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Overview of Pediatric Acute Respiratory Distress Syndrome

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Abstract: **The Present review study was aimed to overview the pediatric acute respiratory distress syndrome (PARDS), from different perspectives, diagnostic procedures, progression of this disease, and treatment. An electronic search was conducted through; PubMed, EMBASE, CINAHL, SCOPUS, databases, from inception until January 2017, this search was concerning the Pediatric acute respiratory distress syndrome (PARDS), and performed using the following keywords in various combinations: "Pediatric acute respiratory distress syndrome (PARDS), treatment, diagnosis, prognosis, complications, and children". English language restrictions were applied with human subjects only. References from identified articles were searched for additional relevant studies. This pediatric-specific definition for acute respiratory distress syndrome builds on the adult-based Berlin Definition, however has been modified to represent differences between grownups and children with acute breathing distress syndrome. Numerous proof utilized this definition for future examinations and clinical care of children with pediatric acute breathing distress syndrome and motivate external validation. Medicinal treatment of PARDS remains challenging due to the fact that the amount of scientific proof is disappointingly low. Although the possible helpful impacts of exogenous surfactant and iNO have been studied to a specific degree, there is no substantial information on glucocorticoids or other ancillary treatment methods. With the exception of susceptible positioning, proposed nonpharmacological therapies are equally unproven with little vigorous screening to support their usage.**

Keywords: **pediatric acute respiratory distress syndrome (PARDS), diagnostic procedures, EMBASE, CINAHL, SCOPUS, Medicinal treatment.**

1. INTRODUCTION

Acute respiratory distress syndrome (ARDS) is a prevalent acute inflammatory lung injury with different degrees of strength that takes place in reaction to a systemic or pulmonary insult and usually leads to irregularities in gas exchange (primarily hypoxemia) and in pulmonary mechanics [(1,2)]. Pediatric acute respiratory distress syndrome (PARDS) is one of the most challenging disease entities in the pediatric intensive care unit (PICU). PARDS was recently specified by the Pediatric Acute Lung Injury Consensus Conference (PALICC) group as acute-onset hypoxic respiratory failure with brand-new infiltrate(s) on chest radiography not completely discussed by heart failure or fluid overload [(3)]. This definition is based upon the Berlin ARDS definition [(4)], with numerous adaptations to more adequately stick to ARDS particularly happening in children. Significantly, this consists of making use of pulse-oximetry obtained data to get the SpO2/FiO2 (S/F) ratio and oxygen saturation index (OSI) in the lots of patients in whom PaO2measurements are unavailable. Of note, due to the relative novelty of the PALICC definition, the short articles consisted of in this evaluation still utilize the Berlin or older AECC meaning of ARDS [(4)].

The incidence and mortality of pediatric ARDS is various than that of grownups. Pediatric ARDS is reasonably uncommon: its occurrence in children in the United States, Europe and Australia is 2-12.8 cases per 100,000 people/year [5,6,7]. In a multicenter study involving children hospitalized in pediatric intensive care units (PICUs) in North America, 1-4% of children going through mechanical ventilation had ARDS(8,9). Despite the low incidence, Spanish scientists have actually shown that a higher number of ventilated children can develop ARDS throughout their stay in the ICU [10].

The 1994 AECC definition has been utilized to identify children with ARDS, however this definition threats ignoring the real occurrence, mostly due to the fact that it requires an intrusive marker of oxygenation (PaO2). The Berlin meaning does not include specific pediatric criteria but appears to have a great diagnostic efficiency in children below 24 months of age [11].

The very first meaning of ARDS was published in 1967 when Ashbaugh et al. described a group of primarily adult patients with different underlying diseases sharing a typical progression to respiratory failure with refractory hypoxemia connected with diffuse seepage on chest radiographs, decreased compliance and practical recurring capability, and who needed the use of favorable end-expiratory pressure (PEEP) to enhance oxygenation. This medical photo was attributed to lung problems secondary to physical and biochemical insults, with impaired surfactant function and the development of hyaline membranes within the alveoli [12]. For this reason, it was initially named "adult-type respiratory distress syndrome" due to the pathophysiological similarities with the neonatal breathing distress syndrome (hyaline membrane disease). This preliminary description used vague requirements and was not specific enough to omit other medical conditions [12].

The Present review study was aimed to overview the pediatric acute respiratory distress syndrome (PARDS), from different perspectives, diagnostic procedures, progression of this disease, and treatment.

2. METHODOLOGY

An electronic search was conducted through; PubMed, EMBASE, CINAHL, SCOPUS, databases, from inception until January 2017, this search was concerning the Pediatric acute respiratory distress syndrome (PARDS), and performed using the following keywords in various combinations: “Pediatric acute respiratory distress syndrome (PARDS), treatment, diagnosis, prognosis, complications, and children”. English language restrictions were applied with human subjects only. References from identified articles were searched for additional relevant studies.

3. RESULTS

Medically, ARDS is identified by hypoxemia, ventilation-perfusion inequality, intrapulmonary shunting, increased dead-space, and reduced lung compliance. These pathophysiologic and clinical functions have activated numerous investigators to study many medicinal techniques for the avoidance and treatment of ARDS in seriously ill grownups [2]. Nevertheless, few of these methods have been thoroughly checked out in critically ill children secondary to a range of factors including the lower incidence and mortality rate in children compared to adults [3]. Pediatric ARDS (PARDS) covers a heterogeneity of underlying diseases that differ considerably between young infants and older children [4]. This irregularity might impact scientific features and reaction to therapy, which need to be thought about when examining the efficacy of pharmacological interventions. As a result, much of the regular treatment for PARDS is based upon data from adults or anecdotal experiences from pediatric important care physicians. The applicability of adult information to PARDS has been questioned [5]. Numerous pulmonary-specific treatments consisting of inhaled nitric oxide (iNO), surfactant, or steroids are implemented regardless of the absence of recognized clinical proof in children [6, 7].

- **Diagnostic approaches of PARDS:**

Thoracic Society (ATS) developed brand-new criteria for ARDS, called the Berlin definition; nevertheless, this meaning still did rule out the pediatric population. The Berlin definition brought significant advances such as restricting the time between the insult and the development of ARDS to seven days, enhancing requirements of the nature of infiltrates on chest radiographs, requiring a minimum PEEP level of 5cm H_2O to utilize $PaO_2/FiO2$ ratio worth in defining the severity of hypoxemia, minimizing the requirement for invasive measurements of pulmonary artery occlusion pressure in the lack of cardiac risk factors, and integrating ALI as a moderate subgroup of ARDS based upon the degree of observed hypoxemia (moderate, moderate and severe) (**Table 1**) [13].

Table 1: The Berlin definition of acute respiratory distress syndrome [13]

Criteria	Observation		
Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms		
Radiological imaging	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		
	Requires objective assessment (echocardiography) to exclude other causes of edema as etiological factors		
Oxygenation	**Mild**	**Moderate**	**Severe**
PaO2/FiO2	300 - 201	200 - 101	< 100
PEEP ≥ 5cmH2O	PEEP/CPAP/NIV	PEEP	PEEP
Estimated mortality	~ 25%	~ 35%	~ 45%

The Berlin meaning became the new recommendation for ARDS in grownups; however, like the AECC definition, its applicability in children stayed restricted given that specific qualities of the pediatric population were ruled out [14]. The need for intrusive measurements of arterial oxygenation may lead to an underestimation of the incidence of ARDS in children, and the distinctions in between grownups and children in regards to risk factors, development, pathophysiology and etiology were ruled out in either of the two definitions.

Radiographic Findings in PARDS:

Both AECC and Berlin meanings of ARDS require the existence of bilateral lung infiltrates on chest radiograph (CXR). The intent of the addition of radiographic requirements in the definition of ARDS is to determine patients who have the distinct pathobiology of ARDS, initially explained histopathologically from autopsy [15]. As has actually been recently demonstrated, the medical syndrome of ARDS does not always mean the histologic look of scattered alveolar damag [16]. While the Berlin Definition of ARDS in adults has high sensitivity in identifying diffuse alveolar damage at autopsy, the specificity is only 30 - 40%. The primary argument to include bilateral infiltrates in the definition of ARDS is to allow for discrimination in between localized processes such as lobar pneumonia and scattered inflammatory procedures seen in both lungs, but it is uncertain whether 1) the CXR sensitivity is enough to discover all lung parenchymal inflammation and edema; 2) findings constant with lung parenchymal inflammation and edema need to be radiographically obvious in both lungs; and 3) the existence of bilateral infiltrates on CXR imparts additional risk of bad outcome not otherwise caught with other elements of the meaning of ARDS, such as the degree of hypoxemia. These considerations are particularly important because if CXR findings are maintained for the definition of PARDS, there is big interobserver irregularity in the analysis of the CXRs. It is unclear if this can be decreased in pediatrics by typical training, as proposed by the Berlin meaning of ARDS in adults [17]. Sensitivity of CXR. The utility of plain frontal CXR in the ICU has actually long been a topic of dispute. Numerous studies have actually shown the energy of CXR in determining positions of tubes and catheters and detection of irregularities that may require an intervention, such as a pneumothorax or pericardial or pleural effusion (18,19). Multiple private investigators have shown low level of sensitivity of CXR to identify subtle modifications in atelectasis, edema, and debt consolidation, although protocolized and standardized analyses may have prognostic ramifications [20]. In addition, the existence of lung infiltrates on CXR in ARDS often lags behind the development of hypoxemia [21,22], and almost all biomarker studies in pediatric and adult ARDS demonstrate that the pathophysiologic processes of inflammation, endothelial injury, coagulopathy, and so on.

- **Progression of PARDS:**

The goals of ARDS treatment are to diagnose and treat the underlying cause, to use supportive therapies and to offer adequate oxygenation so regarding minimize secondary lung injury and extrapulmonary issues [2]. For many years, the most significant modification in the treatment of ARDS has involved ventilation techniques. Mechanical ventilation is necessary in treating ARDS in both adults and children. Nevertheless, ventilation itself may add to lung inflammation and injury, barotrauma, volutrauma, atelectrauma and biotrauma, which are characteristic of ventilator-associated lung injury (VALI). The mechanistic understanding of VALI has actually led to the advancement of lung-protective ventilation strategies, a concept highlighted by Amato et al, [23] Although there is a scarceness of medical research studies in children,

such strategies have been certainly shown in large collaborative research studies including adult patients with ARDS, resulting in a limitation of the plateau pressure, using lower tidal volumes and the application of PEEP titrated to the degree of hypoxemia [24]. Information from studies involving adults with ARDS demonstrated that using big tidal volumes (10-12mL/ kg) during mechanical ventilation triggers a distribution of volume to more certified areas, resulting in alveolar over distension in these healthy locations and new alveolar injury [25,26]. Due to an absence of consensus or robust clinical studies examining the treatment of ARDS in children, pediatric intensivists have embraced protective ventilation techniques based on the suggestions for grownups. Badly injured lungs may require a lower tidal volume, whereas less infected lungs or those in the recovery phase of disease might require a greater tidal volume [27]. The advantages of using 6mL/kg in patients with low breathing compliance and high lung injury scores have been well demonstrated [28]. Thus, the underlying procedure and the seriousness of pulmonary disease need to be considered before restricting this value for each patient. The tidal volume embraced in children with ARDS generally is in between 5 - 8mL/kg. It ought to be noted, nevertheless, that unlike what has been observed in research studies involving adult patients, pediatric studies have actually not identified a particular tidal volume cutoff connected with increased or decreased ARDS-related mortality in children [29]. Some studies suggest that utilizing a tidal volume near 10mL/kg might actually be safe in particular children [25,28]. One possible explanation for this divergent observation relative to adult populations might be because of the etiology of ARDS in children and, particularly, to its imprecise meaning. Another possibility is that in retrospective studies, the patients who got greater tidal volumes were those with increased lung compliance and a better prognosis. It is, for that reason, not surprising that considerable variability exists in how children with ARDS are ventilated throughout the world today [30].

- **PARDS Treatment Strategies:**

Scientific management techniques for ALI/ARDS are targeted at enhancing death and morbidity, speeding up recovery with much shorter period of ventilation, and enhancing long-term pulmonary and neurologic function. Although mechanical ventilation is frequently life-saving, decreased lung compliance and elevated airway pressure can lead to ventilator-induced lung injury from volutrauma (ie, alveolar overdistention), atelectrauma (ie, duplicated alveolar collapse and re-expansion), and oxygen toxicity. The total management method to the adult patient with ALI/ARDS focuses on lung-protective ventilation with low tidal volume (VT) and moderate to high PEEP. With enhanced oxygenation being a constant finding throughout several fairly little research studies, and a highly favorable safety profile, Curley et al [31] carried out a reasonably big multicenter RCT of 102 intubated and mechanically ventilated pediatric patients examining the effect of susceptible positioning within 48 hours of satisfying the criteria for acute lung injury (PaO_2/FIO_2 ratio $\leq$ 300 mm Hg). Patients were randomized to either supine or vulnerable positioning. Patients randomized to the prone positioning arm were put prone within 4 hours of randomization and remained so for 20 hours every day. Ninety percent of the patients randomized to the prone arm were considered responders (defined a priori as a $\geq$ 20 mm Hg boost in the PaO_2/FIO_2 ratio or a $\geq$ 10% decline in the OI after a supine to prone turn). The study was stopped at the prepared interim analysis on the basis of futility. The procedure of proning once again appeared to be safe [32], no distinctions could be spotted in between the 2 treatment arms in terms of ventilator-free days, all-cause mortality, the time to recovery from lung injury, the number of organ-failure-free days, cognitive function, or general health. Due to the findings of this extremely well-designed and performed trial [33], the routine use of vulnerable positioning cannot be suggested for the treatment of PARDS. Nevertheless, that trial concentrated on acute lung injury and not specifically on ARDS which reflects a more considerable impairment of oxygenation ($PaO_2/FIO_2 \leq 200$ mm Hg). In addition, given that the publication of that report, data have surfaced that suggest vulnerable placing might be practical for the most seriously hypoxic patients [34,35]. In 2008, Sud et al [34] released a meta-analysis on the effect of susceptible positioning among patients needing mechanical ventilation for acute hypoxemic breathing failure. Thirteen studies were assessed (1,559 patients; pediatric and adult) consisting of 10 research studies that examined death as an outcome. Although prone positioning was again found to enhance oxygenation, and maybe reduce the occurrence of ventilator-associated pneumonia, there was no demonstrable effect on death (risk ratio, 0.96; 95% CI, 0.84-- 1.09; p = 0.52). Offered its sustained enhancement on oxygenation, the authors recommended that it ought to be thought about in those patients with extremely severe hypoxemia. Following up on that work, this exact same group released a meta-analysis of 10 trials consisting of 1,867 individuals (grownups and children) to examine the impact of vulnerable placing on mortality amongst patients with extreme acute hypoxemic respiratory failure specified as a PaO_2/FIO_2 less than 100 mm Hg [35]. They reported that susceptible positioning was associated with reduced death in patients with a PaO_2/FIO_2 less than 100 mm Hg (risk ratio, 0.84; 95% CI, 0.74-- 0.96; p = 0.01; 7 trials, n = 555) but not in patients with a PaO_2/FIO_2 ratio greater than or equal to 100 mm Hg (risk ratio, 1.07; 95% CI, 0.93- 1.22; p = 0.36; 7 trials, n = 1,169). They concluded that susceptible positioning should not be performed regularly in all patients with acute hypoxemic breathing failure but that it need to be thought about for patients with serious hypoxemia.

Nitric Oxide for treatment of PARDS:

Nitric oxide (NO) is synthesized in the vascular endothelium by NO synthase. Its primary impact is relaxation of the smooth muscle by increasing the intracellular cyclic guanosine monophosphate. Theoretically, iNO is an ideal pulmonary vasodilator because of its local and short action. Vasodilation mainly happens in areas that are sufficiently aerated causing blood to shunt away from inadequately ventilated areas [(36)]. Ventilation/perfusion mismatch is among the trademarks of ARDS [(37)]. iNO may therefore be thought about for use in ARDS to minimize ventilation/perfusion inequality by reducing dead-space ventilation and, therefore, enhance oxygenation. The scientific action to iNO has been reported in various (individual) case series, demonstrating a rapid improvement in oxygenation even with a concentration as low as 1 part per million (ppm) [(38)]. Over the past 2 years, three randomized regulated trials (RCTs) have been carried out in children with ARDS [(39)]. The first RCT was carried out by Day et al [(40)], comparing the results of 10 ppm iNO in 10 pediatric patients with acute bilateral lung disease requiring a positive end-expiratory pressure (PEEP) greater than 6 cm H2O and an FIO2 greater than 0.5 for more than 12 hours with 12 control patients. The main finding of this study was an unsustained however immediate improvement in lung vascular resistance and systemic oxygenation specified by the oxygen index (OI). No beneficial impact on mortality was observed although their study was not developed to evaluate mortality. Following this research study, Dobyns et al [(39)] carried out a prospective multicenter placebo-controlled RCT of 108 children more than 1 month old with extreme acute hypoxemic breathing failure (i.e., OI > 15) randomized to iNO 10 ppm (n = 53 children) or control (n = 55). Patients with a genetic heart problem or after cardiac surgical treatment were not consisted of in this research study. Patients were stratified into 5 groups, including pneumonia with or without concomitant chronic lung disease, sepsis, immunodeficiency, and various (e.g., trauma or pulmonary hemorrhage). Especially, nearly half of the patients experienced underlying diseases (i.e., chronic lung disease or immunodeficiency). Although the RCT confirmed the positive result of iNO on oxygenation, almost half of the patients handled with iNO were identified as failures since there was no improvement in the OI. Mortality was comparable in between the 2 groups although the trial was likewise not created to assess this problem. Subgroup analysis exposed a possible advantageous result of iNO in immunocompromised patients and those with serious hypoxemia (i.e., OI > 25) although the little sample size in these analyses precludes the robustness of these findings. The 3rd RCT was carried out by Ibrahim and El-Mohamady [(41)] who randomized 32 children 2 months to 10 years old with extreme ARDS (PaO2/FIO2 ≤ 200 mm Hg, positive inspiratory pressure ≥ 30 cm H2O, and an FIO2 ≥ 0.5) to one of 3 groups: 1) 24 hours of iNO at 5 ppm in the susceptible position, 2) 24 hours of iNO at 5 ppm in the supine position, or 3) no iNO in the vulnerable position. In line with the two other research studies, these private investigators observed a significant improvement in oxygenation but not in mortality. Based upon these three trials, data suggest that although iNO improves oxygenation in PARDS, it does not favorably affect patient outcomes. This conclusion is enhanced by the outcome of a recent Cochrane analysis of 604 children and grownups with ARDS [(42)].

4. CONCLUSION

This pediatric-specific definition for acute respiratory distress syndrome builds on the adult-based Berlin Definition, however has been modified to represent differences between grownups and children with acute breathing distress syndrome. Numerous proof utilized this definition for future examinations and clinical care of children with pediatric acute breathing distress syndrome and motivate external validation. Medicinal treatment of PARDS remains challenging due to the fact that the amount of scientific proof is disappointingly low. Although the possible helpful impacts of exogenous surfactant and iNO have been studied to a specific degree, there is no substantial information on glucocorticoids or other ancillary treatment methods. With the exception of susceptible positioning, proposed nonpharmacological therapies are equally unproven with little vigorous screening to support their usage.

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