Review Article

A Comprehensive Review on the Management of ARDS among Pediatric Patients

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Abstract

Pediatric acute respiratory distress syndrome (PARDS) is a complex inflammatory syndrome of lungs leading to disruption of alveolar epithelial membrane barrier in the lungs. It includes varying age groups from infants to adolescents. PARDS definition has changed over decades as current definition is given by the Pediatric Acute Lung Injury Consensus Conference group. Although most of management principles are extrapolated from adult data, physiology of Acute Respiratory Distress Syndrome (ARDS) in children is different when compared to adults. The present review mainly focused on current evidence in the management of ARDS with emphasis to pediatric population. MeSH headings such as ARDS, positive end-expiratory pressure (PEEP), and lung protective ventilation were used for searching publications in PubMed, Embase, and SciELO. Publications were limited to human studies in the past 20 years. Core ventilatory strategies in PARDS include use of low-tidal volume, higher PEEP and acceptance of permissive hypercapnia and permissive hypoxemia. Supportive strategies such as restrictive fluid therapy, prone positioning, early enteral nutrition, and adequate analgosedation remain the mainstay of management of principles. As PARDS contains heterogeneous population, personalized mechanical ventilation under umbrella of lung protective ventilator strategies such as low-tidal volume ventilation, open lung strategy, acceptance of permissive hypercapnia, and permissive hypoxia is standard of care.

Keywords: Pediatric acute respiratory distress syndrome, population, positive end-expiratory pressure, ventilation

Introduction

Pediatric acute respiratory distress syndrome (PARDS) is an acute clinical inflammatory syndrome of the lungs wherein there is disruption of the alveolar endothelial-epithelial barrier with interstitial alveolar edema and increased alveolar dead space.[1,2] PARDS can range in severity from mild to severe based on various definitions. Historically, Acute Respiratory Distress Syndrome (ARDS) definitions have changed over the past 6 decades. In 1967, Ashburg defined ARDS as acute respiratory distress with cyanosis refractory to oxygen supplementation with diffuse pulmonary infiltrates.[3] Murray lung injury score in 1988 is the first consensus definition of ARDS based on chest radiographic score, positive end-expiratory pressure (PEEP) score, hypoxemic score, and respiratory system compliance score.[4] In 1994, American–European consensus removed PEEP criteria and simplified radiologic criteria and ruled out cardiac causes of ARDS by pulmonary arterial catheter.[5] Berlin definition in 2012 defined acute onset as <1 week, better defined radiological criteria and set a minimum PEEP of 5 cm of water for defining severity based on oxygenation.[6] All the above definitions were defined primarily in adult populations which were extrapolated to pediatric population. In 2015, Pediatic Acute Lung Injury Consensus Conference (PALICC) published pediatric-specific considerations for defining ARDS which excluded perinatal age group, defined severity based on oxygenation index and also included Spo_2 in place of paO_2 for defining ARDS.[7] Compared to adults, children have greater chest wall compliance because of incomplete rib cage ossification, greater increase in airway resistance with reduction in airway radius, poor alveolar maturation which is age dependent and poor respiratory muscle reserve

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in children.[8] Hence, most of the management protocols based on adult studies is not well accepted in pediatric population because of differed physiology of ARDS.

Methodology

MeSH headings such as ARDS, PEEP, lung protective ventilation were used for searching publications in PubMed, Embase, and SciELO. Publications were limited to human studies in the past 20 years. Furthermore, the publications were hand searched which were not included in the initial search. The priority was given to the Paediatric studies but adult studies were also included when pediatric literature was found scarce.

Management of Acute Respiratory Distress Syndrome

Noninvasive ventilation in acute respiratory distress syndrome

There is a limited role of noninvasive ventilation (NIV) in a selected population of PARDS patients. NIV used early in the course may help in avoiding mechanical ventilation and its complications, including the cost of intensive care unit (ICU) stay but data in children are very sparse. Retrospective analysis of the Randomized Evaluation of Sedation Titration for Respiratory Failure trial data showed that NIV used before intubation had worse outcome in terms of mortality, duration of mechanical ventilation and ICU stay. PALICC does not recommend use of NIV in moderate-to-severe disease but can be used in mild disease with close clinical monitoring. Complications with NIV use are skin breakdown, conjunctivitis, and abdominal distension.[7,9-10]

Mechanical Ventilation

Strategies of mechanical ventilation in ARDS have evolved over the past few decades. Most of the ventilator strategies are based on the adult data however mainstay of ventilator strategies are based on "baby lung concept" and avoiding ventilator-induced lung injury (VILI).[11] Goals of management of ARDS are management of hypoxia and respiratory failure.

ET tube and ventilator circuit

ET tube with cuff is recommended to avoid air leak during invasive mechanical ventilation. The cuff should be inflated to maintain <10% of air leakage and cuff pressure of <20 cm water.[12]

Mode of Mechanical Ventilation

Data are scarce regarding outcome of ARDS based on the mode of mechanical ventilation. Individual settings are more important than the type of mode of ventilation. PALICC does not recommend any specific mode of ventilation for PARDS. However, pressure control ventilation has better control over rapid changes in Peak Pressure (Ppeak) during ventilation and adjusts tidal volume based on the severity of lung disease (low lung compliance vs. preserved lung compliance), though volume control mode is not inferior if the tidal volumes are adjusted to limit Ppeak with re-assessment of lung compliance. Pressure control or volume control mode should be based on unit protocol and familiarity.[13,14]

Setting Tidal Volume

Tidal volume should be titrated to the respiratory lung compliance rather than setting tidal volume according to ideal or predicted body weight, as the body weight does not correlate well with available lung volume in ARDS. ARDS lungs do not tolerate larger tidal volumes. ARDS net trials have also shown that low-tidal volume ventilation improves outcomes. PALICC recommends tidal volume of 3–6 ml/kg for ARDS with poor lung compliance and 5–8 ml/kg for preserved lung compliance with limiting plateau pressure to 28–32 cm of water.[7,15]

Concept of Driving Pressure

Studies have shown that higher driving pressure is associated with higher mortality. PALICC recommends that tidal volume should be adjusted to respiratory compliance such that driving pressure is ≤15. Driving pressure is not a goal but a safety limit. Driving pressure is calculated bedside by Plateau pressure (Pplat)-PEEP.[16]

Positive End Expiratory Pressure Titration

Setting PEEP is the fulcrum of lung protective ventilation. PEEP improves oxygenation by keeping the alveoli open, preventing atelectasis, and improving the oxygenation. PEEP should be dynamically set rather than fixed number. PEEP should be adjusted based on lung compliance, stress index, and pressure volume loop in the ventilator graphics, and using incremental and decremental PEEP strategies. Hemodynamics of the patient should also be considered while setting the PEEP. PALICC recommends PEEP of up to ≤15 in severe ARDS.[7,17]

Blood gas targets

Permissive hypoxemia

Improving the oxygenation does not simply improve the outcomes at the risk of lung injury. PALICC recommends oxygen saturation goals of 92%-97% for mild ARDS and 88%-92% for severe ARDS (PEEP ≥10 cm H2O).[7,18]

Permissive hypercapnia

Most population tolerate permissive hypercapnia and acidosis but should be avoided in children with pulmonary hypertension and intracranial hypertension. Tidal volume should be such that pH should be targeted rather than pCO2 to keep pH above 7.2.[7,19]

Stress, Strain, and Mechanical Power

Stress is defined as force per unit area, the same unit as a measure of pressure. It is the force exerted on the lung during the artificial ventilation. Lung parenchymal stress in ARDS is

difficult to measure as there is heterogeneous distribution of airflow in ARDS lung. Strain is the amplitude of deformation of lung which is the ratio of end-expiratory lung volume and end-inspiratory lung volume.[20] Mechanical power is the amount of energy per unit generated by mechanical ventilation, energy per unit time depends the mechanical properties of the lung, i.e., elastance and resistance, inspiratory flow, PEEP, respiratory rate, and tidal volume. Driving pressure is analogous to stress amplitude which represents the difference between extrinsic PEEP and Pplat.[21] *Post hoc* analysis of acute respiratory management in ARDS trial has suggested that driving pressure is best stratification of stress and strain predicts VILI in PARDS.[22]

Airway pressure release ventilation

Airway pressure release ventilation (APRV) is a pressure control mode, delivers continuous positive pressure with short intermittent release to lower pressure. Spontaneous ventilation is encouraged during the higher pressure phase. Maintaining higher mean airway pressure (MAP) for a longer duration favors open lung strategy of ARDS. Increasing MAP for a long time in APRV achieves homogeneous distribution of ventilation.[23] Although APRV favors open lung strategy which prevents atelectotrauma, the spontaneous breathing during the high-pressure phase may cause self-inflicted lung injury. As the PALICC recommends lower acceptable tidal volume ventilation, it is difficult to accurately measure tidal volume in APRV. Although theoretically APRV has advantage in improving oxygenation by maintaining sustained MAP, its negative effect on cardiovascular system and no large randomized-control trial) (RCTs) in the pediatric population limits its use.[24]

High-frequency oscillatory ventilation

High-frequency oscillatory ventilation (HFOV) avoids overdistension and uses low tidal volumes which leads to better alveolar recruitment and prevents VILI. Although there is theoretical advantage of using HFOV over conventional mechanical ventilation, various studies have shown no benefit of HFOV. OSCAR(OSCillation in ARDS) trial did not show any mortality benefit whereas OSCILLATE(The Oscillation for Acute Respiratory Distress Syndrome Treated Early) trial not only did not show any mortality benefit but also suggested it may be harmful. This explains that just by improving oxygenation, mortality will not be decreased as majority of patients in ARDS die because of Multiple Organ Dysfunction Syndrome rather than refractory hypoxemia.[25,26]

Personalized mechanical ventilation

It is setting a ventilator based on individualized targeted physiological variables rather than set parameters such as low tidal or higher PEEP settings. Personalized mechanical ventilation uses artificial intelligence, measurement of end-expiratory lung volume, inspiratory capacity, and transpulmonary pressure. Personalized mechanical ventilation allows the identification of recruitable patients along with minimizing VILI. Personalized ventilation targets dynamic driving pressure, mechanical energy, lung imaging, and biological phenotypes (hypoinflammation vs. hyperinflammation).[27-29]

Extracorporeal membrane oxygenation

Extracorporeal membrane oxygenation (ECMO) supports both failing heart and lungs in severe ARDS. Prolonged and aggressive mechanical ventilation along with hyperinflammation can lead to VILI which may progress to Multi Organ Failure. ECMO by providing extracorporeal oxygenation prevents VILI due to prolonged mechanical ventilation. Most of the data for ECMO are derived from Extracorporeal Life Support Organization register.

There are no pediatric RCTs comparing ECMO to conventional mechanical ventilation. Given the supporting evidence in neonates and adults, ECMO can be considered in the pediatric population where conventional lung protective ventilation does not suffice to maintain adequate oxygenation. ECMO should be considered when there is a reversible etiology for ARDS and there are no significant comorbidities.[30,31]

Supportive Strategies

Proning in pediatric acute respiratory distress syndrome

Proning helps in better recruitment of alveoli, ventilation-perfusion matching, and homogeneous distribution of airflow on mechanical ventilation. Prone Positioning in Severe Acute Respiratory Distress Syndrome trial showed that proning has significant mortality benefit in severe ARDS.[32] ARDS Prone Position Network (APRONET) trial is the main reason for not using proning in population with mean arterial pressure <65 mmHg.[33] PALICC recommends proning more as a rescue therapy than routine therapy in severe ARDS.[7] The ongoing PRone and OScillation Pediatric Clinical Trial trial may shine a better light on its routine use in PARDS.[34]

Recruitment maneuver

The two most commonly used methods are sustained inflation and incremental PEEP which have been shown to improve oxygenation and decrease atelectasis. Incremental PEEP is associated with less hemodynamic compromise and lung hyperinflation. Stepwise recruitment maneuver like incremental PEEP is also associated with reduced expression of markers of fibrosis, reduced type Ⅱ epithelial and endothelial cell damage. Recruitment maneuver increases end-expiratory lung volume while lung elastance decreases, which in turn leads to lower inspiratory transpulmonary pressure and stress.[35,36] PHARLAP (Permissive Hypercapnia, Alveolar Recruitment, and Low Airway Pressure) study did not show any mortality benefit nor ventilator-free day in ARDS using maximal recruitment maneuvers and PEEP titration.[37] Recruitment maneuvers are simple bedside interventions which have shown improvements in lung compliance and oxygenation. However, optimal recruitment methods and timing of interventions are not defined.

Inhaled nitric oxide

Inhaled nitric oxide (INO) is a local pulmonary vasodilator

with minimal or no systemic side effects. This pulmonary vasodilation improves the ventilation-perfusion matching. INO also has its effects on immune regulation by decreasing the proliferation of Th2 cells and synthesis of interleukin-2. PALICC recommends its use in PARDS with pulmonary hypertension or right ventricular dysfunction or as rescue therapy to bridge for ECMO.[7,38]

Surfactant

PARDS is characterized by alveolar endothelial capillary damage along with destruction of surfactant. Both qualitative and quantitative dysfunction are known in PARDS. Although there is surfactant deficiency, replacement of surfactant in ARDS is bound to many limitations like inactivation of surfactant by phospholipase A2, lack of ideal surfactant delivery method and no optimal dose of surfactant is defined in ARDS.[39,40] At present, there are no pediatric trials that have evaluated the efficacy of surfactant. PALICC also does not recommend its routine use owing lack of data in PARDS.[7]

Sedation, Analgesia, and Neuromuscular Blockade

Protocolized analgosedation with intermittent dosing and use of dexmedetomidine early rather than benzodiazepines have become the standard of care now when compared to continuous sedation with midazolam. COMFORT, Face, Leg, Activity, Cry and Consolability, and multidimensional assessment of pain scale are used for analgesia whereas the Richmond agitation sedation scale and State Behavioural Scale are used for sedation.

Neuromuscular blockade decreases VILI by improving synchrony between ventilator and patient. It also decreases oxygen consumption by respiratory muscle but the caveat is that long-term usage especially with steroids leads to neuromuscular weakness leading to increased ventilator days, ICU stay, and mortality. PALICC recommends usage of neuromuscular blockade in moderate-to-severe ARDS when sedation alone is not effective in maintaining optimal ventilation.[7,41-43]

Fluid Management in Pediatric Acute Respiratory Distress Syndrome

The challenge of fluid management in PARDS compared to adults is its heterogeneous population from infants to adolescents and variety of underlying etiologies such as sepsis, aspiration, and trauma. The fluid homeostasis differs in children compared to adults. Total Body Water (TBW) and the ratio of extracellular water to TBW ratio decrease as the age increases along with higher metabolic rate and insensible losses. The children are known to tolerate fluids better than adults. In another hypothesis, as the children have large lung mass to bodyweight, because of increased rate of alveolar fluid clearance due to over expression of Epithelial Sodium Channel, children will be less prone to edema of lungs secondary to fluid overload. But in PARDS, there are high pro-inflammatory cytokines which damage endothelium and cause breakage in alveolar-capillary barrier which decreases fluid tolerance. In addition, the positive fluid balance enhances the inflammatory process which worsens fluid accumulation and lung edema. It is important to note that children are prone to positive fluid balance, lung inflammation, and edema in the initial days (exudative phase) of ARDS. Hence, the prevention of early fluid overload has an impact on ventilator-free days, ICU stay, and mortality Fluid And Catheter Treatment Trial in adults suggested that early fluid restriction in ARDS was associated with improved oxygenation, decrease in number of mechanical ventilation and ICU stay. Hence, the recommendations from various studies are to avoid positive fluid balance in the early stages of ARDS after hemodynamic stabilization.[22,44-47]

Corticosteroids in Acute Respiratory Distress Syndrome

The main pathophysiological basis for the use of steroids in PARDS is deregulated hyperinflammation in the lungs. The first proposed beneficial effect of steroids was described by Ashbaugh *et al*. with special emphasis on its antiedema and anti-inflammatory effect.[3] During the early stages of ARDS (exudative phase), there is intense pulmonary inflammation mediated by two important cellular signaling pathways, i.e., nuclear factor (NF)-kB and the inhibitory GR-mediated transduction cascade which releases inflammatory cytokines such as TNF, IL-1, IL-6, and other inflammatory mediators. These inflammatory mediators mediate the damage to alveolar epithelial endothelial barrier causing increased permeability to protein-rich exudate leading to alveolar and interstitial edema. Corticosteroids have both genomic and nongenomic effects on reducing the cytokine-mediated hyperinflammation, minimizing the lung damage and improves the lung function.[48-50] Pioneer studies in use of corticosteroids in ARDS was done by Meduri *et al*. who demonstrated significant decrease in ventilator-free days and mortality when steroid was used early or in late ARDS whereas ARDSnet trial showed no difference in mortality benefit with use of corticosteroids.[51-53] The DEXA ARDS trial done in adults has showed a significant increase in ventilator-free days and decrease in mortality when dexamethasone was used early in moderate-to-severe ARDS.[54] PALICC does not recommend the use of corticosteroids owing to its limited pediatric data.[7] The other concerns with corticosteroids are immunosuppression leading to worsening septicemia, hyperglycemia, hypertension, and GI bleeding.[55]

Nutrition in Pediatric Acute Respiratory Distress Syndrome

Adequate nutrition, protein-calorie, and micronutrients are necessary to prevent breakdown of proteins in cardiac and respiratory muscles. Early adequate enteral nutrition is

preferred over parenteral nutrition as it improves intestinal barrier function and decreases systemic inflammatory dysregulation. Immune nutrition such as arginine, glutamine, omega-3 fatty acids, zinc, and selenium have no clear clinical benefit in ARDS. Further research is needed in immune-nutrition for optimal timing and dosage of its use in ARDS.[56-58]

Emergent Therapies in Pediatric Acute Respiratory Distress Syndrome

There are limited data on emergent therapies such as ulinastatin, dilmapimod, solnatide, citrulline, pirfenidone, and mesenchymal stem cell transplant in pediatric population. Better understanding of biological subtypes, immune pathways of ARDS, and clinical research will help in the usage of these agents in future.[59-63]

Conclusion

PARDS is a complex clinical syndrome. It is important for treating physician to be aware of newer definitions and pathophysiological principles. As PARDS contains heterogeneous population, personalized mechanical ventilation under umbrella of lung protective ventilator strategies such as low-tidal volume ventilation, open lung strategy, acceptance of permissive hypercapnia, and permissive hypoxia is standard of care. As most of the management principles in PARDS are extrapolated from adult data, further research and better understanding of pathophysiology are necessary in pediatric population.

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Conflicts of interest

There are no conflicts of interest.

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