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Acute Respiratory Distress Syndrome Management in Pediatric Intensive Care Units in Turkey: A Prospective Survey

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What is already known on this topic?

- *The complexity of pediatric acute respiratory distress syndrome (pARDS) makes it particularly difficult to establish commonly accepted treatment practices in children. It is well-known that the management of pARDS may demonstrate differences even in the same pediatric intensive care unit. Therefore, the treatment and management of ARDS in compliance with international guidelines would be highly helpful.*

What this study adds on this topic?

- *Current mechanical ventilation and non-ventilation treatment strategies in pARDS in Turkey are largely compliant with international practices.*
- *We found that steroid and surfactant use are higher in most of the participating pediatric intensive care units (PICUs) compared to those reported in international studies.*
- *Finally, the study revealed that the use of cuffed endotracheal tubes was more common in closed model PICUs.*

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ABSTRACT

Objective: This study aimed to explore the compliance of management strategies for pediatric acute respiratory distress syndrome in pediatric intensive care units in Turkey with current guidelines.

Materials and Methods: This is a cross-sectional, prospective survey study. We delivered the survey, consisting of questions on topics in the relevant literature on acute respiratory distress syndrome management in children (1 month–18 years), to the heads/staff of the 100 units via email or phone.

Results: In total, 51 (51%) out of 100 targeted pediatric intensive care units responded to the survey. We found out that 17 (33%) units comply with no acute respiratory distress syndrome guideline, while 65% frequently utilize cuffed endotracheal tubes. The majority of the units (86%) achieve their mechanical ventilation targets with the help of pressure control modes. Besides, steroid and surfactant use are present in 47% and 45% of the units, respectively, while 16% and 38% of the units use inhaled nitric oxide and high-frequency oscillatory ventilation, respectively.

Conclusion: Lung-protective ventilation strategies preventing ventilator-associated lung injury are explicit in all responding units. The present survey revealed that current mechanical ventilation and non-ventilation treatment strategies in pediatric ARDS in Turkey are relatively uniform and largely consistent with international practices.

Keywords: Lung injury, mechanical ventilation, non-invasive support, pediatric acute respiratory distress syndrome, pediatrics, pediatric intensive care, ventilatory strategies

INTRODUCTION

Pediatric acute respiratory distress syndrome (pARDS) is one of the most life-threatening conditions, such as acute pulmonary inflammation, alveolar edema, and hypoxemia, often leading to respiratory failure.[1] Thus, pARDS requires following up-to-date guidelines and expert management.

A wide range of treatment strategies has been introduced since the very first diagnosis of lung injury. (High □ low tidal volume (TV), low □ high positive end-expiratory pressure (PEEP), and lung-protective strategies, etc.) Fortunately, these practices were found to reduce mortality in adults, and adult experiences have been taken as a basis for children.[2-5] Yet, it is well-known that pARDS management may demonstrate differences even in the same pediatric intensive care unit.[6] Therefore, the treatment and management of ARDS in compliance with international guidelines would be highly helpful. On the other hand, the complexity of pARDS makes it particularly difficult to establish commonly accepted treatment practices in children. Although there are similarities in the pathophysiology of ARDS in adults and children,

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pediatric-specific comorbidities, differences in clinical practice, and contrasts with adult outcomes clearly indicate the need for a definition of ARDS for pediatric patients.[7] Compared with previous definitions, the Pediatric Acute Lung Injury Consensus Conference (PALICC) criteria for pARDS identified more pARDS cases, and patients had lower rates of complications, severe ARDS, and overall mortality.[8,9]

The incidence of ARDS in children younger than 16 years is less than 3 cases per 100 000.[10] Yet, clinical trials on pARDS also require the long-term commitment of multiple centers to conduct a randomized, controlled trial (RCT) of acceptable quality. Therefore, it is of utmost importance to increase our knowledge on pARDS with mortality rates of 8%-35% and improve its treatment.[10-12]

Ultimately, the present study aimed to investigate the management practices for pediatric ARDS in pediatric intensive care units in Turkey and determine their compliance with international practices.

MATERIALS AND METHODS

Design and Population: Upon the ethical approval of Selçuk University, School of Medicine, Clinical Research Ethics Committee (Approval no: 2018-107), we requested a list of licensed levels 2 and 3 pediatric intensive care units from the Turkish Ministry of Health. As of April 2018, the list included a total of 111 units, among which some did not admit patients, and only 4 provided postoperative service to pediatric cardiac surgery patients. Hence, we delivered the survey to the heads/staff of the remaining 100 units via email or phone. The survey consisted of items on the issues in the relevant literature.[5,6] We performed all stages of the study in accordance with the revised version of the World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects 2013.

Definition of pARDS: Unlike previous ARDS definitions, the definition in the PALICC simplifies the radiological criteria and recommends the use of pulse oximetry measurements when routine arterial blood gas measurement is not practiced and PaO_2 is not available.[13] It also includes the use of oxygenation index and oxygenation saturation index instead of PaO_2/FiO_2 (P/F ratio) to classify ARDS severity. Furthermore, the PALICC definition establishes specific criteria — missing in the previous ones — to define ARDS in children with chronic lung and cyanotic heart diseases. In addition, children with lung injuries that are unique to the perinatal period are excluded, although the PALICC criteria do not identify an upper age limit .[13]

Development and Content of the Survey: The survey inquires about the use of different ventilation modes, pressure and volume settings, inhaled nitric oxide (iNO), prone positioning, high-frequency oscillatory ventilation (HFOV), extracorporeal membrane oxygenation (ECMO), and other ancillary methods. Acute lung injury (ALI), including acute respiratory distress syndrome (ARDS), is a complex syndrome with high morbidity and mortality caused by various pathological injuries, including pulmonary and extrapulmonary conditions, in critically ill patients.[14] Since ALI was excluded from the Berlin Definition in 2012, pARDS comprised both ALI and ARDS in the present study based on the PALICC criteria.[11] Patients of 1 month to 18 years are treated in pediatric intensive care units in Turkey; thus, we specified the questions in the survey regarding the management of pARDS in patients in this age range.

If the patients hospitalized in an intensive care unit are managed by the faculty members of the department who hospitalizes the patients and if the pediatric intensive care specialist acts only as an administrative manager, this is defined as an open unit. In the closed unit, all patient follow-up and administrative work are carried out by a pediatric intensive care specialist. When necessary, consultation is requested from the department that hospitalized the patient.

Statistical Analysis

We presented categorical data in absolute numbers and percentages. We performed the analyses on The Statistical Package for Social Sciences version 21.0 software (IBM Corp.; Armonk, NY, USA).

RESULTS

In the present study, 51 PICUs responded to our call among 111 in the list above. Twenty (40%) of the units operate within university (state) hospitals, 18 (36%) are within training and research hospitals, and 12 (24%) admit patients within state hospitals.

The average number of pARDS cases presenting to these centers range from 1 to 5 patients per month at the rate of 94.2%. Seventeen (33%) of the PICUs reported not complying with any guideline recommendations in the standard treatment of pARDS patients. A pediatric intensivist is responsible for inpatient cases in 22 (43%) PICUs, while a general pediatric specialist is in charge of the remaining units (57%).

We found that cuffed endotracheal tubes (ETT) are primarily used in all closed model PICUs (33; 64.7%), whereas it is not the case for 4 of 18 (7.8%) where PICUs are managed as an open model.

Pressure controlled/pressure support (PC/PS) is the most common ventilation mode reported by 37 (72.5%) PICUs, while 7 (13.7%) utilize volume-controlled (VC) ventilation. Only 1 unit (2%) regularly uses neurally adjusted ventilatory assist mode, whereas it is not the case for the remaining 50 (98%).

While inhaled NO (iNO) and HFOV are present in 8 (16%) and 19 (38%) PICUs, respectively, ECMO is only available in 18 (35%) (Table 1). Nineteen (38%) PICUs generally utilize HFOV as the

Table 1. The Use of Ancillary Treatment Strategies

Intervention	n	%
ECMO	18	35
HFOV	19	38
iNO	8	16
NAVA	1	2
Prone position	38	75
Steroids	24	47
Surfactant	23	45
Sedation/analgesia	50	100

ECMO, extracorporeal membrane oxygenation; HFOV, high-frequency oscillation ventilation; iNO, inhaled nitric oxide; NAVA, neurally adjusted ventilator assist.

Table 2. Mechanical Ventilation Parameters

PEEP		Tidal Volume		Peak Pressure	
Maximum Value (cmH_2O)	PICU, n (%)	Maximum Value (cmH_2O)	PICU, n (%)	Maximum Value (cmH_2O)	PICU, n (%)
<10	35 (69)	<4	4 (8)	<30	4 (8)
10-15	9 (17)	4-6	33 (64)	30-35	42 (82)
16-20	4 (8)	7-8	12 (24)	>35	5 (10)
21-25	1 (2)	9-10	1 (2)		
>25	2 (4)	>10	1 (2)		

PEEP, positive end-expiratory pressure; PICU, pediatric intensive care unit.

first alternative when conventional ventilation is insufficient. Besides, while 24 (47%) PICUs use steroids, 23 (45%) utilize surfactants. In 38 (75%) PICUs, prone positioning is preferred in the treatment of pARDS patients.

Maximum PEEP, TV, and peak pressure values prior to the change of treatment strategies are shown in Table 2. Seven (14%) intensive care units (ICUs) use a maximum PEEP value of >15 cmH_2O in all children regardless of age, while 35 (69%) prefer it of <10 cmH_2O during treatments. Two ICUs responded to the related survey question as "No Limit."

Forty-two (82.4%) ICUs use the same maximum peak pressure value in all children regardless of age, while 5 (9.8%) prefer higher maximum values in children. The most common maximum peak pressure value reported by 42 (82.4%) PICUs ranges from 30 to 35 cmH_2O. Five (17%) ICUs use a maximum peak pressure value < 30 cmH_2O, and 1 reporting "No Limit" sets the maximum value of >35 cmH_2O.

Tidal volume values in ventilation are kept between 4 and 6 mL/kg in 33 (65%) PICUs, >8 mL/kg in 2 (4%) PICUs, and <4 mL/kg in 4 (8%) PICUs. Besides, 12 (25%) PICUs keep it between 6 and 8 mL/kg at all times. In the present study, we determined that permissive hypercapnia and hypoxemia are used in 78.4% of the PICUs.

DISCUSSION

Although it is not an absolute method or consensus in pARDS management worldwide, even within the same units, the present study suggested that current management strategies in pARDS in PICUs in Turkey are relatively uniform and largely consistent with international practices. We found out that 33% of the PICUs do not refer to any guidelines for ventilation. Our findings also showed that the predominant ventilation mode is PC/PS, that the target TV value generally ranges between 4 and 8 mL/kg, and that the most frequently reported maximum peak pressure value is between 30 and 35 cmH_2O. Yet, we discovered that steroid and surfactant use are higher compared to international practices. Finally, the use of cuffed ETTs is more common in closed model PICUs.

The study by Santschi et al.[1] also known as the Pediatric Acute Lung Injury Mechanical Ventilation (PALIVE) study covering 59 PICUs in 12 countries in North America and Europe, aimed to determine the management strategies in pARDS. The recommendations published in 2017 aimed to adopt a consistency in the use of mechanical ventilation in children and can now be proposed as a standard-of-care applicable in routine clinical practices and ARDS research.[15]

In terms of mechanical ventilation in the management of pARDS cases, it was previously reported that 43% of the units use PC mode, 28.2% utilize pressure-regulated VC mode, and 26.6% prefer VC mode . A study in Italy reported that PC is used in 44% and pressure-regulated VC is preferred in 37% of the units.[16] In Brazil, while no unit uses VC, only 1 unit prefers volume-targeted pressure control mode and all other PICUs utilize pressure modes.[17] In Nordic countries, PC/PS ventilation mode is prevalently adopted in PICUs (89%).[6] Although the relevant literature does not offer satisfactory evidence to recommend 1 ventilation mode over another,[15,18] our study revealed that PC/PS is the most common ventilation mode reported by 37 (72.5%) of the PICUs in Turkey.

In the present study, we found that 45 (90%) of the ICUs use target TV between 4 and 8 mL/kg, while only 2 (4%) use it >8 mL/kg. These findings are consistent with the mean TV value (8.3 ± 3.3 mL/kg) that was reported in the PALIVE study. In the literature, target TV use was reported to be 8.0 Ml/kg in Australian and New Zealand PICUs, 8.1 mL/kg in a Canadian group,[10] and 7.1 ± 1.5 mL/kg in a Finnish group. In Nordic countries, 67% of the PICUs use target TV of 6-8mL/kg.[5,6] Santschi et al also indicated that most pediatric intensivists use TV in the range of 5-8 mL/kg.[1] Such findings also overlap the Paediatric Mechanical Ventilation Consensus Conference (PEMVECC) recommendations for targeting physiological TV and avoiding TV >10 mL/kg at ideal body weight.[15]

Adult-oriented guidelines for mechanical ventilation strategies in ARDS recommend maintaining plateau pressure (Pplat) ≤30 cmH_2O.[19] In the absence of transpulmonary pressure measurements, PEMVECC strongly recommends limiting Pplat ≤ 28 cmH_2O and ≤29-32 cmH_2O in the presence of restrictive lung disease.[15] In the present survey, we discovered that the maximum acceptable peak inspiratory pressure (PIP) prior to a change to ventilation strategy is in the range of 30-35 cmH_2O in 42 (82.4%) of the PICUs, similar to the results in the study by Santschi et al.[1] In this regard, both Pplat and PIP can be used as a high-pressure limit, but measuring Pplat may be difficult when using uncuffed ETT.

The present study demonstrated that 35 (69%) PICUs apply a maximum PEEP of 10 cmH_2O and 9 (17%) adopt it in the range of 10-15 cmH_2O. There are only 3 (6%) PICUs applying PEEP > 20 cmH_2O. The same maximum PEEP values were also reported by Santschi et al in Nordic countries and Brazil.[1,6,17] Although PEEP is recommended for respiratory support to prevent alveolar collapse, there are no universal recommendations for PEEP values in pediatric ARDS management.[15] Besides, the current research trend focuses on "higher PEEP and lower TV (peak pressure)," as Khemani and Newth argued.[11,13,17-21]

The use of cuffed ETTs reduces the risk of bronchoaspiration by providing better tracheal sealing and the risk of stridor following extubation . It also diminishes the need to replace the tube due to air leakage, provides more reliable measurements of lung capacity and volume, optimizes the use of capnography, and

finally, prevents an increase in morbidity in children with prolonged mechanical ventilation.[22,23] The PALIVE study reported the use of cuffed ETT in 62.9% of patients.[24] In our research, we found that 47 (96%) centers use cuffed ETT. Considering those not using cuffed ETT, we discovered that they operate as open model intensive care units. Clinics other than PICUs undertake the inpatient management as open model PICUs, which, unfortunately, suggests that the management is not compliant with the current guidelines.

The PALIVE study indicated that iNO is used for 12.7% of children with ARDS.[24] In Nordic countries, almost every unit has access to iNO.[6] Although some studies reported limited benefits of iNO for mechanical ventilation time or survival,[25] iNO can be used as rescue therapy in severe respiratory failure, which may improve oxygenation.[36] In our study, we determined that there is an iNO option in only 8 units (6%), but the success of the adopted method is not questioned over ventilation and assistive techniques.

High-frequency oscillatory ventilation is often used when conventional ventilation fails. Low TVs with HFOV are theoretically the ideal lung-protective ventilation approach to be used in ARDS. The safety and efficacy of HFOV were previously questioned following The Oscillation for Acute Respiratory Distress Syndrome (ARDS) Treated Early (OSCILLATE) trial study in adult ARDS and a retrospective observational pediatric study.[27] A recent study in Australia found survival to discharge to be 75% for the entire study group receiving HFOV and 2-year survival to be 62% for the entire cohort.[28] Another study reported that the HFOV approach is applicable in pediatric patients and does not impair gas exchange or hemodynamics regardless of age or pARDS severity.[29] When it comes to our study, we found that 19 (38%) units use HFOV, but its success is still contradictory in these units. Moreover, we have insufficient evidence to conclude that HFOV reduces mortality or long-term morbidity in pARDS.[15]

In the present study, steroid use in pARDS was reported by 24 (47%) of the ICUs, which was significantly higher than that reported in the PALIVE study[24] but considerably lower than in the Nordic countries.[6] The abnormal inflammation that occurs in ARDS has sparked interest in the use of steroids as anti-inflammatory therapy.[30] Yet, a systematic review of adult ARDS studies reveals mixed results.[31] Two meta-analyses involving studies of different doses of corticosteroids in adults showed that corticosteroids use probably worsens outcomes.[32] However, another meta-analysis reviewing the use of only low-dose corticosteroids (methylprednisolone: 0.5-2.5 mg/kg per day) reported improved morbidity and mortality outcomes in ARDS without increased adverse reactions.31 A meta-analysis by Meduri et al[33] published in 2018 provided moderate to high levels of evidence that low to moderate doses of prolonged glucocorticoid therapy in adult ARDS are safe and reduce mechanical ventilation, ICU and overall length of stay, and mortality. Nevertheless, the most promising results were in studies with a relatively early start of therapies (<3 days during early ARDS or 14 days in late ARDS) using low to medium doses (equivalent to methylprednisolone of 1-2 mg/kg per day), which are gradually reduced over time (12 or more days). While it may be prudent to recommend the routine use of corticosteroids in pARDS, it is a treatment that requires further study to determine the correct patient population, the time of administration, and the dosage regimen. Given the lack of clear evidence in pediatrics,[34] PALICC does not recommend using corticosteroids as routine therapy in pARDS until the prospective results of further research with specific populations.[35]

Routine surfactant therapy is not recommended in pARDS[13] but can be used in primary severe ARDS (Meconium aspiration syndrome and viral or bacterial lung infections).[36] In our study, surfactants are used in 23 (45%) of the participating ICUs. The PALIVE study reported that only 4.2% of children receive surfactants.[24] In Nordic countries, they are used in 39% of the units.[6] However, the efficacy of exogenous surfactant treatment in children and adolescents with ARDS remains controversial. On the one hand, a multicenter, randomized, blind study showed improved oxygenation and reduced mortality in surfactant therapy.[37] On the other hand, another study suggested that the benefits of surfactants are uncertain, and they cannot be recommended for routine use in pARDS .

Numerous meta-analyses in adults provided conflicting results regarding the effect of the prone position. Two recent meta-analyses reported a significant reduction in ARDS-related mortality when prone positioning and lung-protective ventilation were combined.[38,39] Also, in one of these meta-analyses, the proning patients with severe ARDS study reported that prone positioning resulted in a 50% reduction in mortality in adult patients with severe ARDS.[38] In Nordic countries, 89% of pediatric intensive care units use the prone position, which was found to be 75% in our study. Contrary to many other management strategies in ARDS, a multicenter RCT evaluating prone positioning in pediatrics showed prone positioning to be safe[40] but found no difference in mechanical ventilation, mortality, or duration of other health outcomes. Curley reported that prone positioning in children with ALI improved oxygenation but did not significantly reduce ventilator-free days.[12,40] The ongoing PRO-Spect study aims to determine the effectiveness of prone positioning in severe PARDS more precisely.[41] The PALICC guidelines recommend prone positioning to be considered an option in severe cases of PARDS but do not recommend its use as a routine treatment in pARDS, given the available pediatric data.[13]

Sedation and analgesia are used to provide synchronization with mechanical ventilation and facilitate tolerance in patients undergoing invasive mechanical ventilation. They also help in optimizing the work of breathing, oxygen delivery, and consumption.[42] In our study, we noticed that all units use sedation and analgesia in pARDS management. Besides, muscle relaxants can be preferred in cases where sedation is not sufficient for effective mechanical ventilation.[13,42] While sedation and analgesia are used in pARDS management in all units enrolled in the present study, only 37 (72.5%) adopt muscle relaxants. In Finland, sedation is used in 90% of mechanically ventilated children, but no data were presented on the use of muscle relaxants.[5]

The success of ECMO in infantile RDS has led to the use of the technique in children and adults.[43] In pARDS, ECMO increases systemic oxygen delivery thereby allowing damaged lungs to rest and heal. However, ECMO bears serious risks and requires

substantial resources, skills, and expertise.[44,45] Unfortunately, despite robust evidence in neonates and potential benefits in adults, clinical trial evidence for the use of ECMO in pARDS is lacking.[43,46,47] The present study revealed that 18 (35%) units have access to ECMO, which is adopted as a contingent option in suitable patients.

The present study is an up-to-date review of treatment strategies used in PICUs for pARDS in Turkey. We aimed to reach every PICU that can treat children with ARDS in Turkey. However, despite being licensed by the Ministry of Health, there are many centers that are not operative and do not admit patients due to the absence of a physician in charge. Thus, with a 51% response rate, it seems reasonable to assume that the findings of the present study provide a satisfying picture of the current practices for the management of pARDS in Turkey. Our survey aimed to investigate the characteristics of participating PICUs, specifically regarding the guidelines they comply with, among other details. However, we could not extract the patients' treatment data, including those who received steroids, surfactants, HFOV, ECMO, or iNO, and when they received them. Therefore, we also assume that there may be other differences between units that were not revealed through the survey of the present study.

Limitations and Further Study Recommendations

Further studies may attempt to focus on some issues in pARDS management—the current definition of pARDS and pARDS treatments in international guidelines can be revisited. Also, future studies may not only identify the total number of PICUs using the above-mentioned international recommendations but also scrutinize the context of different implementation models. The lack of detailed treatment questions in the survey questions caused the study to be limited .Finally, further research may engage in comparing the detailed percentages by country.

CONCLUSION

Overall, lung-protective ventilation strategies preventing ventilator-associated lung injury are explicit in almost all responding units. Steroid and surfactant use are higher in most of the PICUs surveyed compared to those reported in international studies. Our survey has shown that current mechanical ventilation and non-ventilation treatment strategies in pARDS in Turkey are relatively uniform and largely compliant with international practices. Providing relevant training to physicians serving in the diagnosis and treatment process of pediatric intensive care patients in line with current guidelines will further promote such compliance and may contribute to the prognosis of pARDS cases.

Ethics Committee Approval: This study was approved by Ethics committee of Selçuk University, (Approval No: 2018/107).

Informed Consent: Since the research was a survey study, no personal information was shared about the patients, so it was not necessary to fill out an informed consent form.

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