Lemiale et al. published a randomized controlled trial of 100 immunocompromised adults who were randomized to either high flow nasal cannula (HFNC) or supplemental oxygen via a Venturi mask [33]. At 2 hours, there was no difference in intubation rate, patient comfort, dyspnea, respiratory rate, or heart rate. This study was followed up by the same investigator with a post hoc analysis of a large multicenter randomized controlled trial of HFNC versus standard supplemental oxygen [34]. There were 127 immunocompromised adults for the analysis. In this study, there was no difference in the rate of intubation or mortality between the two groups.

A smaller Japanese study of 56 adults with hematologic disease found that 80% of patients failed HFNC and required intubation or palliative care [35]. So while there is limited data on HFNC use in the immunocompromised, available data suggest that HFNC does not prevent intubation, but also likely does not worsen outcomes. It would be important to ensure that a trial of HFNC does not delay more definitive care.

Noninvasive positive pressure ventilation (NIV) has been used in this patient population. In theory, the application of NIV can reduce work of breathing, decrease the inspiratory load, aid in lung recruitment, and improve oxygenation. In a large randomized controlled trial of general adults, the development of ARDS was associated with NIV failure and the need for intubation [36]. More specific to the immunocompromised population, a promising small, randomized controlled trial was conducted in 40 adults post-solid organ transplantation [37]. The patients were randomized to either NIV or supplemental oxygen. Those randomized to NIV had an improvement in oxygenation, were less likely to get intubated (20% vs. 70%), had a shorter length of hospital stay (5 vs. 9 days), and a lower mortality rate (20% vs. 50%). A year later, another small trial randomized 52 immunosuppressed adults early in the course of respiratory distress to either NIV or supplemental O_2 [38]. In this study, those placed on NIV had a decreased rate of intubation and a lower ICU and hospital mortality [38], suggesting that early application of NIV can be beneficial in the immunocompromised adult. Promising results from these two small studies led to a large multicenter study that included 374 immunocompromised adults randomized to either NIV or supplemental O_2, but there was no difference in the rate of intubation or mortality between the groups [39]. Early use of continuous positive airway pressure (CPAP) has also been investigated in 40 adults with hematologic malignancies randomized to early CPAP or supplemental O_2 via a Venturi mask [40]. Patients randomized to CPAP were less likely to be admitted to the ICU, less likely to need intubation, and more likely to survive [40].

In the general pediatric population, there is a high failure rate of NIV when PARDS is present [41]. While there are no randomized controlled trials, there are studies describing the use of NIV in children with immunocompromised conditions. In a retrospective study of 239 pediatric patients with cancer, 120 children were treated with NIV [42]. Of these, 25.8% failed NIV and required intubation. Hemodynamic instability was a significant risk factor for NIV failure. In 2009, Piastra et al. published an observational study of 23 consecutive immunocompromised children treated with NIV [43]. Of these children, 45% failed NIV and required intubation, and of those requiring intubation, only 20% survived. In 2012, Murase et al. published a report on the use of NIV post-liver transplantation to prevent reintubation. Of the 92 patients, NIV was used in 47. Those treated with NIV had a lower rate of reintubation (6.4% vs. 23.4%) and were discharged from the PICU faster [44]. More recently, a multicenter study of 222 children post-HCT found that children who were placed on NIV prior to intubation had two times the odds of mortality [3]. However, this study had limitations because it did not include children who were successfully treated with NIV. In a multicenter study of 1004 adults, 30% were treated with NIV [45]. Of these, 70% failed NIV and failure was independently associated with a higher mortality. Another study of adults with cancer found no difference in mortality for those who received invasive mechanical ventilation as their first-line respiratory support compared to those treated with NIV prior to intubation [46]. Although those who failed NIV had a higher mortality of 65.3% compared to those who were intubated first with a mortality of 50%, this finding did not meet statistical significance. In summary, the use of NIV may improve outcomes, particularly if used early in the course of respiratory distress. In 2015, the pediatric acute lung injury consensus conference (PALICC) specifically recommended that immunocompromised children may benefit from an early trial of NIV in an attempt to avoid intubation [41], but care should be taken not to delay intubation. This same group also states that NIV is not recommended for severe disease, which may limit applicability to many immunocompromised patients. Furthermore, NIV is likely not a good support modality for those with hemodynamic instability or multiorgan dysfunction.

Invasive Mechanical Ventilation

While there are multiple studies in both pediatrics and adults that discuss ICU outcomes and critical care interventions that are associated with outcomes, there is very little data regarding how to specifically manage the ventilator in the immunocompromised patient. It is clear that the immunocompromised patient is at high risk for the development of PARDS; it happens early and it is generally severe [9]. In fact, many immunocompromised children have significant hypoxia at the time of PICU admission [47]. The early institution and focus on lung-protective ventilation strategies is essential. General adult ARDS data demonstrate improvement with protective strategies that focus on low tidal volume, limitation of plateau and driving pressures, and reliance on high PEEP to reduce the delivered FiO_2 [48–50].

PALICC gave recommendations for mechanical ventilation strategies in the general PARDS patient [51]. The first recommendation, derived from adult data, recommends limitations of tidal volume to ≤8 ml/kg. Tidal volume goals have not been rigorously studied in pediatrics, let alone in children with immunocompromised conditions. Some observational studies in children with PARDS, including some with immunocompromised conditions, demonstrated improved survival in those who were ventilated with higher tidal volumes [6, 52]. In a larger retrospective study of pediatric HCT patients requiring mechanical ventilation, the median tidal volume utilized was approximately 7 ml/kg and tidal volume was not associated with survival [47].

Inspiratory pressures have also been investigated. PALICC recommended limitation in inspiratory pressures with a goal to maintain plateau pressures at or below 28 cmH_2O [51]. High inspiratory airway pressures are associated with mortality in children with PARDS [6, 52], and a cohort of 222 pediatric HCT patients found similar results. A peak inspiratory pressure (PIP) > 31 cmH_2O was independently associated with mortality [47], and this association was cumulative, with increasing PIP being associated with increasing odds of mortality.

High levels of peak end-expiratory pressure (PEEP) are likely needed to maintain lung recruitment and prevent atelectrauma. While not investigated in pediatric clinical trials or in the isolated immunocompromised population, data extrapolated from adults suggest that increased PEEP in severe ARDS is associated with lower hospital mortality [53, 54]. PALICC recommended that high levels of PEEP may be needed in severe PARDS [51]. The unique consideration in the immunocompromised population is that these children are at risk for noninfectious lung disease, such as bronchiolitis obliterans, that can lead to pulmonary fibrosis and nonrecruitable lung [55, 56]. Therefore, the clinician must carefully consider the underlying etiology and the potential for lung recoverability when applying increasing levels of PEEP. Early in the presentation, often before a clear diagnosis is made, the application of high levels of PEEP in the immunocompromised child with severe PARDS is likely warranted and may provide clue to the clinician as to the recruitability of the lung. However, it is unclear if this high PEEP strategy is actively being applied to children with immunocompromised conditions. In a retrospective twelve-center cohort of children post-HCT, many of which had severe PARDS, use of PEEP was modest in the first five days of mechanical ventilation, with median levels ranging between 7 and 9 cmH_2O for both survivors and nonsurvivors [47]. When investigating the use of PEEP compared to the use of FiO_2 in this same cohort, there seemed to be more reliance on higher FiO_2. A high PEEP/low FiO_2 strategy is associated with survival in adults [57]. In a general pediatric study, failure to comply with this PEEP strategy was associated with PARDS mortality [58]. This was also demonstrated in a pediatric HCT cohort with respiratory failure. While there was very little compliance with this strategy in the first few days of mechanical ventilation, compliance with this strategy was associated with improved survival [47].

The classification of PARDS severity determined by PALLIC was associated with increasing mortality and morbidity in the most severe immunocompromised children (the child post-HCT) [9]. This is not surprising with the use of oxygenation index (OI) and/or oxygen saturation index (OSI) as the foundation for classifying PARDS severity. OI, OSI, and PaO_2/FiO_2 are highly associated with mortality. In pediatric lung injury, OI is associated with mortality and was

found to be an even better predictor of mortality in the immunocompromised [59]. In a single-center cohort of pediatric HCT patients, increasing OI was associated with an increasing risk for mortality [60]. This was also demonstrated in U.S. and European multicenter cohorts of children post-HCT [47, 61]. In the US study, controlling for other variables, OSI was independently associated with increasing mortality. With OSI levels consistent with severe PARDS, the odd for morality increased (OR = 11.1, $p < 0.0004$) [47]. Similarly, the European study found cumulative OI to be highly associated with mortality [61].

Nonconventional Mechanical Ventilation

There is limited data to support or negate nonconventional mechanical ventilation use in the immunocompromised child. Because these children can develop severe PARDS, high-frequency oscillatory ventilation (HFOV) and airway pressure release ventilation (APRV) may be considered as support modalities. In a multicenter study of HFOV use in children, those who were immunocompromised had the highest mortality, and an OI >35 had the best predictive power for HFOV-related mortality in this group [62]. A small single-center study of 12 children with cancer or post-HCT found that the use of HFOV can improve gas exchange. Seven of these 12 patients survived to ICU discharge [63]. A larger single-center study of 60 immunocompromised children was published, describing the use of HFOV and APRV [64]. In this cohort, the overall mortality was 63%. Improvements in oxygenation as measured by PaO_2/FiO_2 or OI at 24 hours on the nonconventional mode of ventilation were associated with survival. Recently, a larger multicenter cohort of 85 children post-HCT with severe PARDS who were treated with HFOV demonstrated a PICU survival of only 23.5%. This study suggested that earlier HFOV, within the first 2 days of invasive mechanical ventilation, may have a survival benefit [65]. Survivors were transitioned earlier (day 0 vs. day 2, $p = 0.002$). Also, no one who was transitioned after 1 week of mechanical ventilation survived.

Extracorporeal Membrane Oxygenation

Extracorporeal membrane oxygenation (ECMO) is being increasingly considered in the immunocompromised population, but its benefits remain unclear. Studies have consistently found that immunocompromised status is a significant risk for ECMO mortality [66–69]. Despite this, several case reports exist to support the successful use of EMCO in the immunocompromised population. In 2009, Gow et al. published data from the extracorporeal life support organization on 107 children with malignancies [70]. The majority of children were placed on EMCO for pulmonary support. Survival to hospital discharge was 35%. A study of 14 adults with hematologic malignancies and acute respiratory failure found 50% survival to hospital discharge [71]. There were five major bleeding episodes in this cohort. A similar survival of 44% was found in a pediatric cohort of 14 neutropenic patients with malignancy [72]. The bleeding complication was high at 55%. In a recent cohort of adults post-HCT, the overall ECMO survival was 19% [73]. Survival was only 4% if the patient was within 240 days posttransplant. The authors concluded that the very high mortality rate does not support the use of ECMO in adults within 240 days of HCT. While it is likely that certain immunocompromised children would benefit from ECMO support, certain subsets, such as those post-HCT, have very poor survival. Significant and critical discussions, including prognosis of the underlying immunocompromised condition, bleeding risk, and anticipated time until bone marrow recovery, are necessary prior to deciding to place an immunocompromised child on EMCO for PARDS.

Conclusion

Available data for PARDS in children with immunocompromised conditions are limited to smaller, often single center, studies. The mortality rate for these children is clearly higher than that of the general PICU population. Unfortunately, the immunocompromised population is often excluded from randomized controlled trials,

understandably due to concern for severely affecting results if randomization fails to balance the proportion of immunocompromised patients in each group. Despite the fact that the immunocompromised child comprises a disproportionate source of PICU mortality, there is still hope to improve outcomes. A unique opportunity exists for early intervention because many immunocompromised children, especially children with cancer or who are post-HCT, are already hospitalized at the time their critical illness develops [11]. Cross-center and cross-specialty collaboration is absolutely required to impact survival of these patients. Standardized approaches to the immunocompromised child with acute hypoxic respiratory failure could be of benefit and should be investigated. One potential approach is suggested in Fig. 15.2. Careful consideration of the underlying immunocompromising condition, understanding the dynamic immune system, awareness of existing comorbidities, and anticipation for severe PARDS are all necessary to care for these

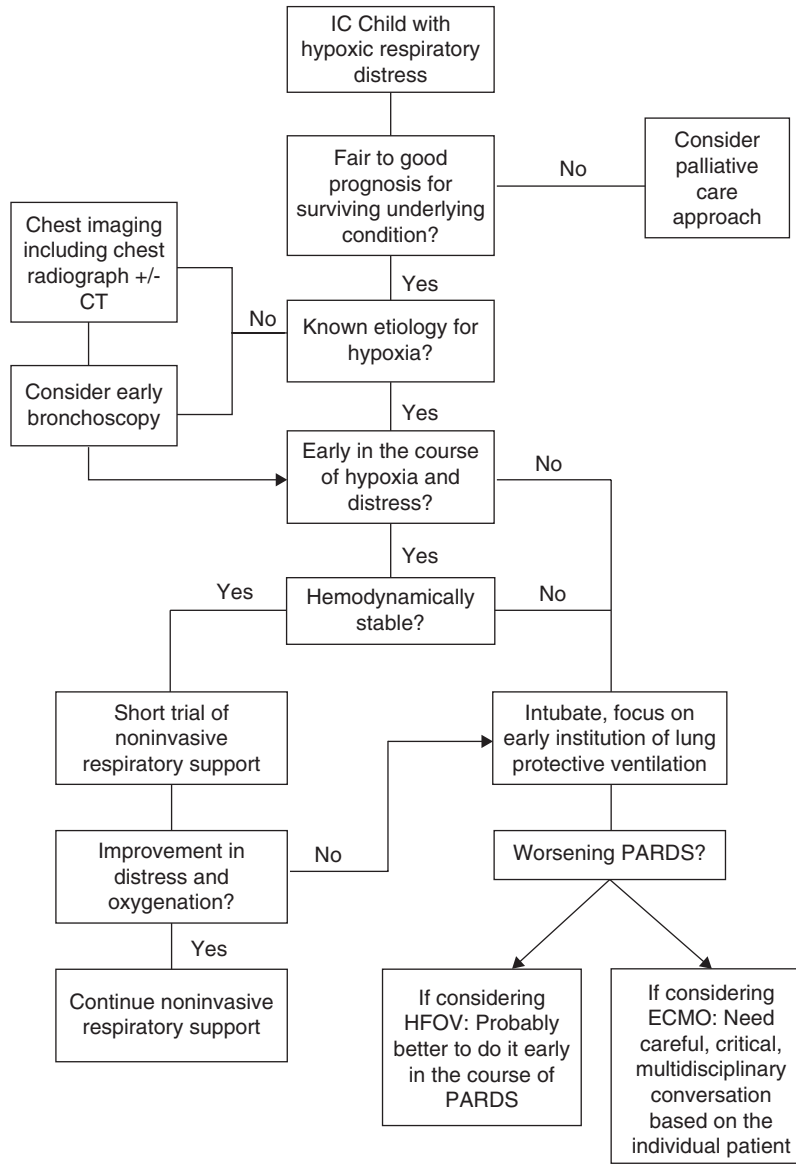

Fig. 15.2 Possible clinical approach for an immunocompromised child with acute hypoxic respiratory failure

children. Intentional collaboration, early recognition and intervention, and inclusion in clinical trials are needed to truly improve the mortality of this high-risk population.

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16 ECMO for Pediatric Acute Respiratory Distress Syndrome (PARDS)

Jesse C. Bain and Doug Willson

Introduction

Respiratory failure is a common reason for PICU admission, with pediatric acute respiratory syndrome (PARDS) among the most common and most severe. This textbook is focused on the etiology, treatment, and outcomes of PARDS, and the reader is directed to appropriate sections for in-depth information. Here we address the use of extracorporeal membrane oxygenation (ECMO) in support of children with severe respiratory failure.

Despite several advances over the last several decades, the morbidity and mortality of PARDS remains considerable, with a mortality rate ranging from 11% [1] to as high as 72% [2]. While much of the mortality relates to comorbidities such as immune compromise, some children with PARDS still die of hypoxia [3]. Morbidity is also high. The need for prolonged sedation, immobility, difficulties with feeding, and complications of vascular catheters and mechanical ventilation contribute to significant morbidity. The longer-term morbidity of children recovering from PARDS is largely understudied, but repeated hospitalizations for respiratory infection, posttraumatic stress syndrome, and neurological deficits are not uncommon [4–7].

Mechanical ventilation is supportive but not physiologic. The human lung was not designed to have air blown into it! Thanks to studies by Gattinoni [8], Kolobow [9], and others [10, 11], we now understand that positive pressure ventilation can be harmful in proportion to the pressure and volume utilized. The primary therapeutic advance in the management of ARDS over the last 50 years has been an understanding that smaller tidal volumes are less harmful than larger tidal volumes [12]. Unfortunately, some patients cannot be adequately supported with noninjurious pressures or volumes and, at some point, lung injury from the ventilator potentially outpaces lung recovery. That is the point at which ECMO is generally considered in order to enable weaning of the toxic ventilator settings.

The essential dilemma is that there is no objective or proven means of weighing the risks of continuing mechanical ventilation versus initiating ECMO for a given patient. Improving predictive models, such as that from Khemani, et al., in the recent PARDIE study [3], can assist in the decision-making process, but advances in both mechanical ventilation and in ECMO make this a moving target. Ultimately, the clinician at the bedside must decide. It is the authors' hope that what follows will help in that decision process.

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Brief History

The history of the evolution of ECMO is well described in the *ELSO Red Book* [13] and the reader is referred there for greater detail. Cardiopulmonary bypass was used for respiratory failure with variable success soon after its introduction for cardiac surgery. After the description of the successful use of "out of the operating room cardiopulmonary bypass" in a motorcycle accident victim (along with other largely anecdotal reports) [14], Zapol and colleagues in 1979 reported on a randomized controlled trial of cardiopulmonary bypass in adults with severe ARDS [15]. Survival was not different between the conventional care group and the "ECMO" group, and was abysmal (7–8%) in both. A subsequent study by Morris, et al. [16] demonstrated that a protocolized approach to mechanical ventilation was equally effective to an approach that included extracorporeal CO_2 removal ($ECCO_2R$). These two studies dampened enthusiasm for the use of ECMO in adults with respiratory failure.

Despite the failures in adults, Barlett and colleagues were able to demonstrate that the technology could be successfully used in small infants [17]. Their first success was a moribund neonate with meconium aspiration named Esperanza and was followed by modest success (3/16 survivors) in other NICU patients with life-threatening respiratory failure. O'Rourke and colleagues in Boston then confirmed the potential utility of ECMO in neonates [18]. Using a controversial "play the winner" statistical design, infants were assigned to either conventional therapy or ECMO according to the last successful therapy. After conventional ventilation failed in 4/10 of their first subjects and 9/9 survived with ECMO, ECMO was used for their next 20 subjects, 19 of whom survived. A subsequent controlled study in the UK clearly demonstrated improvement in outcome with ECMO relative to conventional care in neonates with persistent pulmonary hypertension and meconium aspiration syndrome [19]. Consequently, the use of ECMO in infants with meconium aspiration, diaphragmatic hernias, or "persistent fetal circulation" soon became the standard of care in large university neonatal intensive care units.

The experience in neonates undoubtedly fueled the expansion of ECMO into the care of older infants and children. An early retrospective cohort study by Green et al. [20] suggested that ECMO improved survival in pediatric respiratory failure, but this was not supported by a recent study by Barbo et al. [21]. Using propensity score matching for patients from the RESTORE study, they found no difference in outcomes between ECMO patients and those supported with mechanical ventilation. To date no prospective randomized studies have been performed for ECMO in pediatric respiratory failure. ECMO support for children with cardiac failure is also largely unstudied, although randomized studies are unlikely, given the lack of alternative therapies for severe cardiogenic shock. Unlike respiratory failure, where higher pressures, volumes, or different ventilatory modes can be tried, alternative methods for cardiac support have usually been exhausted and death nearly certain by the time ECMO is considered.

Recently, the adult ICU world seems to have rediscovered ECMO such that now the number of yearly "ECMO runs" in adults greatly outnumber those in neonates and children combined, though this is biased by the larger number of critically ill adults versus children/neonates. This also undoubtedly reflects the results of the CESAR trial, a randomized controlled trial of ECMO versus conventional ventilator support in adults with ARDS [22]. In that study, patients randomized to be transferred to an ECMO center, not all of whom actually received ECMO, had significantly better survival than those managed with conventional ventilation locally. These results were buttressed by reports from both England and Australia of 78% survival with ECMO in patients with H1N1 influenza [22, 23]. The more recent EOLIA trail, however, did not show a statistically significant difference in survival between patients randomized to ECMO versus those receiving conventional ventilation [24]. But, the study was terminated early despite a "trend" toward improved survival (65% vs. 54%, $p = 0.09$) with ECMO. In addition, the interpretation of that

study is limited by the cross-over design allowing 28% of the conventionally managed patients to receive ECMO when conventional ventilation was judged to have failed. The relative risk of "treatment failure" (death or cross-over to ECMO) was significantly less with ECMO than conventional ventilation (RR 0.62; $p < 0.001$). As such, these results are not likely to dampen the current enthusiasm for ECMO in adult intensive care.

As Fackler and colleagues discovered early on [25], randomized controlled studies of ECMO for pediatric respiratory failure are unlikely. Even if clinicians agreed to forego ECMO rescue in patients failing conventional therapy, an adequately powered study of ECMO versus conventional support in PARDS to demonstrate a decrease in mortality from 30% to 25% would require an estimated 1200 patients per group. Enrolling all patients in all of the US Extracorporeal Life Support Organization (ELSO) centers, and assuming a 50% consent rate, it would require 11 years and a rather large budget [26]. As such, the decision of when to employ ECMO in pediatric respiratory patients will rely on uncontrolled reports and clinical judgment for the near future.

ECMO Overview

Most readers will be familiar with the basic circuitry of ECMO, so only a brief overview is offered here. There are essentially three different types of ECMO systems that may be used in children with PARDS: veno-arterial extracorporeal membrane oxygenation (VA ECMO); veno-venous extracorporeal membrane oxygenation (VV ECMO); and extracorporeal carbon dioxide removal ($ECCO_2R$).

Veno-arterial Extracorporeal Membrane Oxygenation (VA ECMO)

VA ECMO extracts blood from the venous side of the circulation, oxygenates it, and returns it to the arterial side. In children, venous access is most often achieved via the internal jugular vein, but femoral venous access and direct access via sternotomy (usually in postoperative cardiac patients) are also possible. The arterial return is generally the carotid artery in small children. As with venous access, femoral or direct cannulation via sternotomy for arterial access is another option. VA ECMO offers both cardiac and respiratory support but has several disadvantages. Blood return to the systemic circulation risks emboli (clot, debris, air) from the circuit going directly to the central nervous system, and neurologic injury is more common with VA than VV ECMO [6, 7]. The sacrifice of the carotid artery or potential limb ischemia when the femoral artery is used for blood return is an additional problem. Attempts have been made to repair the carotid artery after cannulation but have been met with mixed results, though largely dependent on duration of cannulation. Additionally, during femoral artery cannulation, a small reperfusion cannula may be placed distal to the site of femoral cannulation in order to perfuse the distal limb.

Veno-venous Extracorporeal Membrane Oxygenation (VV ECMO)

VV ECMO extracts blood from the venous side of the circulation, oxygenates it, and returns it to the venous side. Because blood is taken from and then returned to the venous side, a variable amount of recirculation occurs and this may limit the resultant arterial oxygen saturation. The absence of cardiac support also precludes the use of VV ECMO for children with severe cardiac failure. Formerly, two sites of venous access were required for VV ECMO (usually the internal jugular and a femoral vein), but the newer double-lumen cannulas allow use of a single vessel – generally the internal jugular vein. These cannulas have a larger diameter, may be difficult to position, and have been associated with a significant incidence of perforation (5–30%) [27]. Properly positioned, however, they minimize recirculation by directing oxygenated blood across the tricuspid valve and allow use of a single access site. VV ECMO has a lower risk of neurologic injury and avoids sacrificing an arterial

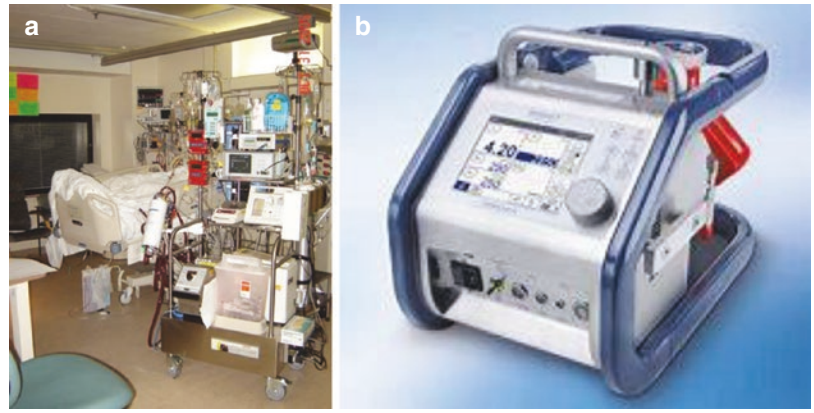

Fig. 16.1 (**a**, **b**) The evolution of ECMO technology over time from large, complex systems to compact modern devices

vessel or rendering a limb possibly ischemic but does not support a failing heart [6, 28]. Diminished cardiac function related to hypoxia or respiratory acidosis, however, frequently reverses with restoration of adequate oxygenation and correction of acidosis in some children who require modest vasoactive support prior to initiation.

Extracorporeal Carbon Dioxide Removal ($ECCO_2R$)

$ECCO_2R$ can either be veno-venous, veno-arterial, and with or without an interposed pump. $ECCO_2R$ is primarily used to achieve CO_2 removal, accomplishing ventilation with potentially less injurious ventilator pressures or volumes. Effective CO_2 removal can be achieved with a fraction (roughly 1/5) of the flows necessary to achieve oxygenation, due to the superior solubility and diffusion of CO_2 relative to oxygen [29]. While $ECCO_2R$ is usually accomplished with an interposed pump, low "pump-less" flow using arterial pressure to drive blood thru a low-resistance oxygenator is also possible [30], although this has not been reported in children. There are few reports of $ECCO_2R$ use in children.

The ECMO Machine

The initial ECMO devices were bulky with circuits that were unique to each institution and with monitoring and other equipment often cobbled together from different manufacturers. Recently, there has been a strong move toward integrating ECMO components. The early ECMO machines consumed half of the room space (Fig. 16.1) and required large volumes of fluid to prime and considerable time to set up. Modern devices are literally portable (Fig. 16.1b), can fit on the end of the bed, and require much smaller volumes for priming and very little time for set up.

Irrespective of the changes over the last several decades, ECMO consists of a small number of essential components: a pump, an oxygenator, a heat exchanger, cannula(s), tubing (circuit), and various monitoring components.

The Pump

Both roller and centrifugal pumps are still in use, although many centers have moved to centrifugal pumps because of their compact size, absence of a need for a bladder, and lower maintenance. Roller pumps move blood thru compression of the blood against the pump head housing, moving it ahead at fairly high pressures (as high as 350 mmHg) depending on tubing size. Advantages of roller pumps include the fact that forward flow can be calibrated and is not determined by downstream pressure and the delivery of blood flow is physiologic. Centrifugal pumps, in contrast, generate flow by a spinning rotor that creates suction and, consequently, a pressure gradient across the pump head. A downside is that flow is affected by downstream pressure (e.g., the patient's vascular resistance); thus, an external

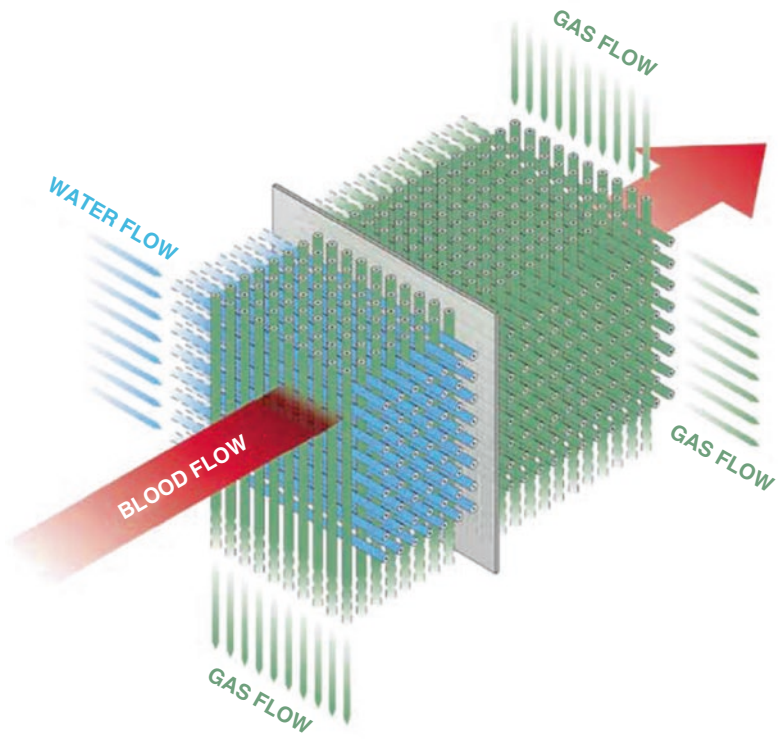

Fig. 16.2 A schematic of the Maquet Quadrox oxygenator

flow probe is required to measure output. The success of centrifugal pumps has been facilitated by lower resistance of the newer hollow-fiber oxygenators. Higher rates of hemolysis and kidney injury have been reported with centrifugal pumps [31], but newer designs appear to have addressed this problem [32, 33]. The advantages and disadvantages of different types of pumps are beyond the scope of this brief review, and the reader is referred to several references as well as the *ELSO Red Book* [13] for further details.

The Oxygenator

Early gas-exchange devices used silicone rubber, required long blood paths, and had high flow resistance. These have now been replaced by hollow fiber polymethylpentane (PMP) oxygenators that have a "gas inside" design with blood flowing around the fibers, thus significantly reducing flow resistance. PMP is hydrophobic, thus minimizing plasma leakage relative to the previously utilized polypropylene or silicone. The heat exchanger is also incorporated into the oxygenator, allowing for compact design and a much smaller footprint. A schematic of the Maquet Quadrox design is shown in Fig. 16.2 (Maquet, Rastatt, Germany) [33]. Oxygenators are rated by blood flow rate at which 75% saturated venous blood with a hemoglobin of 12 mg/dL will exit >95% saturated and generally become less efficient over time as albumin and other plasma proteins coat the membrane or with increasing clot formation. Older oxygenators often required replacement within days because of accumulation of clot, but the newer devices can often go weeks without significant deterioration in performance.

Cannulas

Single lumen arterial and venous cannulae are available from a variety of manufacturers. Double-lumen catheters (Fig. 16.3) used for VV

ECMO are now available for neonates up to adults. Double-lumen catheters are increasingly being used because they require only a single vessel, potentially minimizing recirculation, but they can be difficult to position and have significant flow limitations. Classically, cannulas have been placed by surgical cut-down, but recent advances have made percutaneous placement progressively more common, including by Intensivists [34, 35].

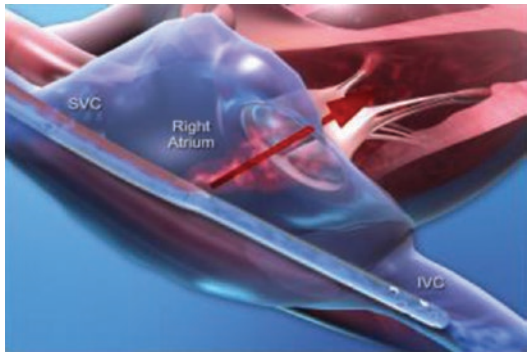

Fig. 16.3 Avalon Bicaval VV ECMO Catheter

The Circuit

The circuit is composed of the tubing, connectors, and stopcocks that connect the ECMO device to the patient (Fig. 16.4). The circuit tubing is composed of PVC mixed with plasticizers and most now incorporates a biocompatible coating to minimize the surface interaction that can provoke both clotting and inflammation (although no coating has been shown to completely eliminate these reactions [36]). Circuits may include a "bridge"

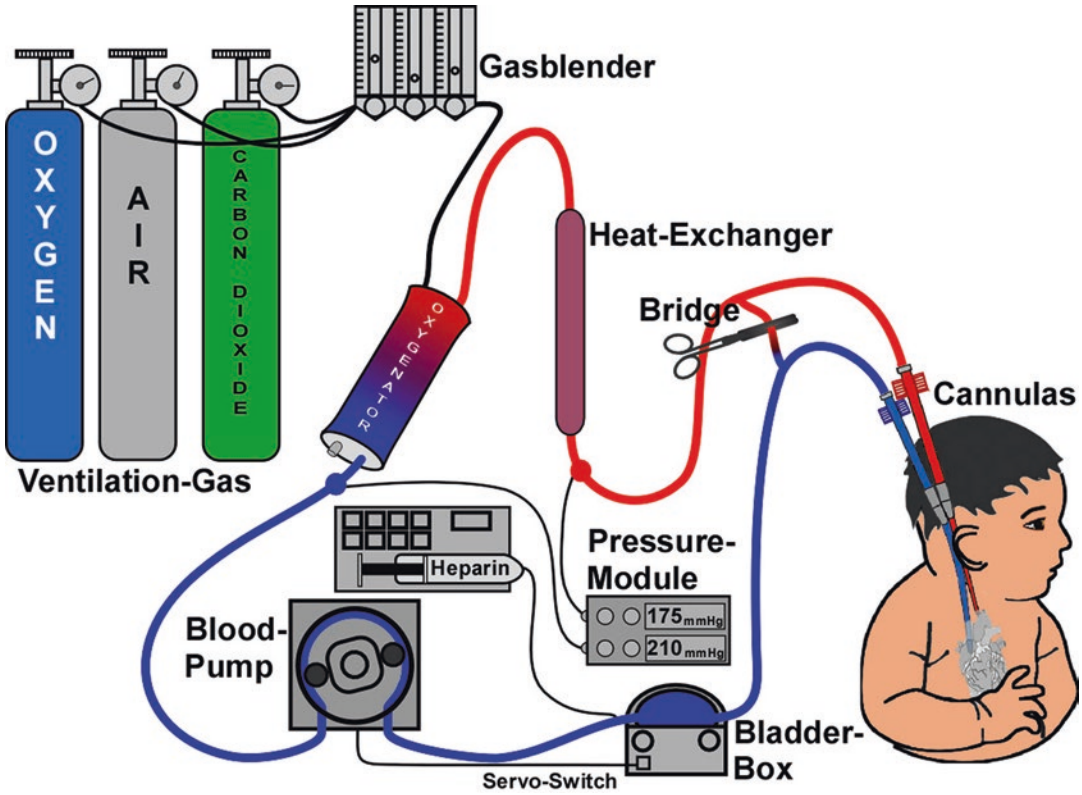

Fig. 16.4 Standard ECMO circuit. (From https://commons.wikimedia.org/wiki/File:Ecmo_schema-1-.jpg [Jürgen Schaub])

that connects the proximal venous and arterial limbs and allows transient removal from ECMO support while on VA ECMO. On VV ECMO, trialing-off can be done by simply turning off the sweep gas flow. Individual centers often customize their circuits, but, in general, fewer stopcocks and connectors lead to less turbulence and lower likelihood of clot formation. The most important aspect of the circuit is its length and diameter, as both impact inflammation and clotting as well as the necessary priming volume.

Monitoring

Standard monitoring includes pump inlet pressure monitor, pre- and postoxygenator pressures, flow monitors, air bubble detector, and oxygen saturation/blood gas. Many centers also employ hemoglobin monitors. The newest ECMO devices have these monitors integrated into the circuit with display on a single LED screen.

Summary on the ECMO Machine

Previous ECMO devices were complicated and often relied on components from different manufacturers that were not necessarily designed for ECMO. The newer ECMO devices have become integrated and more compact, consequently requiring less "babysitting." Monitors are integrated into the circuit such that pressures, flows, and other variables can be visualized continuously with integrated alarms for ease in monitoring and identification of problems. These advances have undoubtedly improved the safety of ECMO. Recent ELSO data suggest that outcomes with ECMO are improving, and this may in part reflect these technologic advances as well as improvements in other aspects of care [39].

ECMO for PARDS

Overview

The general indications for ECMO in PARDS are rarely straightforward, though may be challenging to employ at the bedside of a particular patient. Overarching considerations include the following:

1. Is the trajectory of the lung injury such that the risks of ECMO are outweighed by the risks of continuing mechanical ventilatory support at potentially injurious settings?
2. Is the lung injury recoverable or, if not, is lung transplantation feasible?
3. Is there evidence of other organ failures and, if so, are the additional organ failures potentially recoverable?
4. What are the family's beliefs and considerations regarding the goals of care?

More specific indications and contraindications suggested by experts in the field are listed in Table 16.1 [28], though this list is not exhaustive. A recently developed scoring system for predicting mortality in children with respiratory failure placed on ECMO has been developed based on the ELSO dataset and validated using data from the Pediatric Health Information System (PHIS). The variables that emerged for the Pediatric Pulmonary Rescue with ECMO Prediction Score (P-PREP) [37] included VV versus VA ECMO; duration of pre-ECMO ventilation; PaO2/FiO2 ratio and pH prior to ECMO; primary pulmonary diagnosis; and comorbid conditions. Performance for the scoring system as judged area under the receiver operating curve was reasonably good at 0.66–0.69. A similar predictive score, the Pediatric Risk Estimate Score for Children Using ECMO Respiratory Support (Ped-RESCUERS), with similar sensitivity was reported by Barbaro

Table 16.1 Possible indications and relative contraindications for ECMO

Indications	Relative contraindications
Severe refractory hypoxemia (e.g., P:F ratio <60–80, oxygen index >40)	Duration of mechanical ventilation >14–21 days before ECMO
Toxic ventilator settings (e.g., Pplat >32, MAP >25–30)	Recent intracranial surgery or hemorrhage
Refractory hypercarbia	Chronic illness with poor long-term prognosis
Refractory air leaks	

et al. [38]. Both scores are complex, and it is unproven if they can be used to make judgments in individual cases, but might be considered for benchmarking in individual ECMO programs. Unfortunately, no comparable scores exist to assess the risk of continuing mechanical ventilation in PARDS. It seems unlikely that these or other objective means of risk assessment will replace clinical judgment in the near future.

Patient Populations

PARDS can result from a variety of insults and individual patient factors may greatly influence outcomes: primary diagnosis, comorbidities, age, and pre-ECMO physiologic variables. Primary diagnosis is among the most important ECMO prognostic factors [39]. According to the 2017 ELSO data, "other" is the largest category for pediatric respiratory cases, with "viral pneumonia" and "acute respiratory failure" more frequent than "ARDS." A major weakness in the ELSO data is the precise definitions of each of these categories are unclear and it is probable that many patients in each of the ELSO respiratory diagnostic categories would also meet the definition of PARDS by the time ECMO is being considered. Survival statistics differ somewhat by diagnostic category. Survival is reported as 67% for aspiration pneumonia, 65% for viral pneumonia, 59% for bacterial pneumonia, 56% for ARDS, 55% for acute respiratory failure, and 52% for the "other" category [13]. As reported by Zabrocki and colleagues evaluating the ELSO 1993–2007 data, survival with ECMO ranged from a high of 83% for asthma and a low of 23% for fungal pneumonia [39].

Comorbidities also greatly influence outcomes. In Zabrocki's review [39] of 3213 children from the 1993–2007 ELSO dataset, any comorbidity was associated with a decrease in survival from 57% to 33%, with "immune compromise" the most significant. Overall survival from respiratory failure for children with immune compromise placed on ECMO is 33–35% [39], but survival after hematopoietic stem cell transplant (HSCT) is dismal with one report of no survivors in 20 patients [40] and another reporting survival to hospital discharge in only 3/29 children [41]. Genetic abnormalities are also likely to impact survival, although it would depend on the type of genetic abnormality. In the specific case of Down syndrome, survival on ECMO is comparable to survival of children without trisomy 21 [42]. Renal failure increased the likelihood of mortality by a factor of 1.77 [43], although CRRT did not change survival if it was used for fluid overload (hemofiltration) rather than support of renal failure. At least two studies have demonstrated that congenital heart disease significantly decreased survival [44, 45], although survival with cardiomyopathy/myocarditis according to one meta-analysis was 63% [46]. Liver failure was also associated with very poor survival in the ELSO data (17%).

Age also appears to be a factor, although whether this reflects different underlying diagnoses and comorbidities or is actually a function of age is unclear. In Zabrocki's data [39], children aged 10–18 had a significantly lower survival (50%) compared to infants (57%), toddlers (61%), and children (55%).

Duration of ventilatory support prior to ECMO remains a prognostic factor. Earlier data from Moler et al. [47], suggested that pre-ECMO ventilation for >7 days was the cut-off for successful ECMO, but more recent data support that patients ventilated up to 2 weeks had similar outcomes [48]. The number of patients ventilated for longer than 2 weeks is small, but it is notable that even after ventilation for >2 weeks survival was still 38% [39]. These data reflect duration of pre-ECMO ventilation as a single factor and it is likely primary diagnosis, comorbidities, or other factors affect these statistics. The data cannot tell us the reason for delayed ECMO, and it is probable that many of these children were ventilated for other reasons prior to their development of lung injury requiring ECMO support. Nonetheless, the upper limit of time on prior ventilation continues to be revised upward.

While our ability to predict outcome for the individual child with PARDS is limited, recent data from the prospective observational PARDIE study suggests oxygenation in the first 24 hours after initiation of mechanical ventilation is predictive of mortality [3]. In that study an OI > 16

(or OSI > 12.3) at 6 hours after initiation of mechanical ventilation predicted 34% mortality. Measures of ventilatory efficiency, including Vd/Vt [49] and ventilation index [50], may further add to predicting mortality risk and assist in the determination of if and when to initiate ECMO. While these factors clearly correlate with outcomes with conventional support, whether and to what degree these outcomes can be altered by early use of ECMO is unknown.

Ultimately, the decision to employ ECMO is a clinical one. Sometimes the decision is relatively straightforward because the child is failing despite high ventilator pressures or volumes that are clearly not sustainable. Other times it simply becomes a judgment as to which carries the lesser risk – and that judgment is going to hinge on the experience of the clinician and the ECMO center as much as objective measurements of failing lung function. The decision-making process promises to evolve in the coming years as the technology improves and ECMO becomes simpler, presumably safer, and more routine.

Conduct of ECMO for PARDS: VV ECMO

Both VV and VA ECMO can be used for respiratory support in PARDS. VV ECMO is increasingly favored for reasons previously discussed – fewer neurological complications, avoidance of sacrificing a major artery or jeopardizing an extremity, and improved survival [51, 52]. VV ECMO does not support the heart, but diminishing cardiac function generally improves with restoration of adequate oxygenation and normalization of acid/base balance. Thus, poor myocardial contractility or use of modest-dose vasoactives is not an absolute contraindication to using the veno-venous approach. Because of the recirculation and mixing inherent when venous blood from the oxygenator is returned to the venous system, however, management of VV ECMO differs somewhat from VA ECMO.

Not all blood enters the ECMO circuit, so some deoxygenated blood will pass through the failing lungs and return to the left side of the heart still poorly oxygenated, resulting in oxygen saturations with VV ECMO that may be considerably less than 100%. Indeed, maximally achievable SaO_2 may be as low as 75–80%, but this may be sufficient, depending on the child's cardiac output and metabolic needs. The degree of mixing and recirculation depends on a number of factors [53]:

1. Relative positions of the outflow and inflow venous cannulas: When two cannulas are used, taking blood from the IVC and returning it into the SVC results in demonstrable better SaO_2 than vice versa. With the double-lumen catheters, the position of the outflow lumen toward the tricuspid valve in the right atrium is critical (Fig. 16.3).
2. Size of the cannulas: Larger sizes enable higher flow rates with less negative venous drainage pressure and, consequently, less mixing.
3. Intrathoracic pressure: High intrathoracic pressure (such as with pneumothorax, tamponade, or status asthmaticus) impedes venous return and increases recirculation, though it may also reduce pulmonary blood flow and drive more desaturated blood into the ECMO circuit.
4. Blood flow: As ECMO blood flow increases, the venous limb of the circuit pulls in more deoxygenated blood (i.e., effective blood flow, which increases systemic oxygenation) and also more oxygenated blood (i.e., recirculation of blood that has already passed through the ECMO circuit). At some point, increasing ECMO blood flow further increases recirculation but does not improve systemic oxygenation.

Ultimately, the adequacy of the SaO_2 can be judged by clinical effects (HR, BP, perfusion, urine output) or oxygen delivery (SaO_2–SvO_2), but arterial lactate may be the simplest and best single indicator of the adequacy of a given oxygen saturation.

Inadequate SaO_2 on VV ECMO can be addressed by:

1. Increasing pump flow: Often flows higher than normally used in VA ECMO are needed, although recirculation usually increases proportionately and often reaches diminishing returns.
2. Changing the catheter positions or adding an additional drainage catheter.
3. Augmenting hemoglobin with transfusion to increase SvO_2.
4. Improving cardiac output with volume or inotropes (which may not necessarily improve SaO_2 but may improve oxygen delivery) to increase SvO_2.
5. Using the lungs: Increase ventilator settings.
6. Change to VA ECMO if the above are insufficient to achieve adequate oxygenation.

Weaning on VV ECMO as the lung improves is relatively straightforward. Both sweep gas and/or ECMO flows can be decreased and ventilator settings increased proportionately. Avoidance of high volumes or pressures on the ventilator remains important consideration and weaning ECMO should not be at the risk of inducing lung injury from the ventilator. Unlike with VA ECMO, pump flow rates can be maintained and sweep gas simply turned down and eventually to off as the ventilator (or spontaneous breathing) resumes the work of oxygenation and ventilation.

VA ECMO for PARDS

Despite the benefits of VV ECMO in PARDS, the anticipated or real need for cardiac support may mandate use of VA rather than VV ECMO. Assuming a functioning oxygenator, management of oxygenation in VA ECMO is straightforward and directly proportional to ECMO flow. Inadequate SaO_2 is generally remedied by turning up the pump flow. It may, however, be necessary to decrease the sweep gas flow in order to maintain the desired $PaCO_2$ because carbon dioxide removal is very efficient with current oxygenators. Inadequate ventilation generally responds to turning up the sweep gas flow, although at very low flow rates, it may be necessary to increase pump flow as well. Fortunately, with today's ECMO setup, oxygen provision and carbon dioxide removal can be uncoupled.

Weaning on VA ECMO primarily involves turning down the pump flow. Lower flow rates increase the risk of clot/thrombosis, so anticoagulation may require closer attention. With use of an arterial–venous bridge (described previously), it may be possible to briefly "trial off" without disconnecting or removing cannulas as a means of assessing adequacy of cardiopulmonary function and the likelihood of successful separation from ECMO. While this strategy helps to minimize the risk of clot in the ECMO circuit, the distal portion of the circuit between patient and bridge and the cannulas remain at risk for clot.

Management of the Lungs

Management of mechanical ventilation while on ECMO remains controversial. The ELSO guideline states to "avoid fluid overload and damaging ventilator settings" [13]. For pediatric patients, the recommendations are use of higher PEEP (10–15 $cmsH_2O$), low rates, low peak or plateau pressures (PIP < 28–30 cmH_2O), and FiO_2 < 50%. A meta-analysis of 9 adult studies suggested higher driving pressure (PIP-PEEP) was independently correlated with mortality [54]. The CAESAR study [22] notably maintained peak pressures <25 cmH_2O. In a study in adults, Schmidt, et al., [55] reported higher PEEP levels improved survival. Some authors have advocated for extubation while on ECMO [56], particularly for patients awaiting lung transplant. Management will also be undoubtedly influenced by the type of ECMO support. In VV ECMO, utilization of native gas exchange is often necessary; thus, manipulation and utilization of the ventilator are more common than during VA ECMO during which lung "rest settings" are commonly deployed. This authors' practice has been to maintain lung recruitment and utilization of the lungs during VA ECMO but not to the degree that would be injurious. Minimizing the deleterious effects of further lung injury caused by collapse is likely beneficial. There have been no randomized

studies in children and ELSO data as well as an international survey demonstrates no agreement about the best approach to manage the lungs.

Anticoagulation

Cardiopulmonary bypass and, subsequently, ECMO only became possible with the discovery of heparin. Heparin is inexpensive, has relatively few side effects, has a short (30–60 minutes) half-life, and is easily reversed [57]. Unfractionated heparin remains the mainstay of anticoagulation for both adult and pediatric ECMO, but heparin is far from a perfect anticoagulant. Heparin activity relies on antithrombin III (ATIII), the level of which is variable in neonates (due to ineffective synthesis) and which can fall over time on ECMO due both to ineffective production and dilution related to underreplacement with ATIII directly or with FFP, which contains ATIII. Additionally, heparin can induce development of antibodies that result in bleeding and thrombosis (heparin-induced thrombocytopenia, or HIT).

There is little consensus on how to monitor anticoagulation [58–61]. The activated clotting time (ACT) is time-honored, rapid, and requires little blood, but some studies have suggested that measuring the direct effect of heparin on thrombin by measuring activated factor ten (Xa) levels is more predictive of the degree of anticoagulation [62, 63]. Unfortunately, some hospitals do not measure Xa routinely, its measurement requires a larger blood sample, and the turnaround time for the assay may be prolonged such that "real-time" interventions are limited when using Xa assay as the primary source for decision-making. Utilization of Xa assay only evaluates the coagulation cascade devoid of cellular elements. Thromboelastography (TEG) and rotational thromboelastography (ROTEM) offer a more complete assessment of anticoagulation as well as fibrinolysis and can be done at the bedside [64]. At present, however, few studies have looked at the predictive value of TEG or ROTEM in ECMO. While strict adherence to an anticoagulation protocol has been shown to decrease the incidence of complications [65], what constitutes the best protocol for both anticoagulant administration and monitoring remains to be determined. In clinical practice, most ECMO centers utilize some combination of point of care testing (ACT) with Xa measurement and TEG/ROTEM in circumstances when ACT and Xa alone are equivocal in the setting of uncertainty.

Direct thrombin inhibitors such as bivalirudin show promise for use in ECMO. Anticoagulation is accomplished independent of ATIII and, as such, reduces the need for exogenous ATIII administration and may alleviate the variability seen with unfractionated heparin. Another advantage of bivalirudin is that it inhibits both circulating as well as clot-bound thrombin, whereas unfractionated heparin is not effective on existing clot. This may confer significant benefit, as ECMO circuit clot remains a significant complication during ECMO support. Monitoring of bivalirudin is done through measurement of aPTT rather than Xa. Utilization of ACT and TEG is still effective with bivalirudin as these assays reflect "whole blood" clotting. Data supporting bivalirudin use and superiority in pediatric ECMO are lacking, however, so its use remains center and clinician dependent. In the future, heparin-coated circuits and use of direct thrombin inhibitors may simplify anticoagulation on ECMO, but at present, anticoagulation on ECMO remains more of an art than a science.

ECMO Complications

Several problems are inherent with the use of ECMO. Bleeding and its counterpart, thrombosis, largely related to the exposure of blood to the nonbiologic surface of the ECMO circuit, are common and are associated with significant morbidity and mortality. ECMO patients are also at high risk for infection due to the large amount of foreign material and the need for frequent interruption in the circuit to draw labs and give blood products and medications. Mechanical problems from circuit leakage/rupture or cannula displacement have fortunately become less common but necessitate constant vigilance. Additionally,

other organs can be adversely affected consequent to hemolysis, nonpulsatile flow (VA ECMO), or air or other embolic phenomenon from the circuit. A brief description of the more common problems follows.

Bleeding and Thrombosis

The most common problem in ECMO is bleeding, and this is followed closely by its antithesis, thrombosis. The BATE Study (Bleeding and Thrombosis in Children) was a prospective observational cohort study in 514 children that reported an incidence of all bleeding events just over 70%, with intraventricular hemorrhage (IVH) in 17% [59]. Thrombosis occurred in 37.5% of subjects, while 31% had thrombosis involving the ECMO circuit. Anticoagulation was variably managed in the study, with nearly all using heparin infusions. Methods of monitoring of anticoagulation were highly variable between practices, some monitoring only ACT, others following PTT, and still others Xa. The study documented large variations in use of plasma and ATIII, frequency of monitoring, and rates of thrombosis and bleeding across the 8 sites. Unfortunately, the study offered no conclusions regarding the optimal anticoagulation or monitoring regimen. This appears to be the current state of the science.

Infection

The presence of multiple indwelling catheters and need for frequent interruption of the ECMO circuit for blood draws, medication administration, and delivery of blood products places the child on ECMO at high risk for nosocomial infection. Rates for pediatric infection reported to the ELSO database are 20.8/1000 ECMO days [66], although a Canadian study suggested higher rates [67]. Coagulase-negative *Staphylococcus*, *Pseudomonas*, and *Candida* were the most common. Surprisingly, in at least one study, infection was not independently associated with mortality [68]. A recent study from the CPCCRN reported a 16.6% rate of infection with an average onset at 5.2 days [69]. The most common sites of infection included bloodstream (4.4%), urine (4.2%), respiratory (11%), and others (4.2%). The most common organisms in that study were *Candida albicans, Staphylococcus aureus, Enterobacter cloacae, Pseudomonas aeruginosa, Escherichia coli*, and *Staphylococcus epidermidis.* Recommendation for routine surveillance of both blood and urine for presence of infection is not strongly supported but is often performed given the consequences of infection and the inability to detect fever due to temperature regulation accomplished by the ECMO circuit.

Organ Dysfunction

It is often difficult to know if organ dysfunction is consequent to ECMO or preceded it. Some organ dysfunction, such as poor cardiac contractility, may actually improve with initiation of ECMO because the cause – hypoxia and/or acidosis – has been remedied. Renal dysfunction, however, may sometimes be precipitated by ECMO and may relate to nonpulsatile flow or hemolysis and high levels of free hemoglobin [70]. The most ominous complication is intracranial bleeding or stroke. This is more common with VA than VV ECMO and probably occurs more frequently than is realized [7]. A study by Lockie et al., showed that 16.4% of patients on ECMO had CT scan evidence of bleeding and/or stroke when imaging was performed [7]. Current recommendations suggest obtaining a CT or, preferably, MRI scan prior to discharge. Seizures are also a common complication of ECMO and may be the first indication of intracranial hemorrhage [7].

Cannula Problems

ECMO cannulae are associated with the same complications that occur with comparably sized central cannula placed for other indications. The newer double-lumen catheters used in VV ECMO, however, are more problematic. Because of the bicaval design, precise placement is critical. Unfortunately, the catheters are relatively stiff and placement incurs the risk of the catheter entering the right ventricle rather than the IVC, which can result in perforation and subsequent tamponade [27]. Placement utilizing fluoroscopy and/or echocardiology is strongly recommended. Problems with distal extremity ischemia are not uncommon with femoral artery catheters and

often require bypass grafts or catheters to prevent loss of viability. Bleeding at cannula site is a common occurrence and often difficult to both quantify and remediate.

Neurological Complications

Central nervous system infarct and bleeding are the two most feared complications of ECMO. In a review of 2617 children with respiratory failure supported with ECMO, the overall incidence of CNS hemorrhage or infarct was 9.6%, with a significantly greater incidence in VA (11.8%) compared to VV (6%) ECMO [7]. A very interesting study in adults from the UK, however, demonstrated that VA ECMO was not an independent risk factor for intracranial hemorrhage (ICH) [71]. Furthermore, in that study, there was no significant difference in 6-month survival between patients with and without ICH. The ELSO data quote a 79% mortality with ICH on ECMO compared to only 38% without ICH [7]. This has prompted the suggestions that all patients should if possible have CNS imaging prior to ECMO and prior to hospital discharge.

Long-Term Outcomes on ECMO for PARDS

To quote Zabrocki et al., "Although the survival of pediatric patients with acute respiratory failure treated with extracorporeal membrane oxygenation has not changed, this treatment is currently offered to increasingly medically complex patients" [39]. The increasing complexity of patients supported with ECMO is but one factor that makes broad statements about long-term outcomes in ECMO difficult. The different indications for which ECMO is utilized in children – cardiac failure, respiratory failure, or eCPR – are additional factors. In general, multiple reports suggest that VV ECMO is associated with better long-term outcomes than VA [37–39, 72], but this may reflect the underlying reason for ECMO support rather than the ECMO method. Follow-up studies on infants and children surviving ECMO paint a mixed picture, although perhaps better than would be expected. In a review of over 50 studies of follow-up of children receiving ECMO for a range of diseases that included congenital diaphragmatic hernia to respiratory and post-op cardiac support, more than half of survivors did well [73]. Cognitive deficits ranged from 10% to 50%, behavior problems from 16% to 46%, and severe motor impairment was seen in 12%. Overall quality of life evaluated at school-age or adolescents ranged from 31% to 53% having a score more than 1 standard deviation below norms in their age groups. Clearly, the glass is either half-full or half-empty. Unfortunately, there exists almost only limited data in follow-up of children with PARDS. The need for follow-up studies in PARDS was identified as a major deficiency in the PALICC conference [74].

One argument for earlier or "more aggressive" use of ECMO in PARDS is the potential of better pulmonary outcomes by avoidance of injurious levels of positive pressure ventilation. While an attractive argument, there are almost no data on long-term pulmonary function in children with PARDS [74, 75]. Data on children hospitalized for RSV, some of whom would qualify as PARDS, suggest long-term effects on airway reactivity, but it is not clear that this is a consequence of the acute lung injury or a prior predisposition to wheeze [76, 77]. What little data there are in PARDS suggest that pulmonary outcomes are generally at least okay, with subtle abnormalities identified on pulmonary function testing but few limitations on exercise, etc. PICU patients do appear to be at significant risk for PTSD and generally lower quality of life, but the relationship of these findings to lung injury and its support in the PICU is difficult to distinguish from other causes [78]. This has to be considered in the context of the very real risk of CNS injury from bleeding, clot, or embolization during ECMO. Fortunately, these complications are considerably fewer with VV than VA ECMO and most children with PARDS can be adequately supported with VV ECMO. In a study of the California Patient Discharge Database [79], children who survive ECMO have a high rate of hospital readmission (62% in one study), neurological problems/developmental delay (7–9%), and late deaths (5%).

Conclusion

Unfortunately, similar to the determination that ventilator-induced lung injury is likely to outpace lung repair, determination that ECMO offers a better chance for long-term survival is a matter of clinical judgment. As evidenced by the high survival in status asthmaticus, children with clearly reversible lung disease without other comorbidities can do very well with ECMO. The decision to use ECMO becomes increasingly difficult in the chronically ill child (e.g., stem cell transplant) or child with other organ failures where often it seems the choice is between the slim chance offered with ECMO versus the near-certainty of death without ECMO. Against this backdrop is the improving technology and experience making ECMO more readily available, simpler, and likely more successful. For the foreseeable future, the use of ECMO for PARDS will remain largely a clinical decision.

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17 Clinical Outcomes in Pediatric Acute Respiratory Distress Syndrome

Nadir Yehya

Introduction

Children were included in the initial description of acute respiratory distress syndrome (ARDS) [1]. Despite this, pediatric intensivists were not present for either the 1994 American-European Consensus Conference (AECC) [2] or the 2012 Berlin re-definition [3] of ARDS, and so considerations specific to children were not addressed. Nevertheless, the AECC and Berlin definitions were historically applied to children with ARDS without modification, despite the distinct epidemiology and outcomes in pediatrics. To address this, the Pediatric Acute Lung Injury Consensus Conference (PALICC) was convened to propose specific definitions for pediatric ARDS (PARDS) [4]. Notable differences in the PALICC definition are use of oxygenation index (OI) instead of Pao_2/Fio_2, the ability to diagnose PARDS in the absence of arterial blood gas analysis by using noninvasive measures of hypoxemia based on Spo_2 (oxygen saturation index, OSI), and less restrictive radiographic criteria.

Irrespective of definitions utilized, cohort studies and clinical trials have generally demonstrated lower mortality for PARDS (relative to adults), as well as an appreciable decrease in mortality over time [5, 6]. Adult studies have demonstrated decreased pulmonary capacity, decreased quality of life, and worsened neurocognition among survivors of ARDS [7–9]; however, comparable studies are lacking in PARDS. An appreciation of long-term sequelae is important for characterizing the epidemiology of this syndrome. Additionally, the already low and further decreasing mortality rate makes short-term survival an impractical endpoint for most clinical trials in PARDS, necessitating the identification of clinically relevant patient-centered outcomes to test future interventions. In this chapter, we will discuss the current state of outcomes research in PARDS. Additionally, using adult ARDS as a guide, potential alternative outcomes deserving of further investigation in PARDS are suggested.

Mortality

PARDS has lower mortality than adult ARDS [5, 6], with mortality decreasing over time (Fig. 17.1), making this outcome problematic for use as a primary endpoint in randomized controlled trials (RCTs). Short-term mortality – such as 28–60-day mortality, pediatric intensive care unit (PICU) mortality, and hospital mortality – is an objective, easily obtained, clinically relevant, patient-centered outcome, and is consequently consistently reported in cohort studies [6, 10–24]

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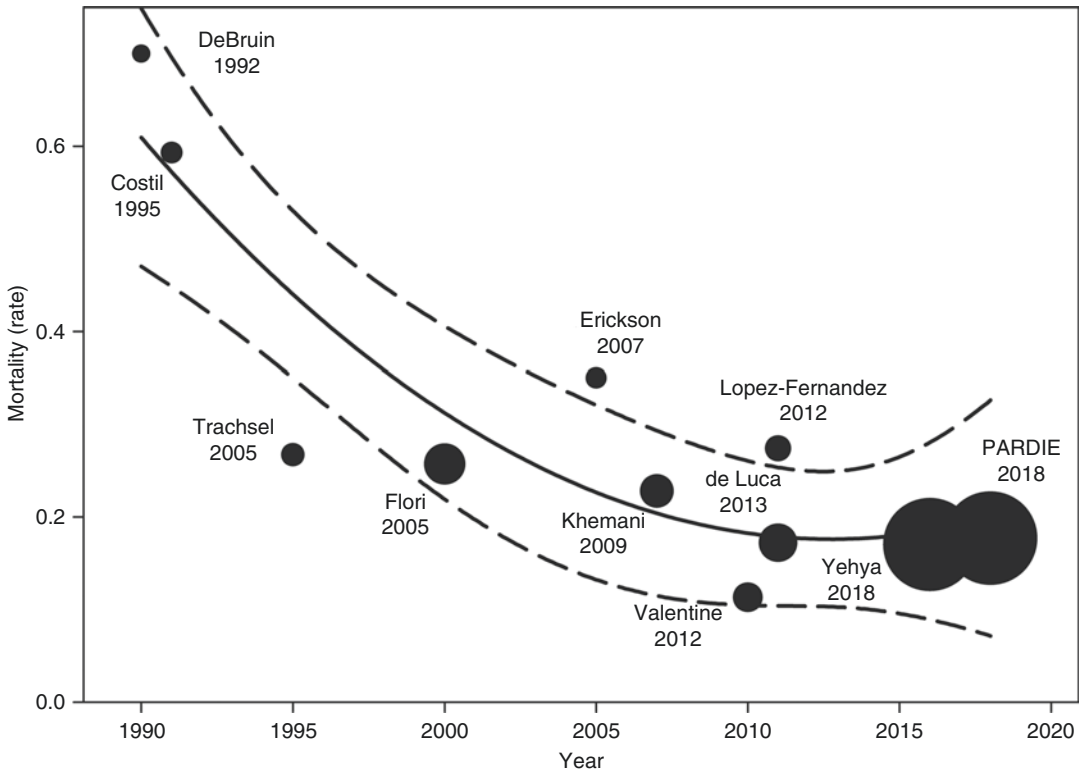

Fig. 17.1 Mortality rates over time in published pediatric observational cohorts, predominantly in the Western hemisphere, with sample sizes ≥100 subjects and with similar PARDS-type inclusion criteria. The solid regression line represents a quadratic function showing decreasing mortality over time, with leveling-off in more recent years. The dashed lines represent 95% confidence intervals. The assigned year represents the final year of patient accrual for a given study. The size of the circles represents the relative sample sizes

and in clinical trials [25–33]. However, several characteristics of mortality call into question its use as a primary endpoint in RCTs or cohort studies.

First, predictors of mortality in PARDS are not necessarily specific to PARDS but, rather, are characteristic of risk factors in several critically ill syndromes. Notably, immunocompromised status [6, 22, 27, 34] and multisystem organ failure (MSOF) [6, 13, 18, 34] are associated with increased mortality risk in several PARDS studies, including RCTs [27]. However, immunocompromised status and MSOF have little pulmonary specificity, are associated with mortality in sepsis, and are components of severity of illness scoring systems. Thus, a generalization of this observation states that children die *with* PARDS, rather than *because of* PARDS. In a two-center North American study examining how and why children with PARDS die, neurologic failure (39%) and MSOF (41%) were responsible for the majority of deaths, whereas a minority (20%) died from persistent hypoxemia from refractory PARDS [35]. In many cases, the associated PARDS has resolved at the time of death, despite the persistence of mechanical ventilation. Thus, even the nominally simple notion of "mortality" actually encompasses at least two mutually exclusive competing events: mortality due to PARDS and mortality not due to PARDS, which complicates any inferences made from studies that investigate and report associations between all-cause mortality and an intervention.

Second, elective withdrawal of potentially futile care complicates use of mortality as an endpoint. Withdrawal of care can occur for MSOF, underlying malignancy, or for poor neurologic prognosis, none of which are specific for

PARDS. Elective withdrawal was the most common mechanism responsible for death (66%), irrespective of whether the cause of death was neurologic, MSOF, or hypoxemia [35]. While single-center studies may have similar approaches to withdrawal of care, this is more difficult to extrapolate to multicenter or multinational studies, where customs and practices surrounding withdrawal or withholding of care may differ.

One example is worth examining in further detail. A multicenter RCT of exogenous calfactant (bovine surfactant) in moderate and severe PARDS (OI > 7) demonstrated improved mortality associated with calfactant treatment [27]. However, imbalance in the proportion of immunocompromised patients, with overrepresentation in the placebo arm, likely contributed to this effect, and after adjustment for immunocompromised status, the association between calfactant treatment and improved mortality was no longer evident ($p = 0.07$). Furthermore, patients received treatment within 48 hours of intubation, but the proportion of patients successfully extubated did not differ between the groups, and curves for cumulative successful extubation did not begin to diverge until 12 days after intubation, suggesting that factors unrelated to the initial PARDS insult, such as immunocompromised status [36], may have been responsible for mortality and prolonged ventilation. A follow-up trial of calfactant was restricted to immunocompromised children (CALIPSO: Calfactant for Acute Lung Injury in Pediatric Stem Cell Transplant and Oncology Patients), using mortality as the primary outcome, and was recently stopped for futility due to slow enrollment [37].

While mortality may be problematic as a primary endpoint for a general PARDS population, there are subgroups of children with PARDS who still have a substantial mortality risk, yet with a reasonable chance of survival. CALIPSO was an example of prognostic enrichment: restricting enrollment for a study to a subgroup with a higher predicted severity of illness and more frequent occurrence of the outcome (mortality), thus improving the power to detect an effect of an intervention. CALIPSO limited their intervention to a subgroup of PARDS with high mortality (>50%), albeit at the risk of difficult recruitment and reduced generalizability. Successful trials in adult ARDS of neuromuscular blockade [38] and prone positioning [39] employed this strategy, as ACURASYS (ARDS et Curarisation Systematique) limited enrollment to patients with $Pao_2/Fio_2 \leq 150$, rather than the typical ≤300. PROSEVA (Prone Position in Severe ARDS) required even more stringent enrollment criteria, as it require $Pao_2/Fio_2 \leq 150$ *after* 12–24 hours of initial stabilization, thereby excluding patients who rapidly improved with standard ventilator management. In both cases, the goal was prognostic enrichment of a higher risk population in which the tested intervention could plausibly impact mortality with a reasonable sample size. This simultaneously avoids unnecessarily exposing patients to treatment when they have low risk of mortality and high probability of survival irrespective of randomization arm, thereby diluting any potential treatment effect. For PARDS to reproduce this, predictors of mortality risk need to be identified and validated. These predictors need to be available early in the PARDS course to allow enrollment within a timeframe amenable for interventions to work, ideally within 48 hours of PARDS onset. This strategy has particular appeal for testing interventions for "refractory" PARDS, such as high-frequency oscillatory ventilation (HFOV), prone positioning, methylprednisolone, inhaled nitric oxide (iNO), and extracorporeal membrane oxygenation (ECMO).

Finally, it is worth discussing why mortality is decreasing in PARDS despite an absence of positive trials. Indirect evidence suggests adoption of management extrapolated from adult ARDS, such as lower tidal volumes [40] and higher positive end-expiratory pressures [41], may be associated with lower mortality. Additionally, as many subjects with PARDS die of MSOF, rather than hypoxemia, it is possible that other temporal changes unrelated to ventilator management have impacted survival, such as protocolized sepsis care and timely antibiotics [42–44]. However, it is also important to note that definitions of ARDS (and PARDS) have evolved over time. The AECC definition [2] allowed for an entity of acute lung injury ($Pao_2/Fio_2 \leq 300$), in addition to ARDS

($Pao_2/Fio_2 \leq 200$), thereby introducing a category of subjects with less severe lung injury. The 2012 revised Berlin definition [3] recoded this category as "mild ARDS," ($200 < Pao_2/Fio_2 \leq 300$), and introduced the requirement for minimal invasive or noninvasive end-expiratory pressure ≥5 cmH_2O. The 2015 PALICC definition of PARDS [4] further liberalized the definition by allowing inclusion of subjects with unilateral infiltrates on chest radiograph, in addition to bilateral. Effectively, the operational definitions of ARDS (and now including PARDS) after 1990 have allowed inclusion of less severe subjects, which may be contributing to the lower mortality rates. Thus, it is entirely possible that the mortality rate for "real" PARDS has not fallen nearly as dramatically as the literature would suggest.

Duration of Mechanical Ventilation

Duration of ventilation is a commonly described outcome in PARDS studies, especially when this outcome is limited to survivors. This outcome has face validity, as more severe PARDS can reasonably be expected to require a longer duration of mechanical ventilation. The 2012 Berlin definition [3] demonstrated an increase in duration of mechanical ventilation in survivors across increasing severity classes of ARDS, which was confirmed in LUNG SAFE (Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure) [45]. This observation has been corroborated in PARDS when using oxygenation between 6 and 24 hours, rather than at PARDS onset [46, 47].

To be valid as an endpoint, "duration of mechanical ventilation" needs to be limited to survivors, given the risk of contamination of this outcome with nonsurvivors with a short-duration of ventilation. Furthermore, given the increased utilization of noninvasive ventilation both prior to [48–50] and after endotracheal intubation, duration of mechanical ventilation requires clear definition regarding whether noninvasive support is included. Both Berlin (mild) ARDS [3] and PALICC PARDS [4] definitions make allowances for noninvasive support, suggesting that screening for studies based on these criteria would allow for inclusion of a substantial number of nonintubated patients, some of whom will subsequently be intubated. This potential for increased enrollment needs consistent and well-delineated reporting of what is meant by "duration of mechanical ventilation."

Therefore, while the endpoint "duration of ventilation in survivors" has face validity and reflects PARDS severity, it is unclear exactly how "patient-centric" this outcome is. Specifically, it is unclear whether a given child would be better served with 10 days of invasive mechanical ventilation and extubated to high-flow cannula, or whether 8 days of invasive ventilation followed by 4 days of noninvasive bilevel positive airway pressure (BiPAP) with full-facemask interface. Indeed, the answer likely varies between patients for a multitude of variables, including sedation requirements, strength, airway status, and indication for intubation.

Finally, duration of ventilation in survivors is complicated by the prevalence of subglottic stenosis, poor secretion tolerance, or severe upper airway obstruction from poor airway tone as an indication for prolonged intubation. Such patients may wean appropriately to minimal invasive support given their underlying PARDS severity, but the actual act of removing the endotracheal tube may be delayed, or ultimately attempted and unsuccessful, for reasons related primarily to their airway. Given the substantial number of comorbidities described in PARDS [46], reasons for prolonged intubation unrelated to the actual PARDS risk factor have the potential to confound the utility of duration of ventilation as an endpoint. An alternative has been proposed to only count the duration of time until successful completion of an extubation readiness test, irrespective of whether or not the patient is actually extubated [51]. However, this has not been validated nor described in an actual practice or trial, and does not address the prior criticism of not being patient-centered, as the child remains intubated.

Ventilator-Free Days

One of the most commonly adopted composite endpoint in PARDS trials is ventilator-free days (VFDs), typically at 28 days. VFDs at 28 days are derived by subtracting ventilator duration in survivors from 28, and scoring nonsurvivors and those requiring ≥28 ventilator days as 0 [52]. It has also been defined as "days alive and free of mechanical ventilation" [53], which creates confusion for cases where the patient is extubated on day 10, but dies on day 20 (10 days alive and free of mechanical ventilation is VFD = 10; nonsurvival at day 28 suggests VFD = 0). This endpoint combines mortality and duration of ventilation by penalizing nonsurvivors, unlike duration of ventilation. Similar to duration of ventilation in survivors, VFDs at 28 days have demonstrated correlation across severity of Berlin ARDS [3] and PALICC PARDS [46, 47] categories, with worse oxygenation categories associated with fewer VFDs. This composite endpoint demosntrates efficiency, as an outcome of an intervention which both reduces mortality and duration of ventilation can be detected with a smaller sample size [53].

The same caveats regarding clarity of noninvasive support are required for VFDs as mentioned for duration of ventilation in survivors [52]. However, VFDs has a major limitation as a composite endpoint, as the merged individual endpoints (mortality and ventilator duration) are *not* equivalent and interchangeable. A child requiring 30 days of mechanical ventilation, but surviving, cannot be considered identical to a child who dies after 7 days of ventilation, although both would be recorded as VFD = 0. Composite endpoints are best utilized when the separate endpoints are of equivalent importance for the patient, such as stroke or myocardial infarction in hypertensive adults. When initially described for adult ARDS, VFDs were demonstrated to be useful only when the more pejorative outcome of mortality was improved alongside shorter duration of ventilation [53]. Given the >30% mortality in adult ARDS [45], this is a reasonable expectation: interventions, which shorten ventilation *should* improve mortality, assuming mechanical ventilation and ARDS are in the causal pathway for nonsurvival. However, even in adults, this assumption can be problematic. The ARDSNet corticosteroid trial [54] failed to demonstrate superiority of methylprednisolone for persistent ARDS for the primary outcome of mortality at 60 days (29.2% mortality in methylprednisolone, 28.6% in placebo, $p = 1$). However, methylprednisolone was associated with 4.4 additional VFDs and 2.7 additional ICU-free days at 28 days. Significantly more patients in the methylprednisolone arm required re-initiation of ventilation (28% vs. 9%, $p = 0.006$). These discrepant results make interpretation of the trial difficult: mortality is reported at 60 days, but VFDs at 28 days. Mortality is nominally higher in the methylprednisolone group, but VFDs are also more favorable for methylprednisolone. Thus, in this case, the reporting of VFDs offers no advantages or power relative to reporting on mortality alone: when an intervention has opposite effects on duration of ventilation and mortality, VFDs merely confuse the interpretation.

In pediatrics, the use of VFDs is potentially suspect for these same reasons, as PARDS mortality is much lower, and persistent hypoxemia is unlikely to be the cause of mortality [35]. Thus, the effect on mortality is less certain to be in the same direction as duration of ventilation. For instance, a trial of ECMO for severe refractory PARDS may result in nominally improved mortality rates but would likely result in prolonged duration of ventilation, thereby complicating the interpretation and utility of VFDs. Finally, several interventions sorely in need of testing in PARDS, including fluid management, sedation protocols, weaning, and extubation readiness, all clearly impact length of ventilation much more so than they will impact mortality, hampering the utility of VFDs as an outcome unless these parameters are protocolized in the context of the trial.

Analysis of VFDs is also not straightforward. VFDs are typically analyzed by comparing means or medians, using t-tests or rank-sum tests, respectively. The skew, excess of zeroes, and ordinal nature of VFDs complicate the use of parametric tests, like t-tests, whereas the

nonparametric equivalents, like the rank-sum tests, do not readily allow for covariate adjustment or efficient description of effect size. Alternative approaches, such as competing risk regression, in which successful extubation is the primary outcome, and death is treated as a competing event, may overcome some of the limitations of traditional tests [55]. Analyzing VFDs in a competing risk framework treats extubation as a time-to-event analysis, censoring after day 28, with nonsurvivors set to be "never extubated" sometime after day 28. This is parallel to setting nonsurvivors to VFD = 0. This framework is less affected by skew or zero-inflation, readily incorporates additional covariates, and clearly imparts information regarding effect size.

Need for Extracorporeal Support as an Outcome

Another composite outcome for PARDS investigations has been the combination of need for ECMO or death [19, 29]. This attempts to address the limitations of VFD and the low mortality (and thus difficult to adequately power) of PARDS. The underlying assumption is that lung injury severe enough to require ECMO is essentially refractory to conventional mechanical ventilation, and thus, need for ECMO would be a death in any center unable to provide ECMO. Therefore, "ECMO" is close enough to "death" to justify combination as a composite endpoint.

The European Society for Pediatric and Neonatal Intensive Care used this definition to test the utility of the Berlin criteria in children [19], and demonstrated that the inclusion of a "severe" ARDS category improved validity with an increased risk of ECMO/death in children with Berlin-defined severe ARDS. It should be noted, however, that the incidence of ECMO/death (18.6%) was only marginally increased over the incidence of mortality (17.2%), and that comparable analyses for mortality yielded identical conclusions.

A recently published RCT [29] for iNO (total $n = 53$) reported both mortality (28% placebo, 8% iNO, χ^2 $p = 0.07$) and ECMO/death (48% placebo, 8% iNO, $p < 0.01$). The trial was powered for a difference in VFD at 28 days, for which it required a sample size of 169 children, and was stopped early for slow enrollment. Of note, the difference in the reported VFD in this trial was also significant. While the primary outcome of more VFD was achieved despite the small sample size, the reporting of ECMO/death in this study points to a potential mechanism whereby iNO improved VFD. Specifically, iNO appeared to decrease the rate of ECMO utilization, suggesting an improvement in hypoxemia, thereby reducing total ventilator days, and potentially impacting mortality. This is significant, as it implies a connection between improvement in hypoxemia and better outcomes in PARDS, a connection that is not consistently observed in adult ARDS trials [56]. The recently completed ECMO to rescue Lung Injury in severe ARDS (EOLIA) trial in very severe, refractory adult ARDS was stopped early for futility for a low probability of achieving its primary endpoint, mortality at 60 days, despite a nominal improvement in mortality with ECMO (relative risk with ECMO 0.76, 95% confidence interval [CI] 0.55 to 1.04, $p = 0.09$). However, 28% of subjects assigned to mechanical ventilation crossed over to ECMO, and when the trial was reanalyzed using "treatment failure" as the outcome, the result was highly significant in favor of ECMO (relative risk 0.62, 95% CI 0.47 to 0.82, $p < 0.001$). The authors defined treatment failure as death for the ECMO arm, and as death/ECMO for the ventilation arm, providing face validity for this outcome in future trials.

For certain trials of salvage therapy, such as methylprednisolone, iNO, prone positioning, and HFOV, the use of ECMO/death as a primary outcome may be rational. However, as in the iNO trial example above, there is little information added by this specific reporting that was not also captured by the more conventional short-term outcome of VFD at 28 days. Additionally, as ECMO is not an outcome per se, but simply an additional mode of supportive care, with subjective thresholds for its utilization among different centers and practitioners, the composite outcome of ECMO/death is difficult to standardize.

Finally, the component variables of ECMO/death are not of equal importance to the patient, thus calling into question its validity as a patient-centered, clinically meaningful composite outcome, similar to the criticism of VFDs.

Technology Dependence and New Morbidity as an Outcome

Development of new morbidity, quantified using scoring systems such as the Functional Status Scale (FSS), which penalize additional technology dependence, has been proposed as outcome for trials in critically ill children [57]. FSS scores subjects from 1 (normal function) to 5 (severe dysfunction) points across six domains (mental status, sensory function, communication, motor function, feeding, respiratory). New morbidity, operationalized as an increase in FSS from baseline of 3 or more points from baseline, was demonstrated to occur nearly 1.5- to 2-fold more frequently than mortality.

In a single-center study of 316 subjects with PARDS [58], new morbidity (ΔFSS $\geq$3 from baseline) occurred in 20% of subjects, whereas hospital mortality occurred in 13%. Thus, use of death *and* new morbidity as a composite outcome would have nearly tripled the event rate for a trial, from 13% to 33%, demonstrating utility of new morbidity as a viable outcome for PARDS. In this PARDS cohort, worsening in the FSS domains of motor function, feeding, and respiratory was associated with discharge to a location other than home.

A criticism of new morbidity is that it is only partly related to the acute PARDS event, but is also substantially impacted by underlying comorbidities. Of the 274 survivors in this study, 56 (18% of the entire cohort; 20% of survivors) had a worsening respiratory FSS, of whom 19 (6% of the entire cohort; 7% of survivors) underwent new tracheostomy placement. Worsening respiratory FSS, which in practice means increased use of supplemental oxygen or varying degrees of noninvasive and invasive respiratory support, may be more directly related to PARDS, and could potentially be combined with death as part of a composite. The criticism of all composite outcomes that the components are of unequal importance, however, still persists, as tracheostomy is typically not considered equivalent to death.

Postdischarge Outcomes

A single study has examined long-term survival of PARDS subjects after hospital survival, and showed that over 1 year and 3 years, an additional 5.5% and 8% of subjects had died [58]. Thus, outcomes such as 90-day, 6-month, or 12-month mortality, commonly used in adult ARDS trials, are unlikely to represent significant differences compared to short-term mortality in PARDS. Additionally, longer-term mortality in PARDS was associated with underlying comorbid conditions, and was not an apparent a sequela of the PARDS event. Therefore, alternative postdischarge outcomes are needed (Table 17.1). Recent attention has focused on the development of new morbidities, defined as above, as a relevant long-term, postdischarge outcome [57, 59]. However, this has not yet been validated for PARDS.

Few studies have investigated the physical or neurocognitive quality of life in survivors of PARDS [60–65]. The existing studies are of extremely limited sample size (all $n \leq 24$) and outdated, with ventilator management not reflective of current PICU practices [66, 67]. In 1985, Fanconi et al. [60] published on pulmonary function testing (PFT) of 9 survivors of PARDS ventilated between 1978 and 1982 (5 of whom experienced peak pressures >40 cmH_2O) at a mean 2.3 years follow-up. Seven of the 9 were considered "hypoxemic," with $PaO_2 < 80$ mmHg on room air, and 8 of 9 had ventilation inequalities on multibreath nitrogen washout. Increased peak pressures and increased exposure to $FiO_2 > 0.5$ during PARDS correlated with increased ventilation inequalities, suggesting a potential association between ventilator management and long-term pulmonary outcome. In a separate study published in 1996, 11 PARDS survivors ventilated between 1986 and 1993 (mean PaO_2/FIO_2 160; 9 of 11 with peak pressures

Table 17.1 Potential outcomes for PARDS studies

Outcome	Timeframe	Advantages	Disadvantages
Mortality	Short term: 28 or 60 day PICU Hospital	Easy to obtain Fixed time-point Related to acute process Patient-centered	Impractical given low baseline mortality
	Medium and long term: 90 day 1 year	Potentially captures longer period of risk for unfavorable outcomes	Low postdischarge mortality Harder to obtain follow-up More related to underlying comorbidities
Ventilator-free days	28 days	Easy to obtain Increases power to detect clinically meaningful improvements related to shortened ventilation and survival	Needs noninvasive support explicitly defined Imbalance in components of the composite outcome Only increases power if intervention benefits both mortality and ventilator days Specific analytic techniques
Ventilator days	28 days PICU LOS	Easy to obtain Related to pulmonary nature of PARDS	Needs noninvasive support explicitly defined Unclear if patient-centered Ignores mortality
ECMO/death	Short term	Increases power to detect efficacy of pre-ECMO "salvage therapies"	Subjective use of ECMO Imbalance in components of the composite outcome Unclear if patient-centered
Neurocognitive and functional (POPC/PCPC)	Medium and long term: 90 day 1 year Pre-return to school	Rapid (POCP/PCPC) Patient-centered Potentially completed over telephone Potentially more practical, as it is a prevalent outcome	More thorough cognitive function requires longer testing Changes with developmental age and with comorbidities
Pulmonary outcomes	Medium and long term: 90 day 1 year Pre-return to school	Patient-centered Related to pulmonary nature of PARDS	Requires infrastructure (expertise and equipment) for in-person follow-up
Need for tracheostomy	Short, medium, and long term: Hospital discharge 1 year Prereturn to school	Easy to obtain Patient-centered More directly related to PARDS diagnosis High probability of return to clinic for follow-up	Low event rate Collaboration with specialties required
New morbidity	Short, medium, and long term: Hospital discharge 1 year Prereturn to school	Easy to obtain More frequent than mortality Patient-centered Partly related to pulmonary nature of PARDS	Definitions of morbidity require long-term validation Potentially more related to underlying comorbidities than to PARDS
Psychiatric	Long term	Patient-centered Potentially completed over telephone	Requires infrastructure (expertise) for in-person follow-up
Health care utilization	Medium and long term: 90-day and 1-year Rehospitalization	Patient-centered Does not require inpatient follow-up Related to pulmonary nature of PARDS Addresses cost to patient/family	Difficult to obtain Sensitive to local practices Potentially more related to underlying comorbidities than to PARDS

ECMO extracorporeal membrane oxygenation, *LOS* length of stay, *PARDS* pediatric acute respiratory distress syndrome, *PCPC* pediatric cerebral performance category, *POPC* pediatric overall performance category, *PICU* pediatric intensive care unit

>40 cmH_2O) with PFT performed at a mean 23 months follow-up demonstrated obstructive physiology in 3 children and mixed obstruction and restrictive physiology in an additional 4 children [62]. In an investigation of PARDS survivors ventilated between 1986 and 1998 (all experienced pressure-controlled ventilation, with all peak pressures <35 cmH_2O), investigators were able to assess PFT in 7 patients, finding one with an abnormal diffusion capacity, and a second with exercise-induced hypoxemia [64]. The most recent investigation of PARDS studied 24 survivors who met AECC ARDS criteria between 2000 and 2005 and who agreed to follow-up [65]. At a mean follow-up of 11 months, in 17 subjects able to complete PFT, 24% demonstrated obstructive disease, and 12% had abnormal diffusion capacity, with an association between worse hypoxemia and subsequent abnormal PFT reported.

Based on these small case series, the PALICC group recommended that survivors of PARDS undergo screening for PFT abnormalities within 1 year of discharge [68]. The small sample size of these existing studies, antiquated ventilator management, and variable follow-up time precludes any real assessment of the prevalence of pulmonary dysfunction in PARDS survivors. Larger-scale, multicenter follow-up is sorely needed, potentially exploiting the infrastructure of existing pediatric critical care research networks and in collaboration with pediatric pulmonologists and rehabilitation providers.

Studies within this framework are becoming more common in pediatric critical care. The out-of-hospital arm of THAPCA (Therapeutic Hypothermia after Pediatric Cardia Arrest) trial [69] was powered for a primary outcome of a dichotomized (good versus bad) version of the Vineland Adaptive Behavior Scale, second edition (VABS-II). Ebrahinm et al. [70] reported on the one-month post-PICU admission outcome of 65 urgently admitted survivors using VABS-II, pediatric cerebral performance category (PCPC), pediatric overall performance category (POPC), and overall Pediatric Quality of Life Inventory, fourth edition. They demonstrated an overall poor quality of life for these patients 1 month after PICU admission. A recent review identified potentially useful health-related quality-of-life (HRQL) metrics for pediatric critical care [71]. This review identified substantial morbidity for PICU survivors (not necessarily defined by FSS), some of which were associated with treatments received during their PICU stay, suggesting modifiable risk factors. Additionally, significant psychiatric morbidity may be occurring in PICU survivors [72], including posttraumatic stress disorder (PTSD), depression, and behavioral disorders, with prevalence of posttraumatic stress symptoms potentially as high as 62% [73]. Finally, the recently completed multicenter Life after Pediatric Sepsis Evaluation (LAPSE) study is a prospective observational study collecting information on quality of life, family dynamics and stress, and healthcare utilization in survivors of pediatric severe sepsis.

Adult ARDS Investigations of Alternative Outcomes

Seminal work in adult ARDS long-term outcome [7, 8] has paved the way for potentially comparable studies in PARDS. In 2002, adult survivors of moderate and severe ARDS were followed at 3, 6, and 12 months, with a primary outcome of 6-minute walk distance [7]. The authors found that survivors of ARDS (median age 45 years) had persistent physical limitations at all timepoints tested, primarily due to muscle wasting and weakness. At 12 months, only 49% of patients had returned to work. In multivariable regression, use of corticosteroids and duration of mechanical ventilation both negatively affected 6-minute walk distance, suggesting a possible relationship between modifiable risk factors and medium-term functional outcome. In the subsequent 5-year follow-up study, the median 6-minute walk distance remained below predicted values [8]. However, pulmonary function had returned to near-normal, and persistent exercise limitations were attributed to continuing weakness and neuropsychological impairments. Healthcare costs continued to be substantial for

survivors up to 5 years after discharge, especially in those with pre-existing comorbidities.

For PARDS investigators, this experience is instructive. The major strengths of these studies are the well-characterized, multicenter cohort, the longitudinal study design, the high rates of follow-up, and the in-person data collection. The granularity of the data allowed significant associations to be made regarding ICU exposures (e.g., corticosteroids) and subsequent medium- and long-term outcomes. While these observations remain hypothesis-generating, these are still essential initial steps toward determining how to design future prospective trials with clinically meaningful, patient-centered outcomes.

An earlier study employing an alternative design is also worth considering [74]. A prospective case–control interview/questionnaire study was performed of adult ARDS survivors matched with non-ARDS survivors with similar severity of illness at a median of 23 months after discharge. ARDS survivors demonstrated worse HRQL in nearly all domains tested, including respiratory-specific domains. The most profound reductions in ARDS survivors were in the domains assessing either physical limitations or on the impact of pulmonary symptoms on activities of daily living. This was the first study to assess the HRQL in ARDS survivors matched to similarly ill non-ARDS patients, thus minimizing the possibility that observations were simply reflections of severity of illness; rather, this study design increased the plausibly that these associations were either actually caused by having ARDS specifically, or by the treatments used for it.

The significance of long-term, patient-centered outcomes is elegantly made when considering neuropsychological function in adult ARDS survivors of the Fluid and Catheter Treatment Trial (FACTT). The initial trial used a 2 × 2 factorial design to test (separately) the utility of pulmonary artery catheters versus central venous catheters, and the effects of a conservative versus a liberal fluid management strategy on hemodynamically stable ARDS patients [75, 76]. The trial failed to demonstrate superiority of either fluid strategy in its primary outcome of 60-day mortality (25.5% mortality in fluid conservative, 28.4% in fluid liberal, $p = 0.30$). However, the conservative arm resulted in 2.5 more VFDs ($p < 0.001$) and 2.2 additional ICU-free days ($p < 0.001$) [75] without additional increase in nonpulmonary organ failures, leading the authors to conclude that conservative fluid management was superior in hemodynamically stable ARDS patients.

The follow-up ARDS Cognitive Outcome Study (ACOS) conducted telephone interviews of FACTT survivors at 2 and 12 months postdischarge [9]. Similar to prior investigations [7, 74], the investigators found that most survivors (55–60%, depending on metric used) experienced long-term cognitive impairment. Interestingly, lower PaO_2 ($p = 0.015$) and allocation to the conservative fluid arm ($p = 0.005$) were independently associated with long-term cognitive impairment. The PaO_2 during ARDS reported in ACOS survivors with cognitive impairment was median 71 (interquartile range 67–80), well within the ARDSNet recommended PaO_2 ranges of 55–80, suggesting that existing, arbitrary guidelines may be too permissive, and that this level of mild hypoxemia may be associated with long-term neurologic sequelae. Additionally, the conclusions of the FACTT trial that conservative fluid management resulted in 2.5 additional VFD without additional organ failures are now called into question, as 12-month neurologic function clearly suggests potential subclinical neurologic dysfunction, leading to long-term functional impairment. To date, parallel studies have not been performed in PARDS, and the efficacy of our interventions on long-term function in growing and developing children remains a mystery.

Conclusion

Mortality in PARDS is decreasing, and while it remains clinically relevant and patient-centered, it is impractical for most purposes, and its use should likely be limited to trials aimed at enrolling predetermined higher-risk groups. VFDs are likely to remain the most common primary endpoint for clinical trials in the foreseeable future,

but advocates should be aware of its limitations, and should be mindful that the power of this outcome rests on whether the tested intervention improves *both* mortality and duration of ventilation in survivors. Finally, given the prevalence of long-term neuropsychiatric morbidity and functional impairment in adult ARDS survivors, it is imperative that these parameters are defined for children. After a better understanding of the burden of surviving PARDS on patients and families is obtained, studies can be designed to demonstrate a return to premorbid functioning, which is fundamentally most important to the child and family.

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