REVIEW

Paediatrics: how to manage acute respiratory distress syndrome

Kam Lun Hon1, Karen Ka Yan Leung1, Felix Oberender2,3, Alexander KC Leung4

1Paediatric Intensive Care Unit, Department of Paediatrics and Adolescent Medicine, Hong Kong Children's Hospital, Hong Kong; 2Paediatric Intensive Care Unit, Monash Children's Hospital, Melbourne, Australia; 3Monash University, School of Clinical Sciences, Department of Paediatrics, Melbourne, Australia; 4Department of Pediatrics, The University of Calgary and The Alberta Children's Hospital, Calgary, Alberta, Canada

Abstract

Background: Acute respiratory distress syndrome (ARDS) is a significant cause of mortality and morbidity amongst critically ill children. The purpose of this narrative review is to provide an up-to-date review on the evaluation and management of paediatric ARDS (PARDS).

Methods: A PubMed search was performed with Clinical Queries using the key term “acute respiratory distress syndrome”. The search strategy included clinical trials, meta-analyses, randomized controlled trials, observational studies and reviews. Google, Wikipedia and UpToDate were also searched to enrich the review. The search was restricted to the English literature and children.

Discussion: Non-invasive positive pressure ventilation, lung-protective ventilation strategies, conservative fluid management and adequate nutritional support all have proven efficacy in the management of PARDS. The Pediatric Acute Lung Injury Consensus Conference recommends the use of corticosteroids, high-frequency oscillation ventilation and inhaled nitric oxide in selected scenarios. Partial liquid ventilation and surfactant are not considered efficacious based on evidence from clinical trials.

Conclusion: PARDS is a serious but relatively rare cause of admission into the paediatric intensive care unit and is associated with high mortality. Non-invasive positive pressure ventilation, lung-protective ventilation strategies, conservative fluid management and adequate nutrition are advocated. As there has been a lack of progress in the management of PARDS in recent years, further well-designed, large-scale, randomized controlled trials in this field are urgently needed.

Keywords: acute lung injury, critical care, paediatric acute respiratory distress syndrome, respiratory failure, therapy.

Citation

Hon KL, Leung KKY, Oberender F, Leung AKC. How to manage acute respiratory distress syndrome. Drugs in Context 2021; 10: 2021-1-9. DOI: 10.7573/dic.2021-1-9

Introduction

Acute respiratory distress syndrome (ARDS) is one of the leading causes of admission into the intensive care unit (ICU).1–3 The syndrome of non-cardiogenic pulmonary oedema and hypoxia also affects children and accompanies significant mortality in paediatric ICU (PICU). Paediatric ARDS (PARDS) is diagnosed by the presence of hypoxia and new chest infiltrate occurring within seven days of a known insult. Hallmarks of ARDS include hypoxemia associated with decreased lung compliance, increased work of breathing and impaired gas exchange. Mortality is often accompanied by multiple organ dysfunction or failure. Like adults, supportive therapies and lung-protective ventilator support remain the mainstay of treatment in children. Paediatric healthcare workers in the non-ICU setting remain unfamiliar with the disease entity. This article provides an up-to-date narrative review on the evaluation, diagnosis and management of PARDS.

Methodology

A PubMed search was performed in November 2020 with Clinical Queries using the key term “acute respiratory distress syndrome”. The search strategy included clinical trials, meta-analyses, randomized controlled trials, observational studies and reviews published between Jan 2010 and Dec 2020. Google, Wikipedia and UpToDate were also searched to enrich the review. The search was restricted to the English literature and children. The information retrieved was used as a basis for the compilation of the present article.
Review

Evolution of definition

ARDS was first defined by Ashbaugh et al. in 1967 as ‘adult-type respiratory distress’ for a group of patients with progressive respiratory failure, refractory hypoxemia, decreased functional residual capacity, loss of lung compliance and diffuse infiltration on chest radiography. In 1994, the American-European Consensus Conference (AECC) formalized the clinical definitions of acute lung injury (ALI) and ARDS. ALI is a disease with acute onset hypoxemia, a partial pressure of oxygen (PaO\textsubscript{2}) to fraction of inspired oxygen (FiO\textsubscript{2}) ratio of ≤300, bilateral infiltrates on chest radiographs and a pulmonary artery wedge pressure less than 18 mmHg, and the absence of left atrial hypertension. ARDS is a more severe form of ALI and largely shares the same criteria, whereby ARDS occurs when the PaO\textsubscript{2}/FiO\textsubscript{2} ratio is ≤200.

Subsequently, in 2012, the international consensus criteria for ARDS were updated and became known as the Berlin definition of ARDS, in which the timing of onset is defined (onset within 1 week) and the degree of hypoxemia is subcategorized to mild, moderate and severe depending on the PaO\textsubscript{2}/FiO\textsubscript{2} ratio. The term ALI was also removed from the Berlin definition to minimize the confusion amongst medical practitioners as the acronym served little to no practical purpose and had become seldom used in any case.

Although ARDS occurs across all age groups, including children, the AECC and Berlin ARDS definitions have limitations when applied to children due to the difference in hypoxemia measurement and in the aetiology and pathophysiology of ARDS in paediatric patients. As the presentation of ARDS in children is different from that in adults, the consensus of a formal PARDS definition was reached only in 2015 during the Pediatric Acute Lung Injury Consensus Conference (PALICC). This latest definition for PARDS is as follows:

A. Age group: All paediatric age groups except patients with perinatal-related lung diseases.
B. Timing: Onset of hypoxemia and radiological change within 7 days after a known clinical insult.
C. Chest radiographs: Presence of new infiltrates consistent with parenchymal lung disease even if unilateral.
D. Definition of hypoxemia: oxygenation index (OI) = \((\text{FiO}_2 \times \text{mean airway pressure} x 100)/\text{PaO}_2\) or oxygenation saturation index (OSI) = \((\text{FiO}_2 \times \text{mean airway pressure} x 100)/\text{saturated oxygen} (\text{SpO}_2)\) to quantify the degree of hypoxemia and to determine the severity of ARDS in patients with invasive mechanical ventilation.

A. PaO\textsubscript{2}/FiO\textsubscript{2} ratio of ≤300 or a SpO\textsubscript{2}/FiO\textsubscript{2} ratio of ≤264 is used to diagnose PARDS for patients with non-invasive, full-face mask ventilation with a minimum continuous positive airway pressure of 5 cm H\textsubscript{2}O. A recent paper compared the OI and PaO\textsubscript{2}/FiO\textsubscript{2} scores in evaluating PARDS requiring mechanical ventilation and found significant differences between the two scores in the severity grading of patients with PARDS. Both scores were consistent in designating patients with severe PARDS but the OI score was more accurate when combined with the prognostic factors.

E. Special populations: Patients with cyanotic heart disease, chronic lung disease and left ventricular dysfunction are also included if the acute deterioration and new infiltrates are not explained by the underlying diseases.

In comparison to the Berlin definition, the PALICC criteria identified more patients with ARDS although there were no differences in clinical outcomes between the groups. Nevertheless, the Berlin definition offers no room for stratifying and identifying ‘true’ ARDS patients because there is no re-evaluation of the hypoxemia under a standard ventilator setting in a specific time period under this definition.

Epidemiology

PARDS is relatively rare but the incidence is likely under-reported due to the lack of a standardized and reliable definition until the development of the PALICC criteria in 2015. The incidence in the United States, Europe and Australia has been estimated to be 2–12.8/100,000 people per year. Studies in China, Europe, New Zealand and Australia suggest that ARDS accounts for 1–4% of PICU admissions. In addition, studies have reported an increased incidence of ARDS in men in comparison to women and immunodeficiency is a common pre-existing condition leading to an increased risk of developing ARDS. In the literature, the mortality of PARDS varies from 18% to 63%, depending on the study locations, whilst a recent systematic review and meta-analysis of 2,274 patients concluded that the overall mortality rate in PARDS is of approximately 24%. Generally, the mortality of ARDS in children is lower than that in adults but age-dependent differences in respiratory viral infections may contribute to the differences in outcome between children and adults.

A 2016 systematic review and meta-analysis showed a low incidence but a high mortality of PARDS and also concluded that both the incidence and mortality of PARDS have not changed over the last two decades although the mortality rate varies depending on the geographic location of studies. The incidence and epidemiology of PARDS have been reviewed in recent years by the Pediatric Acute Respiratory Distress syndrome Incidence and Epidemiology (PARDIE) investigators, who describe predictive models for mortality in PARDS using readily available variables from day 0 of PARDS. These PARDIE models outperform severity of illness scores and demonstrate the utility for composite outcomes and assist with risk stratification for clinical trials.

Aetiology

ARDS is not a specific disease entity but a clinical syndrome that may be triggered by various pathologies, including
trauma, pneumonia and sepsis. As with many other syndromes, the term essentially describes non-cardiogenic pulmonary oedema of various aetiologies. PARDS can be caused by a variety of insults. Depending on whether the lungs are initially affected, the causes can be classified as direct or indirect lung injury. Direct causes of lung injury include pneumonia, aspiration, inhalational lung injury, lung contusion, chest injury and submersion injury. Indirect causes include sepsis, shock, pancreatitis, trauma, cardiopulmonary bypass, transfusion-related ALI, burns and increased intracranial pressure.\textsuperscript{33–37}

On the other hand, lung injury can be secondary to various hyperinflammatory or cytokine release syndromes (CRS). CRS refers to a form of systemic inflammatory response syndrome that can be triggered by a variety of factors such as infections and certain drugs; if severe and acute, it is termed cytokine storm syndrome.\textsuperscript{2} Hemophagocytic lymphohistiocytosis (HLH), being one of the underlying causes of CRS, refers to a life-threatening disorder of severe excessive inflammation caused by uncontrolled proliferation of activated lymphocytes and macrophages and the secretion of inflammatory cytokines. Nahum et al. reported that 7 of 11 children with HLH with multiple organ failure exhibited ARDS after a diagnosis of HLH had been made.\textsuperscript{28}

**Pathophysiology**

ARDS is an acute inflammation of the lung with diffuse alveolar injury and increased vascular permeability with consequent decreased pulmonary compliance, impaired gas exchange and pulmonary hypertension leading to hypoxic respiratory failure.\textsuperscript{4,39,40} The pathogenesis of ARDS can be divided into three phases: (1) the exudative phase, when the resident alveolar macrophages are activated and potent proinflammatory mediators and chemokines are released, resulting in interstitial and intra-alveolar flooding; (2) the proliferative phase, characterized by provisional matrix formation and restoration of endothelial barrier function; and (3) the fibrotic phase, characterized by the development of interstitial and intra-alveolar fibrosis due to extensive damage to the basement membrane.\textsuperscript{41}

The lung of paediatric patients characteristically differs from that of adults in many aspects, including smaller airways, lower rigidity of the chest wall and lower functional residual capacity.\textsuperscript{40,42} Most importantly, the major difference between children and adults is that the lungs of children are developing and growing until the attainment of adult height and the pathophysiological responses to infection and injury are therefore fundamentally different.\textsuperscript{43}

**Clinical manifestations**

ARDS is characterized by tachypnoea, dyspnoea and hypoxemia. The symptomatology of ARDS could begin as early as 2 hours of an inciting event but have been known to take as long as 1–3 days. The signs and symptoms may include shortness of breath, fast breathing, diffuse crackles and tachycardia.\textsuperscript{44} Other common symptoms include muscle fatigue and general weakness, low blood pressure, and either a dry, hacking or productive cough.\textsuperscript{44} In severe cases, diaphoresis and cyanosis may be evident. Depending on the underlying aetiology, the clinical features may include fever, chest pain, pleuritic pain, vomiting and abdominal pain.

**Diagnostic studies**

The diagnosis of PARDS in children is based on the aforementioned diagnostic criteria defined by PALICC in 2015. Studies in adults showed that the Berlin diagnostic criteria for ARDS have a relative low specificity for diagnosing ARDS.\textsuperscript{45} Furthermore, ARDS is a clinical syndrome without a specific diagnostic test, which can explain why the diagnosis is underrecognized, sometimes delayed or missed altogether.\textsuperscript{45,46} The early diagnosis and prompt treatment of ARDS and subsequent implementation of treatment strategies are all key to maximizing the chance of survival.\textsuperscript{45}

To define the degree of hypoxemia with the PALICC criteria, both OI or OSI can be used to quantify this in patients with invasive ventilation. Whilst the PaO\textsubscript{2}/FiO\textsubscript{2} or SpO\textsubscript{2}/FiO\textsubscript{2} ratios can be used in patients receiving non-invasive mechanical ventilation with a minimum continuous positive airway pressure of 5 cm H\textsubscript{2}O,\textsuperscript{13} OI and PaO\textsubscript{2}/FiO\textsubscript{2} are preferred; OSI and SpO\textsubscript{2}/FiO\textsubscript{2} should only be used if arterial blood gas is not available.\textsuperscript{13} Radiological imaging has long been a key diagnostic modality for ARDS. Original AECC definitions of ARDS specified that correlative chest X-ray findings were required for diagnosis although the diagnostic criteria have been broadened over time to include computed tomography (CT) findings. Chest imaging of new infiltrates consistent with acute pulmonary parenchymal disease is one of the diagnostic criteria.\textsuperscript{5,13} However, chest X-rays have limitations in terms of poor interobserver reliability.\textsuperscript{29,47} A prospective, international observational study in children using the PALICC criteria for ARDS evaluating the independent relationship between chest imaging and mortality revealed that chest X-ray findings of bilateral infiltrates or four quadrants of consolidation are associated with higher mortality but only for children with severe oxygenation impairment (PaO\textsubscript{2}/FiO\textsubscript{2} ratio ≤100).\textsuperscript{29} Radiographic findings of pulmonary oedema affecting both lungs and unrelated to increased cardiopulmonary vascular pressure may be suggestive of ARDS. CT of the chest, although not routinely performed, may also be helpful in differentiating between atelectasis and consolidation.

Ultrasonography is an easy method for the further assessment of pleural effusions and differentiation between transudative and exudative fluid. Ultrasound findings suggestive of ARDS include anterior subpleural consolidations, the absence or reduction of lung sliding, pleural line abnormalities (an irregular, thickened and fragmented pleural line) and non-homogeneous distribution of B-lines (suggestive of fluid accumulation in the lungs).\textsuperscript{48} Echocardiography may help
exclude cardiogenic oedema and would provide information regarding cardiac contractility, intraventricular volume, pulmonary hypertension and other potential anatomic abnormalities. The routine use of bronchoalveolar lavage is not recommended in ARDS. Bronchoalveolar lavage can be considered for diagnostic and therapeutic purposes in cases where there is no obvious cause of ARDS, or persistent regional areas of atelectasis or when a direct lung injury is suspected.59 Laboratory testing including haematology and blood chemistry would help identify the potential involvement of other organ systems and inform appropriate management strategies. Arterial blood gas analysis should be done, and the severity of hypoxemia or PaO2 should also be determined. Numerous biomarkers have been examined in the literature to support the diagnosis of ARDS; however, no definitive biomarkers or tools with a high quality of predictability have been identified both in terms of predicting mortality or differentiating between cardiogenic pulmonary oedema and ALI or ARDS.50,51 A recent systematic review of biomarkers suggested that angiopoietin 2 and receptor for advanced glycation end products (RAGE) were associated with an increased risk of ARDS development.51 Combining clinical criteria with validated biomarkers may be one way to improve the predictive accuracy of diagnostic tests in the future. It is also important to discriminate ARDS from cardiogenic pulmonary oedema as the two conditions may coexist, which may be challenging in critically ill patients.52

Management

The main management goals are anchored around treating the underlying cause, maintaining adequate oxygenation as well as avoiding secondary lung injury and extra pulmonary complications.42,53,54 Antibiotics or antivirals are useful for ARDS associated with bacterial or viral infections, but are not indicated or useful if ARDS is due to submersion injury. The management of PARDS is challenging as there is no definitive guideline or conclusive clinical evidence to optimize the treatment regimen.55 Contemporary treatment strategies are largely extrapolated from adult studies even though paediatric patients differ from adults in many pathophysiological aspects and only a handful of randomized control trials have been performed on paediatric patient groups. In this regard, children have a more compliant chest wall, higher baseline airway resistance and lower functional residual capacity.40

Pulmonary support

Non-invasive positive pressure ventilation

Early non-invasive positive pressure ventilation (NPPV) can be considered in children with mild PARDS. The continuous level of positive end expiratory pressure (PEEP) can facilitate airway opening, improve alveolar recruitment and improve oxygenation, whilst the additional inspiratory pressure can raise tidal volumes and reduce respiratory effort.56,57 A randomized controlled trial with 50 patients comparing NPPV with a control group showed that heart rate and respiratory rate improved with NPPV and the frequency of endotracheal intubation was also significantly lowered (from 60% to 28%; p=0.045).58 However, NPPV is not recommended for patients with severe hypoxemia.13 Intubation and invasive ventilation is also indicated when there are signs of increased respiratory effort and oxygen requirement, a decreased PaO2/FiO2 ratio or altered levels of consciousness.57

Lung-protective ventilation strategies – tidal volume and PEEP

The principle of lung-protective ventilation strategies is to avoid volutrauma and minimize atelectrauma. However, studies on lung-protective ventilation strategies in the paediatric population are limited and most recommendations are based on evidence gathered from adult patients. Robust clinical evidence on the optimal lung-protective strategies in PARDS patients is much needed.

The optimal tidal volume remains a subject of controversy and current practices are usually based on data extrapolated from the studies on adult patients in which volutrauma is found to be associated with lung injury in ventilated adult ARDS patients.59 A retrospective study revealed that ventilation with a higher tidal volume resulted in higher mortality and shorter ventilation-free days.60 A lower tidal volume was independently associated with reduced mortality and an increase in ventilation-free days.60 However, another prospective study showed that a high maximum and median tidal volume resulted in a lower mortality.61 A 2014 systematic review and meta-analysis of eight observational studies showed that there was no significant association between the tidal volume and mortality.61 A recent retrospective analysis conducted in 2019 also reported similar findings with no consistent association between tidal volume adjusted for ideal body weight and outcome, suggesting that tidal volume could be an imprecise parameter for titrating ventilation.62 To date, no further randomized controlled trials are known to have been conducted in order to conclusively assess the effect of tidal volume on the mortality of paediatric patients. In 2015, PALICC made a recommendation using patient-specific tidal volume, which is outlined hereafter. In patients with good lung compliance, a physiological range tidal volume of 5–8 mL/kg of ideal body weight should be applied to preserve the respiratory system compliance. On the other hand, in those with poor lung compliance, a tidal volume of 3–6 mL/kg of ideal body weight should be applied.13,63

Common practice in paediatric mechanical ventilation is often based on personal experiences and adoption from adult and neonatal experience. The European Society for Paediatric and Neonatal Intensive Care initiated a consensus conference of international European experts to provide recommendations in paediatric mechanical ventilation.64 The ARDS Network (ARDSNet) used a PEEP/FiO2 model in many studies. Nevertheless, paediatric intensive care physicians often use less PEEP and higher FiO2 than this model.65 Adequate PEEP is necessary to prevent atelectrauma in patients with ARDS and the PALICC recommend the titration of oxygenation and
hemodynamic response with moderately elevated levels of PEEP (10–15 cm H₂O) and a PEEP level of greater than 15 cm H₂O might be required for severe PARDS. A multicentre, retrospective analysis of patients with PARDS showed that children who are managed with PEEP lower than recommended by the ARDSNet PEEP/FiO₂ model had a higher mortality.

**High-frequency oscillatory ventilation**
A retrospective study performed in 2009 reported that high-frequency oscillatory ventilation (HFOV) improved oxygenation in paediatric patients with ARDS. However, a separate retrospective observational study in 2014 revealed that HFOV was associated with a longer duration of mechanical ventilation, longer ICU length of stay and higher mortality in children with acute respiratory failure. A secondary analysis of a prospective cluster-randomized trial in 2016 reported that early use of HFOV was associated with a longer duration of mechanical ventilation but not with mortality when compared with conventional ventilation. A 2016 systematic review including 10 randomized controlled trials comparing HFOV with conventional mechanical ventilation on both adults and children with ARDS found that HFOV was not associated with lower 30-day mortality. The evidence available does not support the use of HFOV as a first-line strategy in patients undergoing mechanical ventilation for ARDS. Later, a randomized controlled study further compared HFOV versus conventional mechanical ventilation in PARDS and demonstrated that HFOV had a superior advantage in improving oxygenation but no significant mortality improvement. Nevertheless, PALICC suggested the use of HFOV for patients with moderate-to-severe ARDS in cases where the plateau airway pressure exceeds 28 cm H₂O and in the absence of clinical evidence of reduced chest wall compliance.

**Partial liquid ventilation**
Although the practice appears to be conceptually sound, partial liquid ventilation was not found to be associated with a decrease in 28-day mortality in a randomized trial. No further studies have been conducted. On this basis, PALICC does not recommend the use of partial liquid ventilation on PARDS.

**Inhaled nitric oxide**
Inhaled nitric oxide (iNO) is a selective pulmonary vasodilator in improving V/Q matching and has been shown to improve oxygenation; however, there is no strong evidence to support a reduction in mortality and, in fact, may actually be harmful. A prospective RCT of 55 paediatric patients with ARDS showed a significant reduction in duration in mechanical ventilation and a greater rate of extracorporeal membrane oxygenation-free survival. PALICC does not recommend the routine use of iNO for PARDS but it can be considered in patients with documented pulmonary hypertension, severe right ventricular dysfunction, or as a rescue or bridge to extracorporeal life support. Further studies are required to study the potential effects of iNO such as platelet aggregation inhibition and effects on the immune system and immunoregulations.

**Surfactants**
In a randomized blinded trial conducted by Wilson et al. in 2005, the use of surfactants was shown to significantly improve oxygenation and decrease mortality in patients with ARDS. In 2013, the same group of investigators conducted a randomized controlled trial with 110 subjects with ARDS and demonstrated that there were no benefits in survival. The adverse events related to the use of surfactants can include transient hypoxia, bradycardia and leukopenia. In aggregate, surfactants are generally considered as non-­‐‐efficacious for the treatment of ARDS in children.

**Prone position**
Prone positioning might improve oxygenation in patient with ARDS by recruitment of collapsed alveoli of the dorsal lung regions, thereby improving the homogeneity of ventilation and ventilation/perfusion matching. A 2012 systematic review of 24 studies with 581 participants demonstrated that the prone position was associated with significantly improved oxygen saturation, arterial oxygen and thoracoabdominal synchrony with no reported side effects. These results were contrary to the findings from a randomized controlled trial conducted in 2005 by Curley et al. which suggest that the prone position did not significantly lower ventilation-free days or mortality or overall health function. Prone positioning is not recommended as a routine therapy for ARDS treatment by PALICC but it can be considered in cases of severe PARDS. In the meantime, paediatric patients in the Prone and Oscillation Pediatric Clinical Trial (PROSpect) are being recruited to address the issue surrounding the uncertainty regarding the role and optimal management of HFOV and prone position for PARDS.

**Extracorporeal membrane oxygenation**
Extracorporeal membrane oxygenation (ECMO) can potentially provide rescue oxygenation and ventilation, preventing ventilator-induced lung injury and multiorgan failure. According to the Extracorporeal Life Support Organization (ELSO) criteria, severe respiratory failure is defined as a sustained PaO₂/FiO₂ ratio of <60–80 or an OI of >40, a lack of response to conventional ventilation and rescue therapy (e.g. HFOV, iNO), and elevated ventilator pressure. Based on the data available on the ELSO registry of neonates and children with respiratory failure requiring ECMO support, the survival rate of neonates (87%) is higher than in children (72%), although these figures represent the overall survival of respiratory failure and are not specific to PARDS. There are no randomized trials assessing the efficacy of ECMO in PARDS; however, a paired cohort study of 122 matched children with acute respiratory failure with and without ECMO showed that there were no differences in the in-hospital mortality, PICU or ventilator-free days between two groups. Patient selection in the use of ECMO is crucial as the range of clinical outcomes can vary widely; however, there is no well-defined criteria for children with PARDS who would manifestly benefit from ECMO. PALICC recommends that ECMO can be considered in...
paediatric patients with severe PARDS when other treatment strategies demonstrably fail to maintain adequate gas exchange.\textsuperscript{13,63}

**Non-invasive monitoring and gas-exchange targets in the management of PARDS**

Non-invasive monitoring of oxygenation has become a standard procedure in critical care. Both transcutaneous $\text{pO}_2$ (tcpO\textsubscript{2}) monitors and pulse oximeters (SpO\textsubscript{2}) should be familiar to those using these devices in infants.\textsuperscript{84,85} Measurements of tcpO\textsubscript{2} are influenced by skin thickness, sensor temperature, amount of contact gel used and the state of peripheral perfusion. Pulse oximeters require careful sensor placement and adequate pulse pressures (>20 mmHg/2.7 kPa). They are extremely prone to motion artifact. TcpO\textsubscript{2} monitoring is currently being replaced by pulse oximetry, which does not measure oxygen concentration in plasma but rather the proportion of haemoglobin molecules in arterial blood that are loaded with oxygen. Pulse oximeters are easier to use than tcpO\textsubscript{2} monitors and provide immediate information about arterial oxygenation.\textsuperscript{84,85} One advantage of transcutaneous monitoring is that tcpCO\textsubscript{2} monitoring can be simultaneously estimated, which is superior to end tidal CO\textsubscript{2} monitoring in paediatric patients aged >4 years with respiratory failure.\textsuperscript{86} Application of this technique should be useful by decreasing the need for repeated and sometimes painful arterial blood gas analysis and the continuity of assessment should facilitate proactive ventilator manipulations.

PALICC recommended that, for mild PARDS with PEEP <10 cm H\textsubscript{2}O, the SpO\textsubscript{2} goal should generally be 92–97%. For those with more severe PARDS with PEEP >10 cm H\textsubscript{2}O, permissive hypoxemia with an SpO\textsubscript{2} of 88–92% should be considered after PEEP optimization.\textsuperscript{13,42,87,88} The use of permissive hypoxemia is cautioned against in those with acute intracranial pathology and clinically important pulmonary hypertension. When oxygen saturations are maintained <92%, PALICC recommended the monitoring of central venous saturation and markers of oxygen delivery.\textsuperscript{13,63,87} Ventilatory approaches should provide adequate tissue/oxygenation whilst minimizing oxygen toxicity and ventilator-induced lung injury. PALICC also recommended permissive hypercapnia as a management strategy to minimize ventilator-induced lung injury for patients with moderate-to-severe PARDS.\textsuperscript{13,63,87} Low-VT tidal volume, pressure-limited ventilation with permissive hypercapnia may improve ARDS outcome.\textsuperscript{63,89,90} A pH range of 7.15–7.30 was also recommended within the use of lung-protective guidelines. Exceptions to the use of permissive hypercapnia include severe pulmonary hypertension, intracranial hypertension, select congenital heart lesions and significant ventricular dysfunction with hemodynamic instability.

**Fluid management**

Appropriate fluid management is critical in patients with PARDS as increased mortality and high cumulative fluid balance are associated with fewer ventilator-free days, worse oxygenation, increased mortality and acute kidney injury in children with PARDS.\textsuperscript{28,91,92} PALICC suggests a goal-directed fluid management approach after the initial stabilization of the patient and titration to maintain adequate intravascular volume, end-organ perfusion and optimal oxygen delivery, all whilst aiming to avoid fluid overload.\textsuperscript{13}

**Nutrition support**

Patients with ARDS are particularly susceptible to malnutrition as these patients are often in a hypercatabolic state because critical illness is associated with an increased basal metabolic rate and protein catabolism. Malnutrition might lead to loss of lean body mass, muscle weakness, and loss of respiratory and cardiac muscle function.\textsuperscript{93} Adequate protein intake and nutrition were found to be associated with better survival in children with PARDS.\textsuperscript{74,93} Nutrition plans should be tailored to meet the patient’s metabolic demand, whilst enteral nutrition is preferred over parenteral nutrition if tolerated.\textsuperscript{13} Despite having target calorie and protein requirements, many critically ill children do not achieve satisfactory levels even at the end of a week in PICU.\textsuperscript{94} The preferred mode of nutrition delivery is early enteral nutrition. Immunonutrition has not conclusively demonstrated benefit in terms of mortality or reduced length of stay in PICU. Immunonutrients in PARDS may include omega-3 fatty acids, arginine, glutamine and vitamin D, although these are yet to be formally recommended.

**Corticosteroids**

Theoretically, corticosteroids can dampen the immune and inflammatory systems, thereby minimizing the disease severity of ARDS.\textsuperscript{95} However, there is a degree of controversy around the use of corticosteroids in PARDS.\textsuperscript{83} In a double-blinded, placebo-controlled, randomized clinical trial, there was no difference in the duration of mechanical ventilation, ICU stay, hospital stay and mortality between steroid and placebo groups in children with ARDS.\textsuperscript{96} Another prospective cohort study showed that corticosteroid exposure of more than 24 hours was independently associated with longer duration of ventilation in survivors, even after adjusting for immunocompromised status, severity of illness, oxygenation index and number of organ failures.\textsuperscript{97} Based on the full body of evidence, the routine use of corticosteroids in PARDS is not recommended.\textsuperscript{13,98}

**Sedation**

Children with ARDS subjected to mechanical ventilation often require sedative or analgesic agents to facilitate synchronization with the ventilator and decrease anxiety or pain.\textsuperscript{63,99} Curley et al. conducted a cluster-randomized trial on 2449 children with ARDS and the use of sedation did not shorten the duration of mechanical ventilation. Patients with sedation were reported to have more postextubation stridor and more days with a high pain score and agitation.\textsuperscript{100} PALICC guidelines suggest that sedation should be titrated to a minimal yet effective level to facilitate effective ventilation.\textsuperscript{13}
Complications

Complications of ARDS may include barotrauma (volutrauma), nosocomial infection, atelectasis, pulmonary embolism, pulmonary fibrosis and ventilator-associated pneumonia. Dysfunction of other organ systems may also be observed, including right ventricular dysfunction, pulmonary hypertension, gastrointestinal complications (stress ulcer and bacterial translocation), hypoxic brain damage, deep vein thrombosis, myocardial dysfunction, acute kidney failure, fluid retention, catabolic malnutrition and electrolyte abnormalities.

Prognosis

The overall prognosis of ARDS is poor, with high relative mortality rates of approximately 40%. Studies on the long-term outcome of PARDS patients are limited in the literature, most of which are small case series. Based on reports on adult and paediatric patients, long-term sequelae in ARDS survivors include prolonged pulmonary dysfunction, neuromuscular weakness, nutritional deficits, anxiety, depression and post-traumatic stress disorders. At the same time, exercise limitations, physical and psychological sequelae, decreased physical quality of life, and increased costs and use of healthcare services are also important sequelae of ARDS. PALICC recommend screening for pulmonary function abnormalities within 1 year after discharge and those with pulmonary function deficits should be followed up by a paediatric pulmonologist.

Conclusion

PARDS is a serious but relatively uncommon cause of PICU admission that is associated with high mortality. However, there is a limited amount of evidence specific to paediatric patients to support the efficacy of most of the clinical practices. The recent development of the paediatric-specific definitions of PARDS in 2015 should facilitate the diagnosis, treatment and research in PARDS. Advances are being made in the management of PARDS in areas including early NPPV, lung-protective ventilation strategies, conservative fluid management and adequate nutritional support, all of which are supported by evidence of efficacy. The use of iNO, HFOV, prone positioning and corticosteroids remain controversial. Extracorporeal membrane oxygenation can be considered as a rescue therapy. A deeper understanding of the pathophysiological mechanism of PARDS can potentially facilitate the development of novel therapeutic interventions to prevent or modulate lung injury as well as targeted therapies. In any case, more well-designed, large-scale, multicentre prospective randomized controlled trials on PARDS are urgently needed.

Key practice points

- Paediatric acute respiratory distress syndrome (PARDS) is a serious but relatively uncommon cause of paediatric ICU admission that is associated with high mortality.
- The recent development of the paediatric-specific definitions of acute respiratory distress syndrome in 2015 should facilitate the diagnosis, treatment and research in PARDS.
- Advances are being made in the management of PARDS in areas including early non-invasive positive pressure ventilation, lung-protective ventilation strategies, conservative fluid management and adequate nutritional support, all of which are supported by evidence of efficacy.
- The use of inhaled nitric oxide, high-frequency oscillatory ventilation, prone positioning and corticosteroids remain controversial.
- Extracorporeal membrane oxygenation can be considered as a rescue therapy.
- A deeper understanding of the pathophysiological mechanism of PARDS can potentially facilitate the development of novel therapeutic interventions to prevent or modulate lung injury as well as targeted therapies.
REVIEW – Paediatrics: how to manage acute respiratory distress syndrome

References

1. Ashbaugh D, Boyd Bigelow D, Petty T, Levine B. Acute respiratory distress in adults. Lancet. 1967;290(7511):319–323. https://doi.org/10.1016/s0140-6736(67)90168-7

2. Hon KL, Leung AK, Wong JC. Proliferation of syndromes and acronyms in paediatric critical care: are we more or less confused? Hong Kong Med J. 2020;26:260–262. https://doi.org/10.12809/hkmj198059

3. Hon KL, Leung ASY, Cheung KL, et al. Typical or atypical pneumonia and severe acute respiratory symptoms in PICU. Clin Respir J. 2014;9:10. https://doi.org/10.1111/crj.12149

4. Cornfield DN. Acute respiratory distress syndrome in children. Curr Opin Pediatr. 2013;25:338–343. https://doi.org/10.1097/MOP.0b013e328360bbe7

5. Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med. 1994;149(3 Pt 1):818–824. https://doi.org/10.1164/ajrccm.149.3.7509706

6. Gupta S, Sankar J, Lodha R, Kabra SK. Comparison of prevalence and outcomes of pediatric acute respiratory distress syndrome using pediatric acute lung injury consensus conference criteria and Berlin definition. Front Pediatr. 2018;6:93. https://doi.org/10.3389/fped.2018.00093

7. Villar J, Kacmarek RM. The American-European Consensus Conference definition of the acute respiratory distress syndrome is dead, long live positive end-expiratory pressure! 2012;36:571–575. https://doi.org/10.1016/j.medin.2012.08.010

8. Ferguson ND, Fan E, Camporota L, et al. The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material. Intensive Care Med. 2012;38:1573–1582. https://doi.org/10.1007/s00134-012-2682-1

9. Monahan LJ. Acute respiratory distress syndrome. Curr Probl Pediatr Adolesc Health Care. 2013;43:278–284. https://doi.org/10.1016/j.ccppeds.2013.10.004

10. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome. JAMA. 2012;307:2526–2533. https://doi.org/10.1001/jama.2012.5669

11. López-Fernández Y, Azagra AM, del Oliva P, et al. Pediatric acute lung injury epidemiology and natural history study: incidence and outcome of the acute respiratory distress syndrome in children. Crit Care Med. 2012;40:3238–3245. https://doi.org/10.1097/CCM.0b013e318260ca83

12. Li CY, Luk MP, Hon KL. Paediatric acute respiratory distress syndrome: a review of recent advances in management. J Paediatr Respir Crit Care. 2016;12:4–9. http://www.hkspra.org/product_image_pub/309_121405.pdf. Accessed May 25, 2021.

13. Jouvet P, Thomas NJ, Willson DF, et al. Pediatric acute respiratory distress syndrome: consensus recommendations from the pediatric acute lung injury consensus conference. Pediatr Crit Care Med. 2015;16:428–439. https://doi.org/10.1097/PCC.0000000000000350

14. Dauger S, Le Bourgeois F, Guichoux J, Brissaud O. Acute respiratory distress syndrome in childhood: changing definition and news from the Pediatric Consensus Conference. Arch Pediatr. 2017;24:492–498. https://doi.org/10.1016/j.arcped.2017.02.019
15. Tolunay O, Tolunay I, Yıldızdaş RD, Çelik T, Çelik Ü. Appraisal of the “pediatric ARDS: consensus recommendations from the pediatric acute lung injury consensus conference” with the AGREE II instrument. *Turkish J Med Sci.* 2018;48:84–88. https://doi.org/10.3905/sag/1-707-197

16. Medina A, Modesto I Alapont V, DelVillar-Guerra P. PALICC definition of ARDS. Don’t remove that brick from the wall and keep it smart and simple. *Med Intensiva.* 2016;40:311–314. https://doi.org/10.1016/j.medini.2015.12.009

17. Shen H, Qu D, Na W, Liu S, Huang S, Hui Y. Comparison of the OI and PaO₂ /FiO₂ score in evaluating PARDS requiring mechanical ventilation. *Pediatr Pulmonol.* 2021;56:1182–1188. https://doi.org/10.1002/ppul.25194

18. Schouten LRA, Veltkamp F, Bos AP, et al. Incidence and mortality of acute respiratory distress syndrome in children. *Crit Care Med.* 2016;44(4):819–829. https://doi.org/10.1097/CCM.0000000000001388

19. Rotta AT, Piva JP, Andreolio C, deCarvalho WB, Garcia PCR. Progress and perspectives in pediatric acute respiratory distress syndrome. *Rev Bras Ter Intensiva.* 2015;27:266–273. https://doi.org/10.5935/1013-507X.20150035

20. Hu X, Qian S, Xu F, et al. Incidence, management and mortality of acute hypoxic respiratory failure and acute respiratory distress syndrome from a prospective study of Chinese paediatric intensive care network. *Acta Paediatr.* 2010;99:715–721. https://doi.org/10.1111/j.1651-2227.2010.01685.x

21. Erickson S, Schibler A, Numa A, et al. Acute lung injury in pediatric intensive care in Australia and New Zealand: a prospective, multicenter, observational study. *Pediatr Crit Care Med.* 2007;8:317–323. https://doi.org/10.1097/PCC.0b013e3180408.64179.FF

22. Dahlem P, vanAalderen WMC, Hamaker ME, Dijkgraaf MGW, Bos AP. Incidence and short-term outcome of acute lung injury in mechanically ventilated children. *Eur Respir J.* 2003;22:980–985. https://doi.org/10.1183/09031936.03.0003303

23. Khemani RG, Smith LS, Zimmerman JJ, Erickson S. Pediatric acute respiratory distress syndrome. *Pediatr Crit Care Med.* 2015;16:523–540. https://doi.org/10.1097/PCC.0000000000000432

24. Wong JJJM, Loh TF, Testoni D, Yeo JG, Mok YH, Lee JH. Epidemiology of pediatric acute respiratory distress syndrome in Singapore: risk factors and predictive respiratory indices for mortality. *Front Pediatr.* 2014;2:78. https://doi.org/10.3389/fped.2014.00078

25. Wong JJJM, Jit M, Sultana R, et al. Mortality in pediatric respiratory distress syndrome: a systematic review and meta-analysis. *J Intensive Care Med.* 2019;34:563–571. https://doi.org/10.1177/0885066617705109

26. Rubenfeld GD, Caldwell E, Peabody E, et al. Incidence and outcomes of pediatric acute lung injury. *N Engl J Med.* 2005;353:1685–1693. https://doi.org/10.1056/NEJMoa050333

27. Zimmerman JJ, Akhtar SR, Caldwell E, Rubenfeld GD. Incidence and outcomes of pediatric acute lung injury. *Pediatrics.* 2009;124:87–95. https://doi.org/10.1542/peds.2007-2462

28. Schouten LRA, Veltkamp F, Bos AP, et al. Incidence and mortality of acute respiratory distress syndrome in children: a systematic review and meta-analysis. *Crit Care Med.* 2016;44:819–829. https://doi.org/10.1097/CCM.0000000000001388

29. López-Fernández YM, Smith LS, Kohne JG, et al. Prognostic relevance and inter-observer reliability of chest-imaging in pediatric ARDS: a pediatric acute respiratory distress incidence and epidemiology (PARDIE) study. *Intensive Care Med.* 2020;46:1382–1393. https://doi.org/10.1007/s00134-020-06074-7

30. Rowan CM, Klein MJ, Hsing DD, et al. Early use of adjunctive therapies for pediatric acute respiratory distress syndrome: a pardie study. *Am J Respir Crit Care Med.* 2020;201:1389–1397. https://doi.org/10.1164/rccm.201909-1807OC

31. Khemani RG, Smith L, Lopez-Fernandez YM, et al. Paediatric acute respiratory distress syndrome incidence and epidemiology (PARDIE): an international, observational study. *Lancet Respir Med.* 2019;7:115–128. https://doi.org/10.1016/S2213-2600(19)30034-8

32. Yehya N, Harhay MO, Klein MJ, et al. Predicting mortality in children with pediatric acute respiratory distress syndrome: a pediatric acute respiratory distress syndrome incidence and epidemiology study. *Crit Care Med.* 2020;48(6):e514–e522. https://doi.org/10.1097/CCM.0000000000004345

33. Kollef MH, Schuster DP. The acute respiratory distress syndrome. *N Engl J Med.* 1995;332:27–37. https://doi.org/10.1056/NEJM199501053320106

34. Chetan G, Rathisharmila R, Narayanan P, Mahadevan S. Acute respiratory distress syndrome in pediatric intensive care unit. *Indian J Pediatr.* 2009;76:1013–1016. https://doi.org/10.1007/s12098-009-0215-x

35. Efrati O, Sadeh-Gornik U, Modan-Moses D, et al. Flexible bronchoscopy and bronchoalveolar lavage in pediatric patients with lung disease. *Pediatr Crit Care Med.* 2009;10:80–84. https://doi.org/10.1097/PCC.0b013e31819373ea

36. Gong MN, Thompson BT, Williams P, Pothier L, Boyle PD, Christiani DC. Clinical predictors of mortality in acute respiratory distress syndrome: potential role of red cell transfusion. *Crit Care Med.* 2005;33:1191–1198. https://doi.org/10.1097/01.ccm.0000165566.82925.14

37. Cullen ML. Pulmonary and respiratory complications of pediatric trauma. *Respir Care Clin N Am.* 2001;7:59–77. https://doi.org/10.1016/s1078-5337(05)70023-x

38. Nahum E, Ben-Ari J, Stain J, Tommy S. Hemophagocytic lymphohistiocytic syndrome: unrecognized cause of multiple organ failure. *Pediatr Crit Care Med.* 2000;1:51–54. https://doi.org/10.1007/00130478-20000700-00010
39. Sapru A, Flori H, Quasney MW, Dahmer MK. Pediatric Acute Lung Injury Consensus Conference Group. Pathobiology of acute respiratory distress syndrome. Pediatr Crit Care Med. 2015;16(5 Suppl 1):S6–22. https://doi.org/10.1097/PCC.0000000000000431
40. Cornfield DN. Acute respiratory distress syndrome in children: physiology and management. Curr Opin Pediatr. 2013;25:338–343. https://doi.org/10.1097/MOP.0b013e328360bbe7

41. Thompson BT, Chambers RC, Liu KD. Acute respiratory distress syndrome. N Engl J Med. 2017;377:562–572. https://doi.org/10.1056/NEJMra1608077
42. Randolph AG. Management of acute lung injury and acute respiratory distress syndrome in children. Crit Care Med. 2009;37:2448–2454. https://doi.org/10.1097/CCM.0b013e3181aae5dd

43. Smith LS, Zimmerman JJ, Martin TR. Mechanisms of acute respiratory distress syndrome in children and adults. Pediatr Crit Care Med. 2013;14:631–643. https://doi.org/10.1097/PCC.0b013e31829175f3

44. Bakowitz M, Bruns B, McCunn M. Acute lung injury and the acute respiratory distress syndrome in the injured patient. Scand J Trauma Resusc Emerg Med. 2012;20:54. https://doi.org/10.1186/1757-7241-20-54

45. Bellani G, Pham T, Laffey JG. Missed or delayed diagnosis of ARDS: a common and serious problem. Intensive Care Med. 2020;46:1180–1183. https://doi.org/10.1007/s00134-020-06035-0

46. Fan E, Brodie D, Slutsky AS. Acute respiratory distress syndrome. JAMA. 2018;319:698–710. https://doi.org/10.1001/jama.2017.21907

47. Figueroa-Casas JB, Brunner N, Dwivedi AK, Ayyappan AP. Accuracy of the chest radiograph to identify bilateral pulmonary infiltrates consistent with the diagnosis of acute respiratory distress syndrome using computed tomography as reference standard. J Crit Care. 2013;28:352–357. https://doi.org/10.1016/j.jcrc.2012.12.002

48. Mongodi S, Bonaiti S, Stella A, et al. Lung ultrasound for daily monitoring and management of ARDS patients. Clin Pulm Med. 2019;26:92–97. https://doi.org/10.1097/CPM.0000000000000311

49. Papazian L, Calfee CS, Chiumento D, et al. Diagnostic workup for ARDS patients. Intensive Care Med. 2016;42:674–685. https://doi.org/10.1007/s00134-016-4324-5

50. Komiya K, Akaba T, Kozaki Y, Kadota J, Rubin BK. A systematic review of diagnostic methods to differentiate acute lung injury/acute respiratory distress syndrome from cardiogenic pulmonary edema. Crit Care. 2017;21:228. https://doi.org/10.1186/s13054-017-1809-8

51. van der Zee P, Rietdijk W, Somhorst P, Endeman H, Gommers D. A systematic review of biomarkers multivariately associated with acute respiratory distress syndrome development and mortality. Crit Care. 2020;24:243. https://doi.org/10.1186/s13054-020-02913-7

52. Brusasco C, Santori G, Tavazzi G, et al. Second-order grey-scale texture analysis of pleural ultrasound images to differentiate acute respiratory distress syndrome and cardiogenic pulmonary edema. J Clin Monit Comput. 2020. https://doi.org/10.1007/s10877-020-00629-1

53. Allareddy V, Cheifetz IM. Clinical trials and future directions in pediatric acute respiratory distress syndrome. Ann Transl Med. 2019;7:514. https://doi.org/10.21037/atm.2019.09.14

54. Saharan S, Lodha R, Kabra SK. Management of acute lung injury/ARDS. Indian J Pediatr. 2010;77:1296–302. https://doi.org/10.1007/s12098-010-0169-z

55. Randolph AG, Meert KL, O’Neill ME, et al. The feasibility of conducting clinical trials in infants and children with acute respiratory failure. Am J Respir Crit Care Med. 2003;167:1334–1340. https://doi.org/10.1164/rccm.200210-1175OC

56. Organized jointly by the American Thoracic Society, the European Respiratory Society, the European Society of Intensive Care Medicine, and the Société de Réanimation de Langue Française, and approved by ATS Board of Directors D 2000. International Consensus Conferences in Intensive Care Medicine: noninvasive positive pressure ventilation in acute respiratory failure. Am J Respir Crit Care Med. 2001;163:283–291. https://doi.org/10.1164/ajrccm.163.1.ats1000

57. Essouari S, Carroll C. Noninvasive support and ventilation for pediatric acute respiratory distress syndrome. Pediatr Crit Care Med. 2015;16:5102–110. https://doi.org/10.1097/PCC.0000000000000437

58. Yañez LJ, Yunge M, Emiforik M, et al. A prospective, randomized, controlled trial of noninvasive ventilation in pediatric acute respiratory failure. Pediatr Crit Care Med. 2008;9:484–49. https://doi.org/10.1097/PCC.0b013e318184989f

59. Acute Respiratory Distress Syndrome Network; Brower RG, Matthay MA, Morris A, et al. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med. 2000;342:1301–1308. https://doi.org/10.1056/NEJM200005043421801

60. Albuaii WH, Singh RN, Fraser DD, et al. Have changes in ventilation practice improved outcome in children with acute lung injury? Pediatr Crit Care Med. 2007;8:324–330. https://doi.org/10.1097/PCC.0b013e3181849869

61. De Jager P, Burgerhof JGM, van Heerde M, Albers MJJ, Markhorst DG, Kneyber MCJ. Tidal volume and mortality in mechanically ventilated children: a systematic review and meta-analysis of observational studies. Crit Care Med. 2014;42:2461–2472. https://doi.org/10.1097/CCM.000000000000546
62. Imber DA, Thomas NJ, Yehya N. Association between tidal volumes adjusted for ideal body weight and outcomes in pediatric acute respiratory distress syndrome*. Pediatr Crit Care Med. 2019;20:e145–e153. https://doi.org/10.1097/PCC.0000000000001846

63. Cheifetz IM. Pediatric ARDS. Respir Care. 2017;62:718–731. https://doi.org/10.4187/respcare.05591

64. Kneyber MCJ, deLuca D, Calderini E, et al. Recommendations for mechanical ventilation of critically ill children from the Paediatric Mechanical Ventilation Consensus Conference (PEMVECC). Intensive Care Med. 2017;43:1764–1780. https://doi.org/10.1007/s00134-017-4920-z

65. Khemani RG, Parvathaneni K, Yehya N, Bhalla AK, Thomas NJ, Newth CJL. Positive end-expiratory pressure lower than the ARDS Network protocol is associated with higher pediatric acute respiratory distress syndrome mortality. Am J Respir Crit Care Med. 2018;198:77–89. https://doi.org/10.1164/rcrm.201707-1404OC

66. Sud S, Sud M, Friedrich JO, Wunsch H, et al. High-frequency oscillatory ventilation versus conventional ventilation for acute respiratory distress syndrome. Cochrane Database Syst Rev. 2016;2016(4):CD004085. https://doi.org/10.1002/14651858.CD004085.pub4

67. Gupta P, Green JW, Tang X, et al. Comparison of high-frequency oscillatory ventilation and conventional mechanical ventilation in pediatric respiratory failure. Cochrane Database Syst Rev. 2013;2013(2):CD003845. https://doi.org/10.1002/14651858.CD003845.pub3

68. Bateman ST, Borasino S, Asaro LA, et al. Early high-frequency oscillatory ventilation in pediatric acute respiratory failure: a randomized controlled trial. J Pediatr. 2016;168:243–249. https://doi.org/10.1016/j.jpeds.2015.07.018

69. El-Nawawy A, Moustafa A, Heshmat H, Abouahmed A. High frequency oscillatory ventilation versus conventional mechanical ventilation in pediatric acute respiratory distress syndrome: a randomized controlled study. Turk J Pediatr. 2017;59:130–143. https://doi.org/10.24953/turkjped.2017.02.004

70. Kaushal A, Mcdonnell CG, Davies MW. Partial liquid ventilation for the prevention of mortality and morbidity in paediatric acute lung injury and acute respiratory distress syndrome. Cochrane Database Syst Rev. 2013;2013(2):CD003845. https://doi.org/10.1002/14651858.CD003845.pub3

71. Gebiirstorf F, Karam O, Wettterslev J, Afshari A. Inhaled nitric oxide for acute respiratory distress syndrome (ARDS) in children and adults. Cochrane Database Syst Rev. 2016;2016(6):CD002787. https://doi.org/10.1002/14651858.CD002787.pub3

72. Bronicki RA, Fortenberry J, Schreiber M, Checchia PA, Anas NG. Multicenter randomized controlled trial of inhaled nitric oxide for pediatric acute respiratory distress syndrome. J Pediatr. 2015;166:365–369.e1. https://doi.org/10.1016/j.jpeds.2014.10.011

73. Hunt JL, Bronicki RA, Anas N. Role of inhaled nitric oxide in the management of severe acute respiratory distress syndrome. Front Pediatr. 2016;4:74. https://doi.org/10.3389/fped.2016.00074

74. Willson DF, Thomas NJ, Markovitz BP, et al. Effect of exogenous surfactant (calfactant) in pediatric acute lung injury: a randomized controlled trial. J Am Med Assoc. 2005;293:470–476. https://doi.org/10.1001/jama.293.4.470

75. Willson DF, Thomas NJ, Tamburro R, et al. Pediatric calfactant in acute respiratory distress syndrome. Pediatr Crit Care Med. 2013;14:657–665. https://doi.org/10.1097/PCC.0b013e3182917b68

76. Lupton-Smith A, Argent A, Rimensberger P, Frerichs I, Morrow B. Prone positioning improves ventilation homogeneity in children with acute respiratory distress syndrome. Pediatr Crit Care Med. 2017;18:e229–e234. https://doi.org/10.1097/PCC.0000000000001145

77. Gillies D, Wells D, Bhandari AP. Positioning for acute respiratory distress in hospitalised infants and children. Cochrane Database Syst Rev. 2012;2012(7):CD003645. https://doi.org/10.1002/14651858.CD003645.pub3

78. Curley MAQ, Hibberd PL, Fineman LD, et al. Effect of prone positioning on clinical outcomes in children with acute lung injury: a randomized controlled trial. J Am Med Assoc. 2005;293:229–237. https://doi.org/10.1001/jama.293.4.229

79. Kneyber MCJ, Cheifetz IM, Curley MAQ. High-frequency oscillatory ventilation for PARDS: awaiting PROSPect. Critical Care. 2020;34:118. https://doi.org/10.1186/s13054-020-2829-3

80. Erickson S. Extra-corporeal membrane oxygenation in paediatric acute respiratory distress syndrome: overrated or underutilized? Ann Transl Med. 2019;7:S12. https://doi.org/10.21037/atm.2019.09.27

81. MacLaren G, Conrad S, Peek G. Indications for Pediatric Respiratory Extracorporeal Life Support. 2015. Extracorporeal Life Support Organization (ELSO). https://www.elso.org/Portals/0/Files/ELSO%20guidelines%20paeds%20resp_May2015.pdf. Accessed April 11, 2021.

82. Extracorporeal Life Support Organisation. ECLS registry report. 2020. www.elso.org/Registry/Statistics/InternationalSummary.aspx. Accessed April 11, 2021.

83. Barbaro RP, Xu Y, Borasino S, et al. Does extracorporeal membrane oxygenation improve survival in pediatric acute respiratory failure? Am J Respir Crit Care Med. 2018;197:1177–1186. https://doi.org/10.1164/rcrm.201709-1893OC

84. Poets CF, Southall D. Noninvasive monitoring of oxygenation in infants and children: practical considerations and areas of concern. Pediatrics. 1994;93:737–746.

85. Poets CF. Noninvasive monitoring and assessment of oxygenation in infants. Clin Perinatol. 2019;46(3):417–433. https://doi.org/10.1016/j.clp.2019.05.010
86. Berkenbosch JW, Lam J, Burd RS, Tobias JD. Noninvasive monitoring of carbon dioxide during mechanical ventilation in older children: end-tidal versus transcutaneous techniques. Anesth Analg. 2001;92:1427–1431. https://doi.org/10.1097/00000539-200106000-00015

87. Rimensberger PC, Cheifetz IM, Jouvet P, et al. Ventilatory support in children with pediatric acute respiratory distress syndrome: proceedings from the pediatric acute lung injury consensus conference. Pediatr Crit Care Med. 2015;16:551–60. https://doi.org/10.1097/PCC.0000000000000433

88. Abdelsalam M, Cheifetz. Goal-directed therapy for severely hypoxic patients with acute respiratory distress syndrome: permissive hypoxemia. Respir Care. 2010;55:1483–1490.

89. Hickling KG, Walsh J, Henderson S, Jackson R. Low mortality rate in adult respiratory distress syndrome using low-volume, pressure-limited ventilation with permissive hypercapnia: a prospective study. Crit Care Med. 1994;22:1568–1578. https://doi.org/10.1097/00003246-199422100-00011

90. Milberg JA, Davis DR, Steinberg KP, Hudson LD. Improved survival of patients with acute respiratory distress syndrome (ARDS): 1983–1993. JAMA. 1995;273:306–309. https://doi.org/10.1001/jama.1995.03520280052039

91. Ingelse SA, Wösten-van Asperen RM, Lemson J, Daams JG, Bem RA, vanWoense LJB. Pediatric acute respiratory distress syndrome: fluid management in the PICU. Front Pediatr. 2016;4:21. https://doi.org/10.3389/fped.2016.00021

92. Zinter MS, Spicer AC, Liu KD, et al. Positive cumulative fluid balance is associated with mortality in pediatric acute respiratory distress syndrome in the setting of acute kidney injury. Pediatr Crit Care Med. 2019;20:323–331. https://doi.org/10.1097/PCC.0000000000001845

93. Wong JJ, Han WM, Sultana R, Loh TF, Lee JH. Nutrition delivery affects outcomes in pediatric acute respiratory distress syndrome. J Parenter Enter Nutr. 2017;41:1007–1013. https://doi.org/10.1177/0148607116637937

94. Iyer R, Bansla IA. What do we know about optimal nutritional strategies in children with pediatric acute respiratory distress syndrome? Ann Transl Med. 2019;7:510–510. https://doi.org/10.21037/atm.2019.08.25

95. Hartmann SM, Hough CL. Argument against the routine use of steroids for pediatric acute respiratory distress syndrome. Front Pediatr. 2016;4:79. https://doi.org/10.3389/fped.2016.00079

96. Drago BB, Kimura D, Rovnaghi CR, et al. Double-Blind, placebo-controlled pilot randomized trial of methylprednisolone infusion in pediatric acute respiratory distress syndrome. Pediatr Crit Care Med. 2015;16:e74–81. https://doi.org/10.1097/PCC.0000000000000349

97. Yehya N, Servaes S, Thomas NJ, Nadkarni VM, Srinivasan V. Corticosteroid exposure in pediatric acute respiratory distress syndrome. Intensive Care Med. 2015;41:1658–1666. https://doi.org/10.1007/s00134-015-3953-4

98. Monteverde-Fernández N, Cristiani F, McArthur J, González-Dambrauskas S. Steroids in pediatric acute respiratory distress syndrome. Ann Transl Med. 2019;7:508–508. https://doi.org/10.21037/atm.2019.07.77

99. Vet NJ, Kleiber N, Ista E, deHoog M, deWildt SN. Sedation in critically ill children with respiratory failure. Front Pediatr. 2016;4:89. https://doi.org/10.3389/fped.2016.00089

100. Curley MAQ, Wypij D, Watson RS, et al. Protocolized sedation vs usual care in pediatric patients mechanically ventilated for acute respiratory failure: a randomized clinical trial. JAMA. 2015;313:379–389. https://doi.org/10.1001/jama.2014.18399

101. Himbeauch AS, Yehya N, Wang Y, et al. Early right ventricular systolic dysfunction and pulmonary hypertension are associated with worse outcomes in pediatric acute respiratory distress syndrome. Crit Care Med. 2018;46:e1055–e1062. https://doi.org/10.1097/CCM.0000000000003358

102. Lewis SR, Pritchard MW, Thomas CM, Smith AF. Pharmacological agents for adults with acute respiratory distress syndrome. Cochrane Database Syst Rev. 2019;2019(7):CD004477. https://doi.org/10.1002/14651858.CD004477.pub3

103. Ward SL, Turpin A, Spicer AC, Treadwell MJ, Church GD, Flori HR. Long-Term pulmonary function and quality of life in children after acute respiratory distress syndrome. Pediatr Crit Care Med. 2017;18:e48–e55. https://doi.org/10.1097/PCC.0000000000001014

104. Yehya N, Thomas NJ. Relevant outcomes in pediatric acute respiratory distress syndrome studies. Front Pediatr. 2016;4:51. https://doi.org/10.3389/fped.2016.00051

105. Mehta NM, Bechard LJ, Zurakowski D, Duggan CP, Heyland DK. Adequate enteral protein intake is inversely associated with 60-d mortality in critically ill children: a multicenter, prospective, cohort study. Am J Clin Nutr. 2015;102:199–206. https://doi.org/10.3945/ajcn.114.104893