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ORIGINAL ARTICLE

Early Use of Adjunctive Therapies for Pediatric Acute Respiratory Distress Syndrome: A PARDIE Study

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Abstract

Rationale: Few data exist to guide early adjunctive therapy use in pediatric acute respiratory distress syndrome (PARDS).

Objectives: To describe contemporary use of adjunctive therapies for early PARDS as a framework for future investigations.

Methods: This was a preplanned substudy of a prospective, international, cross-sectional observational study of children with PARDS from 100 centers over 10 study weeks.

Measurements and Main Results: We investigated six adjunctive therapies for PARDS: continuous neuromuscular blockade, corticosteroids, inhaled nitric oxide (iNO), prone positioning, high-frequency oscillatory ventilation (HFOV), and extracorporeal membrane oxygenation. Almost half (45%) of children with PARDS received at least one therapy. Variability was noted in the median starting oxygenation index of each therapy; corticosteroids started at the lowest oxygenation index (13.0; interquartile range, 7.6–22.0) and HFOV at the highest (25.7; interquartile range, 16.7–37.3). Continuous neuromuscular blockade was the most common, used in 31%, followed by iNO (13%), corticosteroids (10%), prone positioning (10%), HFOV (9%), and extracorporeal membrane oxygenation (3%). Steroids, iNO, and HFOV were associated with comorbidities. Prone positioning and HFOV were more common in middle-income countries and less frequently used in North America. The use of multiple ancillary therapies increased over the first 3 days of PARDS, but there was not an easily identifiable pattern of combination or order of use.

Conclusions: The contemporary description of prevalence, combinations of therapies, and oxygenation threshold for which the therapies are applied is important for design of future studies. Region of the world, income, and comorbidities influence adjunctive therapy use and are important variables to include in PARDS investigations.

Keywords: acute respiratory distress syndrome; prone position; extracorporeal membrane oxygenation; nitric oxide; neuromuscular blocking agents

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A complete list of PARDIE V1 Investigators is available in the online supplement.

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At a Glance Commentary

Scientific Knowledge on the Subject: Adjunctive therapies are used in pediatric acute respiratory distress syndrome; however, few data exist to inform this practice.

What This Study Adds to the Field: This study provides global, contemporary data on adjunctive therapy use that can provide a framework for future investigations of pediatric acute respiratory distress syndrome.

Adjuvant therapies are often considered when managing children with pediatric acute respiratory distress syndrome (PARDS). Most data regarding management in children are extrapolated from adult or neonatal clinical trials. There is a general acceptance, driven by adult data, to support a low V_T and low driving pressure ventilation strategy in PARDS (1–3). However, clinical manifestations and underlying pathophysiology have resulted in the exploration of numerous adjunctive therapies. Although many of these therapies have been investigated in adults with early ARDS (<72 h) (4–11), there are minimal data to guide early practice in children.

Therapies such as continuous neuromuscular blockade (cNMB) and prone positioning used in the first 72 hours of ARDS improve survival in adults (5–7) and are considered frontline therapy combined with low V_T ventilation. However, in pediatrics, data are less conclusive (12–15). Although early institution of some therapies has demonstrated improved oxygenation in children (15–17), the effect on clinically relevant outcomes remains elusive. Furthermore, therapies such as high-frequency oscillatory ventilation (HFOV) have fallen out of favor in adult practice secondary to negative trials (8, 18), and observational pediatric data question the utility of such therapies in children (19, 20). Before embarking on more controlled trials in pediatrics, it is crucial to better understand current practices regarding the use of adjuvant therapies in early PARDS.

Recently, the PARDIE (PARDS Incidence and Epidemiology) study was completed in 145 pediatric ICUs (PICUs) worldwide. In a preplanned substudy (PARDIE V1), additional clinical data were collected to describe the use of adjunctive therapies over the first 3 days of PARDS management. The aim of this study was to provide contemporary data on the early use of common adjunctive therapies for PARDS to establish a framework for future studies. Focusing on therapies used in early, acute PARDS will better inform clinical trials, as this is the most common timeline for patient enrollment.

Methods

This is a planned secondary analysis of the PARDIE study: a large, international, cross-sectional study of PARDS. Specific details of the main PARDIE study design, data collection, and regulatory approval have been previously published (21). PARDIE consisted of 708 subjects from 145 PICUs in 27 countries (21), with each site deciding *a priori* whether to participate in the planned substudies.

Study Design

The V1 substudy included additional data collection over the first 3 days of PARDS. Sites received approval from their local institutional review boards or relied on the Children's Hospital of Los Angeles Institutional Review Board. Each site prospectively screened for eligibility over 5 days during 10 nonconsecutive weeks between May 2016 and June 2017. Patients were eligible if they met Pediatric Acute Lung Injury Consensus Conference PARDS criteria (22). As PARDIE only recruited new cases of PARDS, eligibility criteria had to be met within 24 hours from enrollment. Subjects were excluded if they were perioperative from a cardiac intervention or had active perinatal lung disease.

Additional Data Collection

Additional data collected included daily (calendar day): organ failure (Pediatric Logistic Organ Dysfunction 2 [PELOD 2] score), vasopressor requirement, fluid balance, and use of ancillary therapies over the first 3 days after PARDS diagnosis.

We investigated the frequency of use of adjunctive therapies, including cNMB, corticosteroid use specifically for PARDS, inhaled nitric oxide (iNO), prone positioning, HFOV, extracorporeal membrane oxygenation (ECMO), prostacyclin, surfactant, and β-agonists. Patient- and hospital-level factors were analyzed to determine associations between choice and order of use of these adjunctive therapies. *A priori* factors hypothesized to relate to the choice of adjuvant therapy included: demographics, admission source, severity of illness, comorbidities, type of PARDS (direct versus indirect), geo-economic differences, oxygenation/PARDS severity, and hospital-related characteristics.

Definitions

Direct PARDS included pneumonia, aspiration, drowning, respiratory viral infections, pulmonary hemorrhage, and smoke inhalation. Indirect PARDS included sepsis, trauma, pancreatitis, neurologic injury, transfusion-related acute lung injury, intraabdominal process/surgery, and cardiac arrest.

Geo-economic differences were investigated. Subjects were categorized into four geographic groups: North America, Europe, Central/South America, and Asia/Middle East/Australia/New Zealand. Countries were also classified as either high

Author Contributions: R.G.K., N.J.T., and N.Y. were responsible for study conception and oversight. M.J.K., M.K.D., G.E., H.R.F., Y.M.L.-F., S.L.S., M.C.J.K., L.S.S., R.G.K., N.J.T., and N.Y. were involved with study design and development of the data collection forms. C.M.R. and M.J.K. were the primary data analysts. C.M.R., M.J.K., L.S.S., R.G.K., N.J.T., and N.Y. were responsible for the primary interpretation of the results. C.M.R., D.D.H., P.C.S., A.B.H., B.E.P.-O., B.H., R.S.C., A.B.M., J.L., and L.I. provided additional data collection and interpretation of results. All authors have read, edited, and approved the manuscript. C.M.R. is the guarantor of the manuscript.

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This article has a related editorial.

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org.

Table 1. Description of the Cohort Based on Receiving Pulmonary Adjunctive Therapies

Variable	Received Adjunctive Therapies?		*P* Value
	Yes (*n* = 279)	No (*n* = 345)	
Demographics			
Age, yr (*n* = 619)	4.2 (0.8 to 9.5)	3.0 (0.8 to 10.5)	0.912
Sex, F (*n* = 623)	102 (36.6)	145 (42.2)	0.156
White (*n* = 619)	160 (57.8)	216 (63.2)	0.350
Hispanic (*n* = 515)	64 (22.9)	75 (21.9)	0.584
Admission source (*n* = 623)			0.8437
Emergency department	128 (46.0)	158 (45.8)	
Inpatient floor	100 (36.0)	119 (34.5)	
Other	50 (18.0)	68 (19.7)	
Severity of illness at PARDS onset			
PIM3	−3.4 (−5.0 to −2.8)	−3.4 (−5.2 to −2.5)	0.598
PRISM IV	6.0 (2.0 to 13.0)	7.0 (3.0 to 13.0)	0.3164
PELOD-2	5.0 (3.0 to 7.0)	5.0 (3.0 to 7.0)	0.546
Comorbidities			
None	103 (36.9)	130 (37.7)	0.845
Home ventilation	13 (4.7)	12 (3.5)	0.454
Chronic pulmonary disease	81 (29.0)	99 (28.7)	0.926
Prematurity	50 (17.9)	61 (17.7)	0.938
Congenital heart disease	27 (9.7)	44 (12.8)	0.229
Neuromuscular disease	50 (17.9)	62 (18.0)	0.987
Oncologic	21 (7.5)	30 (8.7)	0.596
Immunosuppressed	38 (13.6)	44 (12.8)	0.750
PARDS etiology (*n* = 619)			0.3401
Direct	206 (75.2)	244 (71.8)	
Indirect	68 (24.8)	96 (28.2)	
OI equivalent at PARDS onset	10.5 (5.8 to 19.4)	9.7 (6.0 to 18.7)	0.542
PICU beds	24 (15.0 to 40.0)	24 (16.0 to 38.0)	0.939
Annual PICU admissions (*n* = 615)			0.675
<500 per yr	47 (17.2)	52 (15.2)	
500–1,000 per year	49 (17.9)	69 (20.2)	
>1,000 per year	178 (65.0)	2,120 (64.5)	
Other hospital factors			
24-h Attending (*n* = 600)	195 (72.8)	240 (72.3)	0.898
Fellowship program (*n* = 624)	248 (88.9)	299 (86.7)	0.401
HFOV available (*n* = 624)	275 (98.6)	340 (98.6)	0.987
ECMO program (*n* = 624)	198 (71.0)	247 (71.6)	0.863
Region			0.2285
North America	181 (65.0)	232 (67.2)	
Europe	36 (12.9)	55 (16.0)	
Central/South America	40 (14.3)	42 (12.2)	
Middle East/Asia/Australia/New Zealand	22 (7.9)	16 (4.7)	
Income			0.7534
High	240 (86.0)	300 (87.0)	
Middle	39 (14.0)	45 (13.0)	

Definition of abbreviations: ECMO = extracorporeal membrane oxygenation; HFOV = high-frequency oscillatory ventilation; OI = oxygenation index; PARDS = pediatric acute respiratory distress syndrome; PELOD-2 = Pediatric Logistic Organ Dysfunction 2; PICU = pediatric ICU; PIM3 = Pediatric Index of Mortality 3; PRISM IV = Pediatric Risk of Mortality IV.

Results are reported in *n* (%) or as median (interquartile range) for continuous variables. Adjunctive therapies were defined as continuous neuromuscular blockade, corticosteroids for PARDS, inhaled nitric oxide, prone positioning, HFOV, and EMCO.

income or middle income on the basis of the 2016 World Bank classification (23).

Oxygenation index (OI) was calculated as follows: OI = [(mean airway pressure × $F_{I_{O_2}}$)/Pa_{O_2}] × 100. If Pa_{O_2} was unavailable, an oxygen saturation index was calculated, provided the saturation was ⩽97%, and transformed into an equivalent OI. Subjects were grouped into severity of PARDS, by Pediatric Acute Lung Injury Consensus Conference criteria, using the worst OI or oxygen saturation index in the 72-hour study period (22).

Statistical Analysis

Data were summarized and distributions examined. Results are presented in frequencies with percentages for categorical variables or medians with interquartile ranges (IQRs) for continuous variables. Categorical variables were compared with chi-square or Fisher exact tests for overall *P* value with *post hoc* Bonferroni correction for multiple comparisons within groups. Continuous variables were compared using the nonparametric Mann-Whitney *U* test. The threshold for statistical significance was set at $P < 0.05$. Statistical Package of Social Science (SPSS) for Windows, Version 22 (SPSS Inc.) was used for the analyses.

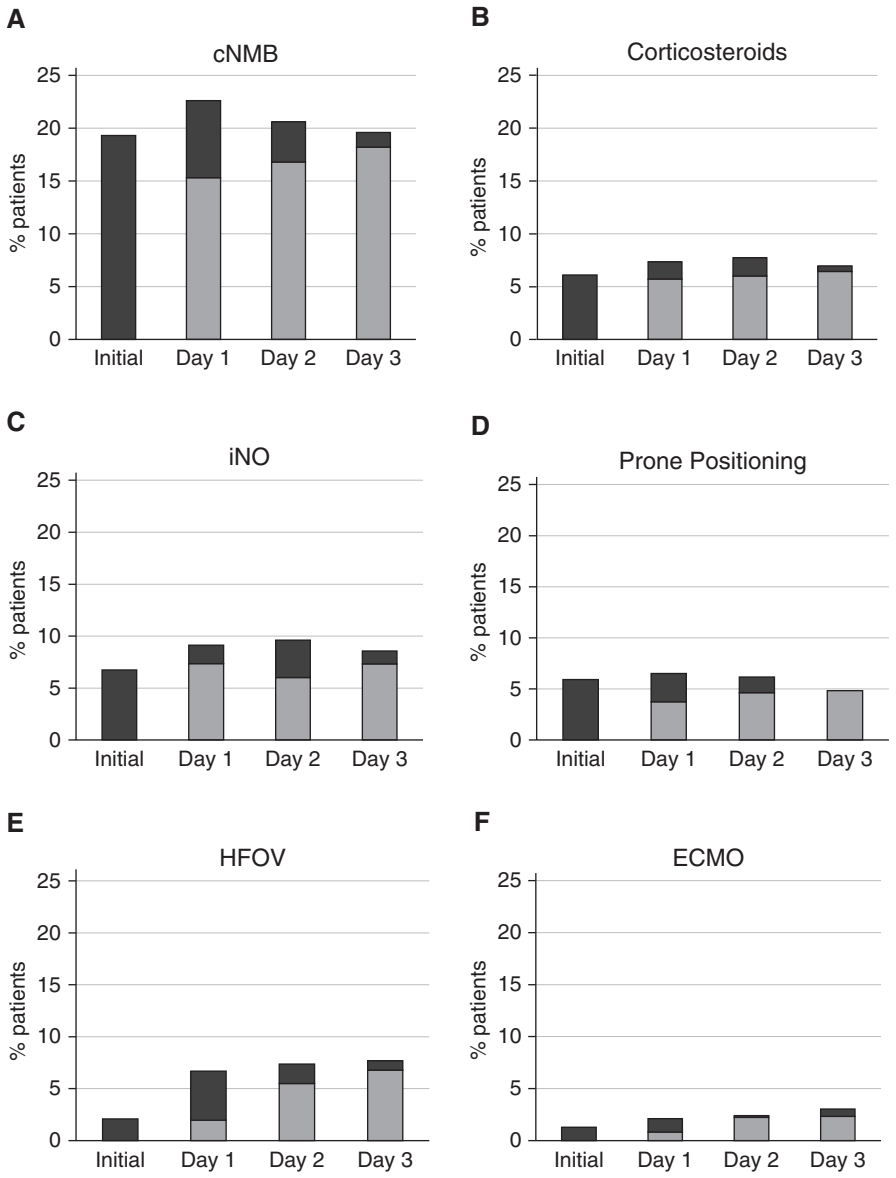

Figure 1. Individual adjunctive therapy use in pediatric acute respiratory distress syndrome (PARDS) over time. Each panel illustrates the percentage of patients receiving a specific therapy on the initial day of PARDS through Day 3, with a separation of those who were newly started on that day. Total number of patients for each day was as follows: Initial, $n = 624$; Day 1, $n = 613$; Day 2, $n = 583$; and Day 3, $n = 560$. Those who were started on the therapy on the indicated day are shown in black. Those already receiving the therapy, defined as receiving the therapy the day prior, are shown in gray. (*A*) Continuous neuromuscular blockade (cNMB), (*B*) corticosteroid use for PARDS, (*C*) inhaled nitric oxide (iNO), (*D*) prone positioning, (*E*) high-frequency oscillatory ventilation (HFOV), and (*F*) extracorporeal membrane oxygenation (ECMO).

Results

There were 624 subjects from 100 centers included in the study. The most common therapies were inhaled β-agonists (47% of patients), cNMB (31%), and iNO (13%). β-Agonist use was associated with preexisting pulmonary disease ($P < 0.001$) and chronic respiratory support before the PICU admission ($P < 0.001$) and were likely home medications for many children. Furthermore, β-agonists were used frequently, nonspecifically, and regardless of PARDS severity, in contrast to the other therapies that were more common as PARDS severity increased. Prostacyclin and surfactant were used in <1% of the cohort. For these reasons, β-agonists, prostacyclin, and surfactant were excluded from further analysis.

The six remaining adjuvant therapies were cNMB, corticosteroids specifically for PARDS, iNO, prone positioning, HFOV, and ECMO. More than half ($n = 345$; 55.3%) did not receive any of these six therapies during the first 72 hours of PARDS diagnosis, whereas 150 (24.0%) patients received one therapy, 75 (12.0%) received two, 39 (6.3%) received three, 11 (1.8%) received four, and four patients (0.6%) received five therapies. Demographics for the cohort stratified by receiving at least one adjunctive therapy in the first 72 hours of PARDS are found in Table 1. There were no differences in patient or hospital demographics, region of the world, country income, comorbidities, or severity of illness between those who received a pulmonary adjunctive therapy and those who did not.

Timing and Severity of PARDS for Starting an Adjunctive Therapy

The majority of patients received the adjunctive therapy, except HFOV and ECMO, on the initial day of PARDS diagnosis (Figure 1). There was an increase in adjunctive therapy use as PARDS severity increased, as indicated by increasing OI. Use of all adjunctive therapies with the exception of corticosteroids was associated with PARDS severity and was highest in children with severe PARDS (Table 2). The prevalence of each adjunctive therapy among patients with PARDS remained consistent over the first 3 days of PARDS diagnosis, with the exception of HFOV ($P < 0.001$), which has the lowest utilization on the initial day of PARDS diagnosis (Table 3).

Adjunctive therapies were more commonly used in those with severe PARDS, but there was variability in the worst median OI on the day the therapy was started. As illustrated in Figure 2, HFOV was started at the highest median OI of all the therapies examined and corticosteroids for PARDS at the lowest median OI. Interestingly, ECMO was started at a lower median OI than prone positioning, iNO, and HFOV.

Individual and Combination Therapies

There was no readily identifiable pattern to the combinations of therapies used on the same calendar day (*see* Figure E1 in the online supplement). cNMB was the most commonly used therapy ($n = 196$; 31%) during the first 3 days of PARDS. Although

Table 2. Any Day Ancillary Use for Overall Maximum PALICC ARDS Severity in the 72-Hour Study Period

Adjunctive Therapy, Any Day (*n* = 624)	NIV (*n* = 66)	Mild (*n* = 124)	Moderate (*n* = 178)	Severe (*n* = 256)	All (*n* = 624)	*P* Value
cNMB	0 (0.0)	16 (12.9)	51 (28.7)	129 (50.4)	196 (31.4)	<0.001
Corticosteroids for PARDS	6 (9.1)	5 (4.0)	20 (11.2)	33 (12.9)	64 (10.3)	0.059
iNO	1 (1.5)	2 (1.6)	11 (6.2)	67 (26.2)	81 (13.0)	<0.001
Prone positioning	1 (1.5)	1 (0.8)	14 (7.9)	47 (18.4)	63 (10.1)	<0.001
HFOV	0 (0.0)	1 (0.8)	1 (0.6)	56 (21.9)	58 (9.3)	<0.001
ECMO	0 (0.0)	1 (0.8)	2 (1.1)	16 (6.3)	19 (3.0)	0.002

Definition of abbreviations: ARDS = acute respiratory distress syndrome; cNMB = continuous neuromuscular blockade; ECMO = extracorporeal membrane oxygenation; HFOV = high-frequency oscillatory ventilation; iNO = inhaled nitric oxide; NIV = noninvasive ventilation; PALICC = Pediatric Acute Lung Injury Consensus Conference; PARDS = pediatric acute respiratory distress syndrome.
Results are presented as *n* (%). Subjects were grouped into worse severity in the first 72 hours of PARDS diagnosis.

it was often used as the only ancillary therapy, it was frequently combined with another ancillary therapy, particularly iNO and HFOV (Figure E1A). When evaluating all the risk factors in Table 1 among those who did and did not receive cNMB, children receiving cNMB had higher initial Pediatric Risk of Mortality IV (PRISM IV) IV and PELOD-2 scores (Table E1A). They were less likely to be white (54% vs. 64%; $P = 0.027$) and to have an underlying neuromuscular disease (10% vs. 22%; $P < 0.001$). No other clinical or demographic factors were associated with cNMB use.

iNO was used in 13% ($n = 81$) of the cohort. It was rarely used as an isolated adjunctive therapy, frequently being combined with cNMB (Figure E1B). Those who received iNO had higher initial PRISM IV ($P = 0.004$) and PELOD-2 ($P = 0.001$) scores than those who did not receive iNO (Table E2). There was an association with having an underlying comorbidity ($P = 0.042$). Specifically, those who received iNO were more likely to have prematurity (26% vs. 17%; $P = 0.040$) and congenital heart disease (21% vs. 10%; $P = 0.004$). Geographical region and income were not associated with iNO use (Figure 3).

Corticosteroids specifically for PARDS were used in 10% of patients ($n = 64$), often as the only adjuvant therapy (Figure E1C). Corticosteroid use was associated with having direct PARDS ($P = 0.029$) (Table E3). Those who received steroids were more likely to have underlying chronic pulmonary disease (50% vs. 26%; $P < 0.001$) and congenital heart disease (22% vs. 10%; $P = 0.005$). The remainder of the clinical and demographic factors examined were not statistically significant.

Prone positioning was used in 10% ($n = 63$) of subjects, and >60% of prone-positioned patients also received cNMB (Figure E1D). Multiple clinical and demographic factors were associated with prone positioning (Table E4). Those who received prone positioning were younger ($P = 0.001$) and more likely to be Hispanic ($P = 0.009$). Patients were more likely to be admitted to the PICU from an inpatient floor ($P = 0.022$). Prone positioning was associated with being in a PICU with fewer median beds (13 [IQR, 3–20] vs. 24 [IQR, 18–40]; $P < 0.001$) and fewer annual admissions ($P < 0.001$). Those who were treated with prone positioning were less likely to be treated in a unit with 24-hour attending coverage ($P = 0.010$) or an ECMO program ($P < 0.001$) than those who did not receive prone positioning. Also, as evident in the presented heat map, prone positioning was used less in North America than in Europe, Central/South America, and Middle East/Asia/Australia/New Zealand ($P < 0.001$) (Figure 3). Furthermore, there was an association with higher use of prone positioning in middle-income countries ($P < 0.001$). Those treated with prone positioning had a higher initial PELOD-2 score ($P = 0.028$), and prone positioning was more commonly applied in those who had direct PARDS ($P = 0.001$). There were fewer patients with an underlying neuromuscular disorder who received prone positioning ($P = 0.029$). The duration of prone positioning on a given day was variable (Figure E2).

HFOV was used in 9% of the cohort and was rarely used as the only adjunctive therapy. It was frequently combined with cNMB or iNO (Figure E1E). Those placed on HFOV were less likely to be white ($P = 0.044$), more likely to be admitted from an inpatient floor ($P = 0.017$), and less likely to be at an institution with an ECMO program (50% vs. 74%; $P < 0.001$). HFOV

Table 3. Use of Adjunctive Therapies for PARDS over Time for the Entire Cohort

Adjunctive Therapy	Anytime (*n* = 624)	Day 0 (*n* = 621)	Day 1 (*n* = 613)	Day 2 (*n* = 583)	Day 3 (*n* = 560)	*P* Value
cNMB	196 (31.4)	121 (19.5)	139 (22.7)	120 (20.6)	110 (19.6)	0.494
Corticosteroids for PARDS	64 (10.3)	38 (6.1)	45 (7.3)	45 (7.7)	39 (7.0)	0.727
iNO	81 (13.0)	42 (6.8)	56 (9.1)	56 (9.6)	48 (8.6)	0.351
Prone positioning	63 (10.1)	37 (6.0)	40 (6.5)	36 (6.2)	27 (4.8)	0.639
HFOV	58 (9.3)	13 (2.1)	41 (6.7)	43 (7.4)	43 (7.7)	<0.0001
ECMO	19 (3.0)	6 (1.0)	13 (2.1)	14 (2.4)	17 (3.0)	0.224

Definition of abbreviations: cNMB = continuous neuromuscular blockade; ECMO = extracorporeal membrane oxygenation; HFOV = high-frequency oscillatory ventilation; iNO = inhaled nitric oxide; PARDS = pediatric acute respiratory distress syndrome.
Results are presented as *n* (%).

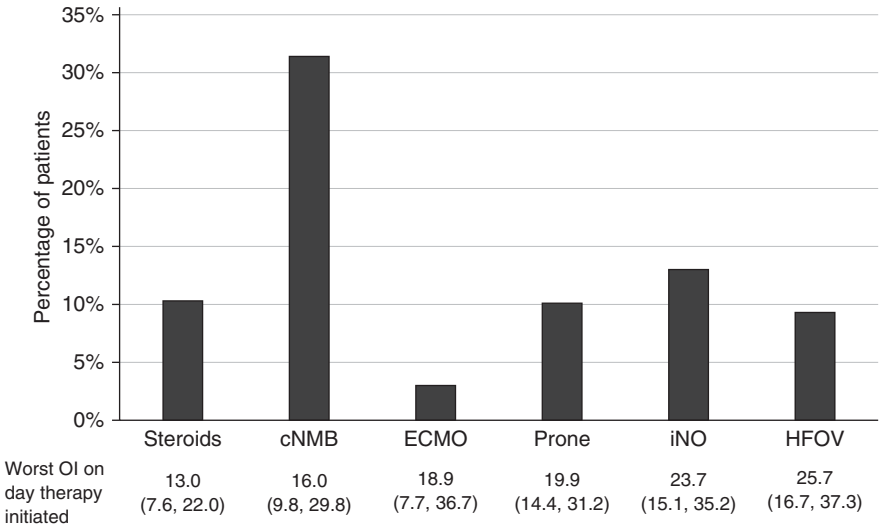

Figure 2. Percentage of patients who received adjunctive therapies for pediatric acute respiratory distress syndrome, ordered by worst median oxygenation index on the day adjunctive therapy was started. Values displayed are percentage of the entire cohort. Worst oxygenation index (OI; median and interquartile range) on the day the adjunctive therapy was started is shown. If Pa_{O_2} was not available, an oxygen saturation index was used and converted to OI equivalent. cNMB = continuous neuromuscular blockade; ECMO = extracorporeal membrane oxygenation; HFOV = high-frequency oscillatory ventilation; iNO = inhaled nitric oxide; Prone = prone positioning.

was used less often in patients from North America than from other regions of the world ($P < 0.001$) (Figure 3 and Table E5). A higher proportion of subjects from middle income countries were treated with HFOV than those who were not treated with HFOV (24% vs. 12%; $P = 0.012$). Those treated with HFOV had higher initial severity of illness scores: Pediatric Index of Mortality 3 (PIM3) ($P = 0.047$), PRISM IV ($P < 0.001$), and PELOD-2 ($P < 0.001$). The presence of a comorbidity in general also was not associated with HFOV. However, specifically having an immunocompromised condition was associated with increased use of HFOV ($P < 0.001$) (Table E5).

Nineteen patients (3.0%) were treated with ECMO, and this was very rarely used in isolation after initiation (Figure E1F). It was more commonly combined with cNMB, steroids, and iNO. Thirteen patients were treated with venoarterial ECMO and six with venovenous ECMO. Patients treated with ECMO were older (7.3 vs. 3.5 yr; $P = 0.004$). For those treated with ECMO, there was a trend to be at a larger institution with a higher median number of beds (32 [IQR, 23–40] vs. 23 [IQR, 15–40]; $P = 0.097$) and a higher number of annual admissions ($P = 0.072$) than those who did not receive ECMO (Table E6). Although not reaching statistical significance, 90% of patients receiving ECMO originated from North America (Figure 3). All patients treated with ECMO were in high-income countries. Those treated with ECMO had higher initial PRISM IV ($P = 0.001$) and PELOD-2 ($P = 0.001$) scores. Having any comorbidity was not associated with the use of ECMO, although no patient with an underlying neuromuscular disorder received this therapy ($P = 0.022$) (Table E6).

The order in which therapies were initiated was variable. The use of multiple ancillary therapies slightly increased over the first 3 days; however, there was not an easily identifiable pattern of combination or order of use. The specific combination therapies per day of PARDS are detailed in Table E7.

Discussion

In this international, prospective cohort, the early use of adjunctive therapies in children with PARDS was common, with almost half the cohort receiving at least one therapy during the first 72 hours. Adjunctive therapies increased with increasing PARDS severity, similar to adult data (4, 24). However, many therapies with no evidence of benefit in adult ARDS are commonly used in PARDS. The focus on use of these therapies in first 72 hours of PARDS is important for both the design of clinical trials, which historically have focused enrollment within the first 48 to 72 hours of pediatric and adult ARDS (4–6, 8–11, 14, 15, 25), and to better understand the early practice patterns in PARDS. In the absence of clear pediatric evidence demonstrating superiority of any particular ancillary therapy, a description of early practice patterns allows a better understanding of how these therapies are currently applied and what factors may influence use. This time frame is crucial, not necessarily to investigate what patients may receive before death but to appreciate what therapies may be applied to prevent secondary injury, such as ventilator-induced lung injury.

Controlled trials in adults with ARDS support early use of neuromuscular blockade (5), although a recent trial has questioned these findings (25). We found neuromuscular blockade was used very frequently in PARDS, and perhaps pediatric practice is heavily influenced by adult data because pediatric controlled trials are limited. In contrast, prone positioning, which has good evidence for benefit in adults, was used uncommonly, despite pediatric consensus-based recommendations to consider it in severe PARDS (26). It is notable that the sole pediatric trial of prone positioning to date was stopped for futility, with no evidence of benefit (14). Interestingly, HFOV is still used in >20% of patients with severe PARDS, despite negative adult studies. This is important because the sole pediatric trial on HFOV (before the ongoing PROSPECT (Prone and Oscillation Pediatric Clinical Trial) trial, NCT03896763) was conducted before routine use of low V_T mechanical ventilation (27). This has left practitioners questioning the applicability and best approach to HFOV in children with PARDS. Clearly, there is a need for studies in children that can inform pediatric practice.

Age-related factors, comorbidities, and underlying etiologies of ARDS are different between children and adults (28, 29). We found that comorbidities influence the choices of adjunctive therapies. This is particularly evident in the use of iNO, which was more commonly used in children with prematurity and congenital heart disease, both of which are associated with pulmonary hypertension (30, 31). Although there are inconclusive data

supporting routine use (15), and some data expressing concern for an increased risk of harm (32), it is clear that pediatric practitioners believe that subpopulations of patients benefit from iNO. These data may be important to consider for phenotypic enrichment in the design of future interventional trials in ARDS, given the heterogeneity of treatment effect for many therapies (33). Similarly, corticosteroids were more commonly used in children with an underlying chronic pulmonary condition, where there may be a differential treatment effect. Interestingly, HFOV was more commonly used in immunocompromised patients, although this is likely confounded by higher severity of ARDS (34, 35) in this population.

Geo-economic factors as well as unit-specific characteristics were associated with the use of some adjunctive therapies. Prone positioning and HFOV were more common in middle-income countries, less common in North America, and more common in smaller ICUs with fewer PICU beds and annual admissions. Prone positioning was more common in units that did not have 24-hour attending coverage, and HFOV was more common in units that did not have an ECMO program. These data suggest that resource availability affects adjunctive therapy use and highlights the possibility that units with robust resources underutilize inexpensive therapies such as prone positioning.

Although not statistically significant, 90% of subjects treated with ECMO originated from North America. Despite a recent publication demonstrating nonsuperiority of ECMO in adults with ARDS (36), ECMO use in pediatrics is increasing (37). This increase is likely due to improvement in ECMO technology as well as increasing indications and a decrease in the number of absolute contraindications for EMCO. As clinicians become increasingly comfortable with this support modality, they may be quicker to apply it to critically ill children. It may also be possible that smaller units, or units in low- to middle-income countries with fewer resources, may be more likely to try adjunctive therapies when ECMO is not readily available or would require a transfer to a different facility. It is difficult to interpret the data that ECMO was used at a lower median OI than prone positioning, iNO, and HFOV. Patients treated with ECMO had worse PRISM and PELOD scores than patients not treated with ECMO, and the majority of patients receiving ECMO were treated with venoarterial ECMO, suggesting that some of the patients receiving ECMO may have received this therapy for cardiovascular support rather than just respiratory failure. In the absence of clear pediatric evidence for a specific therapy, some centers and clinicians may be more likely to place a child with PARDS directly on ECMO as opposed to trying different adjunctive therapies first, a phenomenon also observed

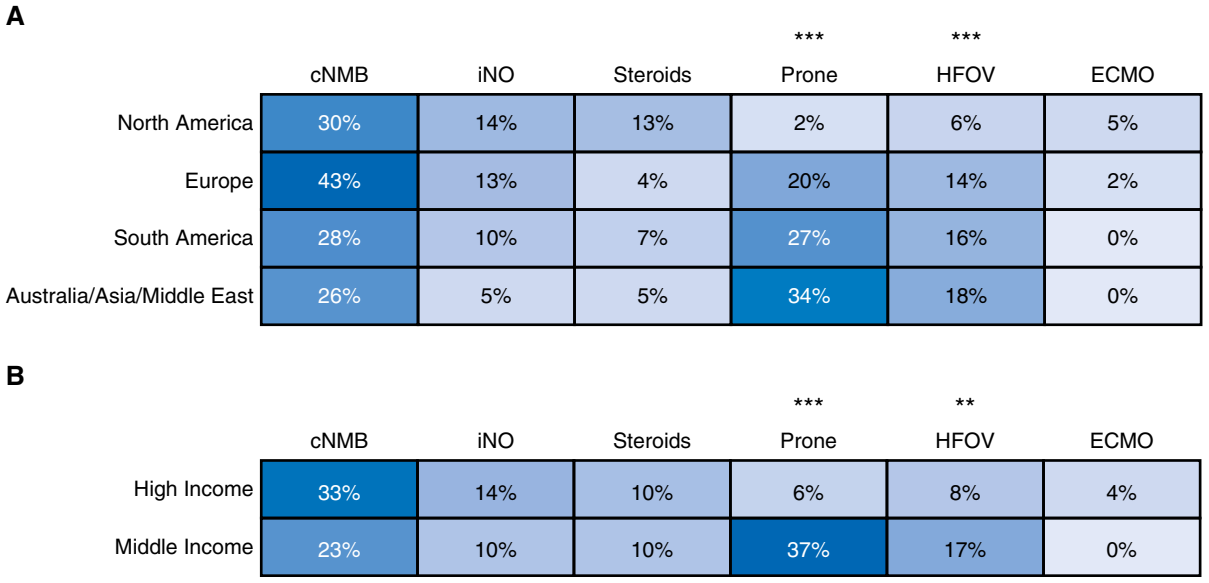

Figure 3. Heat map of adjunctive therapy use stratified by region of the world and country income determined by the 2016 World Bank geo-economic groups. (*A*) Heat map of adjunctive therapies stratified by region of the world. Values displayed are percentages of patients from each region who were treated with the indicated adjunctive therapy. Darker color indicates a higher percentage of use in that region. There were 413 patients originating from North America, 91 from Europe, 82 from Central and South America, and 38 from Australia, Asia, and the Middle East. Prone positioning and high-frequency oscillatory ventilation (HFOV) were both less commonly applied in North America, both with $P < 0.001$. *P* values were determined using chi-square with application of the Bonferroni correction. ***$P < 0.001$. There was not a significant difference among geographic regions in use of continuous neuromuscular blockade (cNMB), inhaled nitric oxide (iNO), corticosteroids specifically for pediatric acute respiratory distress syndrome, or extracorporeal membrane oxygenation (ECMO). (*B*) Heat map of adjunctive therapies stratified by country income. Values displayed are percentage of patients in high- or middle-income countries. Darker color indicates a higher percentage of use. There were 540 patients from high-income countries and 84 patients from middle-income countries ($n = 84$). High- and middle-income groups were compared using the chi-square test. Prone positioning ($P < 0.001$) and HFOV ($P = 0.01$) were more commonly applied in middle-income countries. **$P = 0.01$ and ***$P < 0.001$. There was not a significant difference among income groups in use of cNMB, iNO, corticosteroids specifically for pediatric acute respiratory distress syndrome, or ECMO.

in adults (38). In adults with severe ARDS, the vast majority of patients who received ECMO did not receive prone positioning (38). This trend may be driven by a variety of factors, including equivocal or negative studies of many ancillary therapies, provider comfort, or beliefs that more-advanced technologic therapies are superior. Finally, negative trials of HFOV in adults (8, 18) may also have dampened enthusiasm for HFOV in pediatrics, with practitioners directly going to ECMO without trying HFOV.

Although most of the therapies were more common in patients with severe PARDS, our data highlight there was no clear discernable pattern regarding timing, order of application, oxygenation severity, and combination of different therapies used in patients with PARDS. Perhaps this reflects the lack of evidence-based recommendations for routine use of any of these adjunctive therapies in pediatrics (26, 39) or guidelines for timing of initiation or order of application.

The severity of oxygenation failure, as determined by worst median OI on the day the adjunctive therapy was started, was wide ranging. ECMO was started at a lower OI than iNO, prone positioning, and HFOV. Notably, HFOV is often applied later in the course of the severity of PARDS and also had the highest median starting OI of all the therapies examined, although this may be affected by resource availability. This highlights a lack of consensus for a specific oxygenation threshold where the benefits of a therapy outweigh the risk. It is unclear whether oxygenation thresholds solely should drive the choice of adjuvant therapies, as severity of oxygenation alone is unlikely to fully capture the individual risk–benefit profiles of each of these adjuvant therapies. Methods to better understand these risk–benefit thresholds for adjuvant therapies are needed.

Our study has several strengths. This is the largest multicenter PARDS cohort described to date. Data were prospectively collected from 100 institutions worldwide and reflect modern PARDS management. In addition, data collection was granular for severity of illness, severity of PARDS, and comorbidities, allowing for some insight into which variables were associated with use of therapies. However, this study has some limitations. First, the data were only collected for the first 72 hours of PARDS, so later use of these adjunctive therapies cannot be determined; this may be particularly important for ECMO and HFOV, which are often used as late rescue therapies. An additional limitation is that we were only able to examine whether therapies were used on a given day, as the database lacked specific start and stop times of each individual therapy. However, the presence of multiple time points for measures of oxygenation during each day helped to overcome this limitation by allowing us to focus on the worst OI on the day the therapy was initiated, although this may overestimate the severity of PARDS at the start of each therapy. Finally, although all patients in the cohort had PARDS, we did not collect the specific indication for starting therapy, which is often multifactorial.

Conclusions

This study describing the real-world utilization of ancillary therapies in the first 72 hours of PARDS in a large number of centers across the world offers insight to the current landscape of adjunctive therapy practice patterns for PARDS. The first few days of PARDS are critical for trial design and prevention of ventilator-induced lung injury. Clearly, even in the early period of PARDS, there is extreme variability with respect to timing of initiation, severity of PARDS at the start of each therapy, and the manner in which adjunctive therapies are combined. The variability seems to be affected by many factors, including comorbidities and geo-economic status. These data are crucial to plan future randomized trials and comparative effectiveness studies in ARDS. ■

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