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Perspective

Acute Respiratory Distress Syndrome in Children: Recent Perspective

BS Sharma*, Hari Mohan Meena, Vinita Garg, and Prity Sharma

Department of Pediatrics, SMS Medical College, India

***Corresponding author**

BS Sharma, Division of Pediatric Pulmonology Department of Pediatrics, Sawai Mansingh Medical College, India, Email: drbssharma@gmail.com

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Abstract

Acute respiratory distress syndrome is a syndrome of acute onset characterized by hypoxemia and infiltrates on chest radiographs that affects both adults and children of all ages. It is an important cause of respiratory failure in pediatric intensive care units and is associated with significant morbidity and mortality. The management of pediatric acute respiratory distress syndrome (PARDS) is still difficult because there is no definite guideline available for treatment of this entity. At present, the cornerstone of treatment of PARDS is sound intensive care management and early optimal anticipatory ventilatory support. This article reviews recent updates in definition & management of PARDS.

INTRODUCTION

Acute respiratory distress syndrome (ARDS) is a heterogeneous syndrome with a complex pathology and mechanisms of disease which results in important cause of PICU admission with significant contribution to mortality and morbidity in children. ARDS is less frequent reported in infants as well as children than in adults and the severity of respiratory failure is lower in children than adult [1,2].

The ARDS was first defined in 1967 by Ashbaugh et al., as respiratory distress in adult with various underlying pathology sharing common feature of progression to respiratory failure with refractory hypoxemia associated with decreased compliance and functional residual capacity of lungs with presence of diffuse infiltrates on chest skiagram and who required positive end expiratory pressure (PEEP) to improve tissue oxygenation [3].

In 1994, American-European Consensus Conference (AECC) proposed "acute respiratory distress syndrome" as a clinical entity with acute onset hypoxemia, PaO_2 / FiO_2 ratio ≤200, bilateral infiltrates on chest radiographs and the absence of left atrial hypertension [4].

In 2012, The Berlin definition became the new reference for ARDS in adults; however, like the AECC definition, its applicability in children remained limited since specific characteristics of the pediatric population were not considered. Berlin Definition of ARDS Statement has been classified into three exclusive categories on the basis of the degree of hypoxemia, thereby eliminating the acute lung injury (ALI) terminology [5,6].

Until recently, there were no definitions and diagnostic criteria for acute respiratory distress syndrome in children have been established. In this article, we review the evolution of the definition and recent management strategy of acute respiratory distress syndrome in children over recent decades.

INCIDENCE

The incidence of pediatric ARDS is different than adult and it's relatively rare but it is also under diagnosed due lack of specific guidelines. Its prevalence in children in the United States, Europe and Australia is 2-12.8 cases /100,000 people per year [7].

In North America, multicenter study reported that 1-4% of children undergoing mechanical ventilation had ARDS among children hospitalized in PICU [8].

Many studies revealed that the mortality rate in children suffering from ARDS is lower than adult and ranges between 18-27%. However, data from Australian study suggested that children mortality due to ARDS is quiet high (35%) as observed in adult [9].

PATHOPHYSIOLOGY

Acute respiratory distress syndrome is characterized by an acute inflammation of lung with diffuse alveolar injury and increased vascular permeability, resulting in hypoxic respiratory failure [10]. The pathophysiology of ARDS in children is complex and multifactorial [11].It can be either due to direct pulmonary insult like pneumonia, aspiration of gastric contents, pulmonary contusion or non-pulmonary insult including sepsis, severe trauma and blood transfusion [12].

CLINICAL FEATURES

ARDS is characterized by acute onset fast breathing,

breathlessness, hypoxemia and chest skiagram may show bilateral infiltrates [13].

Newer definition of pediatric ARDS

The American-European Consensus Conference (AECC) and Berlin definitions of acute respiratory distress syndrome (ARDS) were specifically focused on adult ARDS and pediatric considerations were not addressed.

The Pediatric Acute Lung Injury Consensus Conference (PALICC) was convened to propose specific definitions for pediatric acute respiratory distress syndrome (PARDS) in 2015. The main 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 non-invasive measures of hypoxemia based on SpO_2 [oxygen saturation index (OSI)], and less restrictive radiographic criteria [14].

The criteria of PALICC to diagnose of PARDS as following

Age: Pediatric ARDS can affect all pediatric age groups, from the neonatal period through adolescence.

Evidently, perinatal causes of acute hypoxemia are excluded, including

- Prematurity- associated lung disease,
- Perinatal lung injury (such as meconium aspiration syndrome, pneumonia and sepsis acquired during delivery)
- Congenital abnormalities (such as congenital diaphragmatic hernia or alveolar capillary dysplasia).

Timing: Symptoms of hypoxemia and radiological changes must occur within 7 days of a known clinical insult.

Myocardial Dysfunction. Patients with heart disease are not excluded. Children with left ventricular dysfunction presenting with acute-onset hypoxemia and new changes on chest radiographs not explained by left ventricular failure or fluid overload and who meet all other pediatric ARDS criteria are defined as having the syndrome.

Chest Radiographs. The presence of new infiltrates consistent with lung parenchymal disease is required for the diagnosis, even if unilateral.

Definition of Hypoxemia. The oxygenation index (OI = MAP x FiO_2/ PaO_2, in which MAP corresponds to the mean airway pressure) to be used instead of PaO_2/FiO_2 ratio to quantify the degree of hypoxemia and to determine the severity of ARDS in pediatric patients undergoing invasive mechanical ventilation.

If the PaO_2 is not available, the oxygen saturation index (OSI = MAP x $FiO_2/SatO_2$) can be used under the same conditions proposed for the Oxygenation index.

When $SatO_2$ was used as a criterion for the diagnosis of pediatric ARDS, oxygen therapy should be titrated to achieve $SaO_2 \leq 97\%$ for the OSI calculation.

In patients undergoing non-invasive ventilation, there is currently no means to stratify the severity of PARDS.

PaO_2 / FiO_2 ratio should be used to diagnose PARDS for children receiving non invasive, full face mask ventilation (CPAP or BiPAP) with minimum 5 cm of H_2O.

If PaO_2 / FiO_2 ratio not available, oxygen saturation ($SatO_2$)/ FiO_2 ratio can be used in patients receiving non invasive full face mask ventilation.

Management of pediatric ARDS

The main objectives of management are to diagnose and treat underlying cause of ARDS, maintain adequate oxygenation, minimize secondary lung injury and extra pulmonary complications. It comprises as ventilatory and non ventilatory management.

Ventilatory management of PARDS

While dealing the ventilatory strategies in management of pediatric ARDS, the special attention must be given on the choice of tidal volume, PEEP, recruitment maneuvers and high-frequency ventilation, ventilator induced lung injury and infection related to ventilation. it can be concluded that although ventilatory support has been used in this group of patients for more than four decades, there are still conflicting aspects of the process that await adequate scientific support.

Tidal Volume

Albuali et al in 2007 showed that ventilation with higher tidal volume resulted in higher mortality [odds ratio (OR) 1.59; 95% confidence interval (CI): 1.20-2.10, $p<0.001$] and shorter ventilation-free days [95% CI: -1.24, -0.77, $p<0.001$] [15].

To minimize ventilator induced lung injury and improve outcome, the low tidal volume (VT) strategies and appropriate PEEP levels have been considered in management of adult ARDS.

Similarly, a low VT strategy can be considered a milestone in the study of ventilation for ARDS and acute respiratory failure in the pediatric age [16].

The low VT ventilation may result in hypercapnia despite increased respiratory rate. Increase in $PaCO_2$ (permissive hypercapnia) is acceptable - instead of increasing tidal volume or peak inspiratory pressure (PIP) - but $PaCO_2$ should remain ≤ 50-55 mm Hg to be on the safer side. Minute ventilation can be reduced by lower tidal volumes as long as $PaCO_2$ is balanced by serum bicarbonate levels to determine a pH above 7.20 [17].

Permissive hypercapnia is suggested as a protective ventilation strategy but the real benefits on cardiac output improvement, reduction of the artery- venous difference and of lactate production remain unconfirmed.

Till now, No further randomized controlled trial regarding the effect of tidal volume on the mortality of pediatric patients had been conducted.

The use of tidal volume is still controversial and current practices usually based on studies extrapolated from the studies on adults.

PALICC recommended that pediatric patients with good lung compliance to be treated with tidal volume of 5-8 mL/kg while those with poor lung compliance should receive ttidal volume of 3-6 mL/kg [14].

PEEP/ LUNG RECRUITMENT

The level of PEEP is decided by markers of oxygen delivery, respiratory system compliance and hemodynamics. In severe PARDS, the PEEP level more than 15 cm of H_2O may be needed, although attention should be given to limiting the plateau pressure.

The careful recruitment maneuvers in attempt to improve oxygenation in severe hypoxia by slow increment or decrement of PEEP is recommended [14].

HIGH FREQUENCY OSCILLATING VENTILATION (HFOV)

High-frequency oscillatory ventilation (HFOV) is an emerging ventilation modality with greater acceptance among neonatologists and pediatric intensivists.

Systematic review with 10 randomized controlled trials comparing HFOV with conventional mechanical ventilation on both adults and children with ARDS in 2016 showed that HFOV was not associated with lower hospital stay and 30-day mortality [18].

Their findings do not support the use of HFOV as a first-line strategy in people undergoing mechanical ventilation for ARDS [14].

However, in the pediatric consensus, HFOV is recommended as an alternative in children with hypoxemic respiratory failure refractory to conventional ventilation using a plateau pressure >28cm. Moreover, when HFOV is indicated, the concomitant optimization of lung volume through the application of recruitment maneuvers is recommended [14].

EXTRACORPOREAL MEMBRANE OXYGENATION (ECMO)

A retrospective study conducted in 2011 Revealed that the use of ECMO was associated with an overall mortality of 57% in pediatric acute respiratory failure [19].

A retrospective review was conducted in 2012 showing that the use of ECMO could improve survival rate in refractory respiratory failure patients [20].

PALICC recommended the use of ECMO in pediatric patients with severe ARDS when other management failed [14].

NON INVASIVE POSITIVE PRESSURE VENTILATION

Non invasive positive pressure ventilation (NIPPV) is frequently applied in patients with clinical and radiographic evidence of lung disease, supplemented with FiO_2 of greater than 50% [21].

NIPPV can be used in early mild and in early moderate forms of ARDS in children.

A randomized controlled trial comparing NIPPV with control group demonstrated that heart rate and respiratory rate improved with NIPPV. The frequency of endotracheal intubation was also significantly lowered from 60% to 28% (p=0.045) in mild form of ARDS [22].

Intubation must be considered in children suffering from ARDS receiving NIPPV but do not show clinical improvement or rather having symptoms of worsening of disease [14].

NON VENTILATORY MANAGEMENT OF PEDIATRIC ARDS

Non ventilatory management of pediatric ARDS also have crucial role in outcome of disease. The treatment of underlying cause of ARDS must be introduced apart from other adjunctive therapy.

NUTRITION

Children with ARDS should receive nutrition to facilitate their recovery, maintain their growth and meet their metabolic demands. Enteral feeding should be given instead of parenteral feeding until it is tolerated [14].

A retrospective cohort study conducted in 2016 demonstrated that the adequate nutrition in term of calorie and protein intake reduced the mortality rate of children with ARDS [23].

A prospective multicentre cohort study in 2015 reported that adequate enteral protein intake is significantly associated with lower mortality in mechanically ventilated pediatric patients [24]. Therefore, adequate nutrition intake is highly recommended.

FLUID MANAGEMENTS

A systematic review of Ingelse et al., revealed that fluid overload is associated with deterioration of clinical condition and worsened oxygenation. A more conservative fluid management is suggested [25].

The goal-directed fluid management is advocated by PALICC to prevent positive fluid balance [14].

SEDATION AND USE OF NEUROMUSCUALR BLOCKING AGENTS

The pediatric patients with ARDS should receive minimal yet effective targeted sedation to facilitate their tolerance to mechanical ventilation and to optimize oxygen delivery, oxygen consumption and work of breathing. If sedation alone is not adequate to achieve effective mechanical ventilation, neuromuscular agent should be considered [14].

PRONE POSITION

The randomized controlled trial conducted in 2005 by Curley et al., demonstrated that prone position did not significantly reduce the mortality rate and did not alter the outcome of children [26].

Therefore prone position cannot be recommended as routine therapy in pediatric ARDS. However it may considered as option in cases of severe ARDS in children [14].

Table 1: The Berlin definition of acute respiratory distress syndrome.

Criteria	Observation		
Timing	Within 7 days of a known clinical insult or new or worsening respiratory symptoms		
Radiological imaging(chest skiagram)	Bilateral opacities- not fully explained by lobar/lung collapse, nodules or effusions		
Origin of edema	Respiratory failure not fully explained by fluid overload or cardiac failure, require objective assessment(echocardiography) to exclude other causes of edema as etiological factors		
Oxygenation(hypoxemia)	Mild	Moderate	Severe
PaO_2/FiO_2	300-201	200-101	<100
PEEP ≥ 5 cm of H_2O	PEEP/CPAP/NIV	PEEP	PEEP
Estimated mortality	~25%	~35%	~45%

Table 2: PALICC definition of pediatric acute respiratory syndrome [14].

Age	Exclude patients with perinatal related pulmonary disease			
Timing	Within 7 days of known clinical insult			
Origin of edema	Respiratory failure fully not explained by cardiac failure or fluid over load			
Chest skiagram	Chest imaging finding of new infiltrates consistent with acute pulmonary parenchymal disease			
Oxygenation	Non invasive mechanical ventilation	Invasive mechanical ventilation		
	PARDS(No severity stratification)	Mild	Moderate	Severe
	Full face mask ventilation(CPAP or BiPAP) with minimum CPAP of 5 cm of H_2O PaO_2 / FiO_2 ≤ 300 $SatO_2$ / FiO_2 ≤ 264	4 ≤ OI <8 5≤OSI< 7.5	8 ≤ OI <16 7.5≤OSI<12.3	OI≥16 OSI≥12.3

INHALED NITRIC OXIDE

Inhaled nitric oxide cannot be recommended for ARDS children.

It results in a transient improvement in oxygenation but does not reduce mortality and may even be dangerous [27].

SURFACTANT THERAPY

The randomized control trial by Willson and colleagues did demonstrate that there were no benefits in survival, ventilation-free and ICU-free oxygenation with the use of surfactant. However, there were adverse events related to the use of surfactant including transient hypoxia, bradycardia and leucopenia [28].therefore routine surfactant therapy in children with ARDS is not recommended.

Further study should give attention on specific patient's populations that may likely to benefit with specific dosing and delivery of surfactant [14].

BLOOD TRANSFUSION

Packed red blood cells transfusion should not be done in clinically stable children with evidence of adequate oxygen delivery except congenital cyanotic heart disease, bleeding and severe hypoxemia if hemoglobin is more than 7 gram/dl [14].

STEROID THERAPY

Corticosteroid therapy cannot be recommended as routine basis in treatment of pediatric ARDS [14].

CONCLUSION

The acute respiratory distress syndrome is one of the common causes of PICU admission. The new definition of pediatric ARDS can help us to diagnose and assess the severity of ARDS in children. The management of pediatric ARDS remains supportive and is aimed to improve gas exchange and preventing the complication while underlying disease that precipitated ARDS is treated. Currently, mechanical ventilation strategies aiming at optimal alveolar recruitment with the judicious use of PEEP and optimal tidal volume remains crucial part of management of respiratory failure in children.

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