KESANS : International Journal Of Health and Science
e-ISSN : 2808-7178, p-ISSN : 2808-7380
Web : http://kesans.rifainstitute.com/index.php/kesans/index

Pediatric Acute Respiratory Distress Syndrome (PARDS) On Pediatric COVID-19 Patients

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Article Information
Accepted : **10 Nov 2021**
Submitted : **13 Nov 2021**
Online Publish : **20 Nov 2021**

Abstract
Background: *At the end of 2019, there was a pandemic happening in the world, called the novel Coronavirus disease-19 (COVID-19). Various spectrums of disease from COVID-19, one of which is ARDS. The incidence of COVID-19 in children is not as much as in adults. However, in children under one year of age it can get worse. The main characteristic of worsening infection is the occurrence of ARDS. Objective: To find out the best treatment for PARDS in COVID-19 patients. Method: The writing of this article uses various sources from scientific journals to government guidelines and related institutions. Search articles using the keywords "Acute Respiratory Distress Syndrome", "ARDS", "Pediatric Respiratory Distress Syndrome", "PARDS", and "PARDS on COVID-19" Result and Discussion: PARDS was defined based on PALICC in 2015. Pathophysiology of PARDS in COVID-19 patients is still unclear. However, there is a theory that explains the way SARS-Cov-2 enters cells, namely through membrane fusion, giving rise to ARDS. The difference in handling PARDS for COVID-19 patients is that the handling technique is more alert to the risk of aerosols. Conclusions: There are differences in the handling of PARDS for COVID-19 patients in the technique by reducing the risk of virus transmission by preventing leakage when using a ventilator and using a bacterial/virus filter, as well as rescuers and staff using complete PPE during the procedure.*

Keywords : PARDS; COVID-19; Treatment;

Introduction

In the end of 2019, a pandemic was spreading worldwide called novel Coronavirus disease-19 (COVID-19). It is caused by severe acute respiratory syndrome coronavirus-2 (SARS-Cov-2) that starts from Wuhan, China. This disease mainly infects adults and elderly with co-morbidities. It less commonly infects children. The typical symptoms are cough and pharyngeal erythema. Additional symptoms include fever, diarrhea, fatigue, rhinorrhea, and omitting (Pandit, Gupta and Sharma, 2020; Patel *et al.*, 2020; Venturini *et al.*, 2020). Covid-19 causes spectrum of illness such as asymptomatic cases to mild upper respiratory illness (URI) like symptoms, severe pneumonia, ARDS, multi-organ involvement, hyper-inflammatory syndromes like Kawasaki Disease (KD), KD shock syndrome, Toxic Shock Syndrome, and Macrophage activation Syndrome (Pandit, Gupta and Sharma, 2020).

Based on a case series of 2143 pediatric patients in the China Center In the Disease Control and Prevention (CDC) database, laboratory tests confirmed 731 cases, 94 asymptomatic cases (4.4%), 1091 mild symptoms (50.9%), and 831 moderate symptoms (38.8%). Only 125 (5.8%) patients developed severe or critical illness (Panzeri Carlotti *et al.*, 2020). Even though the children who infected by SARS-Cov-2 prevalence is low than adults, but without more systematic testing for children, asymptomatic children as part of contact tracing, or seroprevalence studies, makes the true burden of pediatric SARS-Cov-2 is remain unclear (National Institutes of Health, 2021).

Although those young children who are younger than one years old may experience greater disease severity (Kneyber *et al.*, 2020). The main characteristic of the critical infection is the occurrence of ARDS with hypoxemic acute respiratory distress and bilateral pulmonary infiltrates that are not explained by cardiac dysfunction or fluid overload (Panzeri Carlotti *et al.*, 2020).

Method

The writing of this article uses various sources from scientific journals to government guidelines and related agencies. Access these sources through online portals such as the National Center for Biotechnology Information / NCBI (ncbi.nlm.nih.gov), pubmed. In addition, journal searches were carried out through Google Scholar. Search articles using the keywords "*Acute Respiratory Distress Syndrome", "ARDS", "Pediatric Respiratory Distress Syndrome", "PARDS", and "PARDS on COVID-19".*

Research Result

Definition of Pediatric Acute Respiratory Distress Syndrome

At the 1994 US-Europe Consensus Conference (AECC) and the subsequent 2012 Berlin Conference, the characteristics of acute lung injury (ALI) or ARDS in children were based on the definition of adults. The Pediatric Acute Lung Injury Consensus Conference (PALICC) developed a new definition and guidelines for pediatric acute respiratory distress syndrome (PARDS) after the recognition of the differences between ARDS in adults and children (Medina, Modesto and Villar-guerra, 2016; Orloff, Turner and Rehder, 2019). In 2015, PALICC had officially developed pediatric-specific definitions for acute distress syndrome (Nayak, Roth and Mcgavern, 2015). The criteria are explained on Figure 1.

Age	Exclude patients with peri-natal related lung disease			
Timing	Within 7 days of known clinical insult			
Origin of Edema	Respiratory failure not fully explained by cardiac failure or fluid overload			
Chest Imaging	Chest imaging findings of new infiltrate(s) consistent with acute pulmonary parenchymal disease			
Oxygenation	**Non Invasive mechanical ventilation**	**Invasive mechanical ventilation**		
	PARDS (No severity stratification)	Mild	Moderate	Severe
	Full face-mask bi-level ventilation or CPAP ≥5 cm H_20 [2] PF ratio ≤ 300 SF ratio ≤ 264 [1]	4 ≤ OI < 8 5 ≤ OSI < 7.5[1]	8 ≤ OI < 16 7.5 ≤ OSI < 12.3[1]	OI ≥ 16 OSI ≥ 12.3[1]
Special Populations				
Cyanotic Heart Disease	Standard Criteria above for age, timing, origin of edema and chest imaging with an acute deterioration in oxygenation not explained by underlying cardiac disease. [3]			
Chronic Lung Disease	Standard Criteria above for age, timing, and origin of edema with chest imaging consistent with new infiltrate and acute deterioration in oxygenation from baseline which meet oxygenation criteria above.[3]			
Left Ventricular dysfunction	Standard Criteria for age, timing and origin of edema with chest imaging changes consistent with new infiltrate and acute deterioration in oxygenation which meet criteria above not explained by left ventricular dysfunction.			

Figure 1. Pediatric Acute Respiratory Distress Syndrome Definition

OI = oxygenation index, OSI = oxygen saturation index. Use Pao2-based metrics when available. If Pao2 is not available, disable Fio2 to keep Spo2 ≤ 97% to calculate OSI or oxygen saturation/Fio2 ratio. For non-intubated patients receiving supplemental oxygen or noninvasive nasal ventilation. The acute respiratory distress syndrome severity group stratified by OI or OSI should not be used in children with chronic lung disease or children with cyanotic congenital heart disease who usually receive invasive mechanical ventilation. OI = (Fio_2 × mean airway pressure × 100)/Pao_2. OSI = (Fio_2 × mean airway pressure × 100)/Spo_2.

Pathogenesis

The exact pathogenesis in children is unknown. However, there are mechanism that explain as the pathogenesis of ARDS in children. The studies of entry mechanism of SARS-CoV-2 virus are various, one of them is by membrane fusion that are facilitated by ACE-2 receptors which interacts with the spike protein. In cytoplasm, the viral RNA genome is released and translated into 2 polyproteins and structural protein which trigger the viral replication. Then, it leads to viremia. Symptom that involves many organs may present, because ACE-2 receptor are also expresses on other organs. In adult cases, lymphopenia occur with the mark of decreases in CD4+ and CD8+. However, on a large case series in children showed only 3.5% children presented with lymphopenia. Major histocompatibility complex (MHC-1) present the viral antigenic peptides and then virus-specific cytotoxic T lymphocytes (CTLs) recognize it. HLA stimulate virus-specific B and T cells. There are several HLA polymorphisms that susceptibility to SARS-Cov-2 infection. At the end of week 12, SARS-specific IgM antibodies disappear. On the other hand, the SARS-specific IgG antibodies, primarily are S-specific and N-specific antibodies, can last for long time. Cellular damage and antibody dependent enhancement (ADE) are induced by the rapid viral replication which leads to aggressive inflammation. Activation of Cytotoxic T cells and other cells leads to exaggerated inflammatory response which release huge amounts of pro-inflammatory cytokines and chemokines affected or immune cells presenting interstitial inflammation, exudates, and severe pneumonitis. Inflammatory responses are accelerating due to the interleukin which expressed by the result of CD14+ and CD16+ circulation. These circulation occurs because of the pathological T cells release granulocyte monocyte colony stimulating factor (GM-CSF). From the violent cytokines storm triggers a systemic inflammatory response causing multi organ involvement, ARDS, and shock (Pandit, Gupta and Sharma, 2020; Jurado Hernández and Álvarez Orozco, 2021).

Treatment

The current best therapy of PARDS on pediatric patients non covid-19 are summarize on the table 1 (Orloff, Turner and Rehder, 2019; Saguil and Fargo, 2020) :

Table 1. Therapy of PARDS as PALICC recommendation

Therapy	PALICC recommendation
Lung-Protective ventilation	Low tidal volumes 3–6 mL/kg if poor compliance 5-8 mL/kg if preserved compliance $P_{plateau} \leq 28$cm H2O Permissive hypoxemia Mild PARDS : 92-97% Severe PARDS : 88-92% and PEEP>10cmH2O Permissive hypercapnia Moderate/severe : pH 7.15-7.30 with exception for certain populations.
Fluid Management	After initial resuscitation, use a goal-directed fluid management protocol to maintain intravascular volume while minimizing fluid overload
Sedation	Targeted sedation to ensure patients can tolerate MV to optimize oxygen delivery/consumption. Pain and sedation scales to titrate sedation per a goal-directed protocol.
NMB	Consider NMB if sedation alone is inadequate to achieve effective MV. Target minimal effective dose.
HFOV	Consider in patients with moderate to severe PARDS and $P_{plateau}$ >28cm H2O
Prone Positioning	Consider it as an option in cases of severe PARDS. Cannot recommend its use as a routine therapy given current pediatric data.
Recruitment maneuvers	Careful incremental titration of PEEP
Nitric oxide	Consider in patients with known pulmonary hypertension, severe right ventricular dysfunction, or as bridge to ECMO. Cannot recommend routine use of iNO.

ECMO	Consider ECMO in severe PARDS When lung-protective strategies result in inadequate gas exchange, after serial evaluations demonstrate deteriorating trend. Disease process must be deemed reversible or lung transplant a suitable treatment.

ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; HFOV, high-frequency oscillatory ventilation; ICU, intensive care unit; iNO, inhaled Nitric Oxide; MV, mechanical ventilation; NMB, neuromuscular blockade; PEEP, positive-end-expiratory pressure.

In the case of PARDS, high-quality data about the treatments are lacking, which make the understanding of which therapies is the best. Based on a survey from 59 centers across 12 countries found that adjunctive therapies are commonly used. More than 80% says they would use iNO, three-quarter would prone patients, and around half would consider to support the efficacy of these adjuncts (Orloff, Turner and Rehder, 2019).

Due to pediatric data is lacking, the panel recommends to use the treatment from adults with COVID-19 and published it before they recommend using it for clinical pediatric practice (Kneyber *et al.*, 2020).

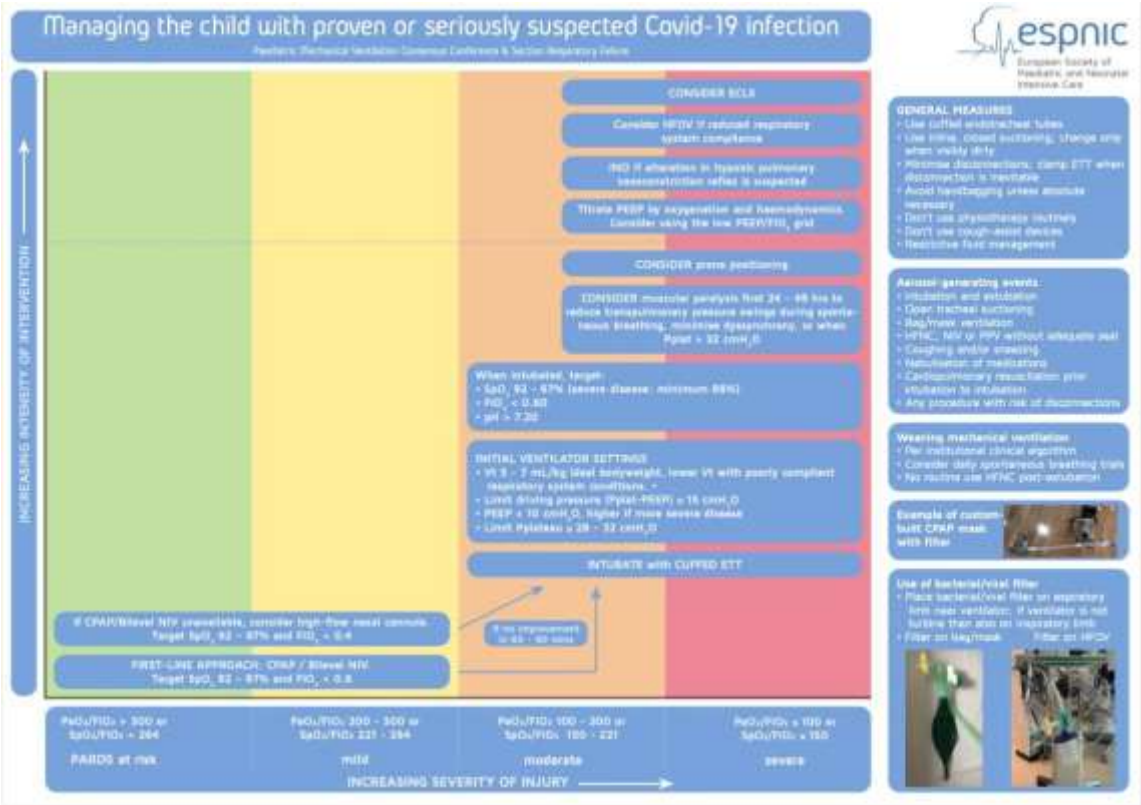

Figure 2. Pediatric Acute Respiratory Distress Syndrome on Pediatric COVID-19 Patients

Based on PEMVECC and PALICC, the expert group recommends monitoring the SpO2/FiO2 ratio and oxygenation saturation index (OSI) of noninvasive respiratory patients or oxygenation index (OI) of invasively ventilated children for severity classification. The FiO2 level should be guided by SpO2 ≤ 97% in order to effectively measure the SpO2/FiO2 ratio and OSI (Kneyber *et al.*, 2020). The explanations are summarized in the diagram on Figure 2.

Recommendation for the first line is Continuous Positive Airway Pressure (CPAP) or Bi-Level Non-Invasive Ventilation (NIV) rather than high-flow nasal cannula (HFNC), in condition the patient with SpO2/FiO2 > 221 and < 264. If the patient's condition is SpO_2/FiO_2 < 221, intubation should be assembled. For NIV, using certified helmet is suggested, to minimise the leak; if not available then non-vented oro-nasal or full-face mask, a double limb circuit (or a single limb with filter before the leak site) and appropriate bacterial/viral filters should be used to prevent infection. If there is a leak, CPAP/NIV increased risk of aerosol contamination. Equipment for personal protection should be strictly done when managing patients with suspected or confirmed COVID-19. If there is no improvement in oxygenation (target SpO2 92 – 97% and FiO < 0.6) within 60 – 90 minutes then intubation should be done. If CPAP/NIV is not available, consider to use High-flow Nasal Cannula (HFNC) for patients with SpO2/FiO2 > 264 (FiO2 < 35 – 40). On HFNC is essential to Careful monitoring the patients. After 30 – 60 minutes, if there is no improvement in oxygenation (target for HFNC treatment success: SpO2 92 – 97% with FiO < 0.4), escalation of therapy (i.e. non-invasive ventilation or intubation) should not be delayed. For intubation, the panel recommends to performed it by an expert in a closed environment with a minimal staff around. When performed intubation, should be minimising the risk of virus transmission by using the bacterial/viral filters on bag/mask and prevent leak on the seal of the mask around the mouth with "two-person technique". The panel recommends the use of cuffed endotracheal tubes, inflating the cuff immediately after intubation before verification of the position of the tube by end-tidal CO2, chest X-ray, auscul- tation or ultrasound exam (Kneyber *et al.*, 2020).

For the initial ventilator settings, the panel recommends applying lung protective ventilation along with today recommendation (Vt-exp 5-7 mL/kg ideal bodyweight (Pplat) <28-32 cmH2O, driving pressure ≤ 15 cmH2O) per PALICC recommendation. Initial PEEP should be around 10 cmH2O and might need for further increase, for which best but limited pediatric evidence based guidance can be given by the ARDS Network PEEP/FiO grid. The panel recommends allowing for permissive hypercapnia, thereby accepting pH > 7.20 unless specific clinical indications dictate otherwise (Kneyber *et al.*, 2020).

Early use of neuromuscular blocking agents (NMBA) for 24 – 48 hours in moderate-to-severe PARDS (i.e. PaO2/ FiO2 < 150; OI ≥ 12; OSI ≥ 10) is recommended. The intention on using NMBA is to avoid spontaneous breathing at high

transpulmonary pressures, minimising persistent ventilator dyssynchrony, need for ongoing deep sedation, prone positioning, or avoid high plateau pressures. There no recommendation on threshold of plateau pressures when to start NMBA. If PaO2/FiO2 ≥ 150; OI < 12; OSI < 10, NMBAs can be discontinued (Kneyber *et al.*, 2020).

Early and prolonged prone positioning in moderate-to-severe PARDS (i.e. PaO2/FiO2 < 150; OI ≥ 12; OSI ≥ 10) is recommended. Patients can practice it vary between 12 – 18 hrs per day with the patient in prone position. In the disease trajectory, consideration of Prolonged prone positioning (>24 hrs) may be done early. If PaO2/FiO2 ≥ 150; OI < 12; OSI < 10, prone positioning can be discontinued. Special care should be taken when prone positioning the patient to avoid circuit / ETT disconnection. A bolus of NMBA before turning the patient might be considered (Kneyber *et al.*, 2020).

Escalating therapies can be considered when (refractory) hypoxemia (define by PaO2/FiO2 < 150; OI≥12;OSI≥10 and/or FiO2> 0.6) is present. The therapies continue with titrating PEEP or best recruitment maneuver. It is important to balancing oxygenation and haemodynamic when titrating PEEP. If an alteration in the hypoxic pulmonary vasoconstriction reflex is presumed (i.e. when there is no improvement in oxygenation despite all other measures), the panel recommends a nitric-oxide trial, especially on COVID-19 cases with normal lung compliance. However, the use of corticosteroid is not recommended. For refractory hypoxemia, it is reasonable to consider of using HFOV in COVID-19 induced ARDS with reduced respiratory system/lung compliance using a staircase titration of the mean airway pressure (mPaw). In using it, need should be cautiously consider if there is little or no experience with this modality. If refractory hypoxaemia persists despite all measures used, the using extracorporeal membrane oxygenation (ECMO) is accepted according to the panel. In the decision-making, there are influences of human resources and equipment that limited on availability. In pediatric COVID-19 patients, restrictive fluid strategy is recommended (Kneyber *et al.*, 2020).

Discussion

In PARDS, the main criteria is acute onset, a known clinical insult, and chest imaging supporting new onset pulmonary parenchymal disease, and acute deterioration in oxygenation from baseline (Nayak, Roth and Mcgavern, 2015). Studies related to the pathophysiology of PARDS is still lacking (Nayak, Roth and Mcgavern, 2015; Pandit, Gupta and Sharma, 2020). It needs more studies to provide the information about pathophysiology of PARDS in the future. Due to pediatric data relates to the treatment of COVID-19 patients is lacking. The panel recommends to use the treatment from adults with COVID-19 and published it before they recommend using it for clinical pediatric practice (Kneyber *et al.*, 2020). Basically, pediatric treatment focuses on supportive care by respiratory support with supplemental oxygen and invasive or non-invasive ventilation, fluid and electrolyte support, judicious use of empiric antibiotics as

indicated for community-acquired or healthcare-associated pneumonia, systematic clinical follow-up, and laboratory monitoring. Special attention must be given to adequate nutritional support and temperature control (Jurado Hernández and Álvarez Orozco, 2021). Management of ARDS in adults is largely focused on supportive management, lung-protective ventilation and minimizing iatrogenic forms of lung injury, with extracorporeal life support as an option for patients who continue to deteriorate despite these supportive therapies (Bakhtiar and Maranatha, 2018; Fernando *et al.*, 2021).

According to a research that held in New York, it said that as suggested from PALICC to do lung-protective strategy of using a low tidal volume and limiting the plateau pressure seem to be effective in COVID-19 ARDS (Derespina *et al.*, 2020). There are slightly differences between the therapy of PARDS on general patient and covid-19 patient. In pandemic condition, the more concern in doing the therapy especially on the action that may produce aerosol since COVID-19 are spreading through droplet. The action that may produce aerosol such as intubation and extubation, open suctioning, ventilation with mask and bag, CPAP/NIV, HPNC and HFOV which not closed/installed properly, cough or sneeze, nebulisation, CPR before and while intubation, and every procedure in detachment the ventilator (IDAI, 2020; Kneyber *et al.*, 2020).

Conclusion

Definition of PARDS according to PALICC is characterized by acute onset, a known clinical insult, and chest imaging supporting new onset pulmonary parenchymal disease, and acute deterioration in oxygenation from baseline. Pathophysiology of PARDS associated with COVID-19 is paucity. However, there is a theory that explain about it which activation of Cytotoxic T cells and other cells leads to exaggerated inflammatory response which release huge amounts of pro-inflammatory cytokines and chemokines affected or immune cells presenting interstitial inflammation, exudates, and severe pneumonitis, which can lead to ARDS. Management of PARDS on COVID-19 patients are adapted from ARDS on adult patients then apply it on daily clinical pediatric practice to therapy of PARDS on general patient and covid-19 patient, there are slightly differences. In conclusion, during the pandemic, therapy should more concern on doing the therapy especially on the action which may produce aerosol since COVID-19 are spreading through droplet. By preventing leaks in using ventilator, it can lower the risk of spreading. It can also be done by using the bacteria/virus filter and helper and staff wear protection equipment strictly

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