OBSERVATIONAL STUDY

OPEN

Nutritional Support in Children Meeting the At-Risk for Pediatric Acute Respiratory Distress Syndrome Criteria

Theodore T. Pei, MD, MPH[1,2]
Steven L. Shein, MD[3,4]
Ira M. Cheifetz, MD[3,4]
Katherine N. Slain, DO[3,4]

IMPORTANCE: Pediatric acute respiratory distress syndrome (PARDS) is a prevalent condition in the PICU with a high morbidity and mortality, but effective preventative strategies are lacking.

OBJECTIVES: To examine associations between early enteral nutrition (EN) and PICU outcomes in a cohort of children meeting the 2015 Pediatric Acute Lung Injury Consensus Conference "at-risk" for pediatric acute respiratory distress syndrome (ARF-PARDS) criteria.

DESIGN, SETTING, AND PARTICIPANTS: This was a single-center, electronic health record-based retrospective chart review. We included children less than or equal to 18 years-old admitted to our mixed medical-surgical PICU from January 2017 to December 2018 who met ARF-PARDS criteria within 48 hours of admission. Children were categorized as receiving "early" EN if feeds were initiated within 48 hours of admission. All others were categorized as "delayed" EN.

MAIN OUTCOMES AND MEASURES: Extracted data included demographics, illness characteristics including primary diagnosis and Pediatric Risk of Mortality (PRISM) III score, respiratory support and oxygenation indices, nutritional data, and PICU length of stay (LOS). The primary outcome of interest was subsequent diagnosis of PARDS.

RESULTS: Of 201 included children, 152 (75.6%) received early EN. The most common admission diagnoses were pneumonia, bronchiolitis, and influenza. Overall, 21.4% ($n = 43$) of children developed PARDS. Children receiving early EN had a subsequent diagnosis of PARDS less often then children receiving delayed EN (15.1% vs 40.8%; $p < 0.001$), an association that persisted after adjusting for patient demographics and illness characteristics, including PRISM III and diagnosis (adjusted odds ratio, 0.24; 95% CI, 0.10–0.58; $p = 0.002$). Early EN was also associated with a shorter PICU LOS in univariate analysis (2.2 d [interquartile range, 1.5–3.4 d] vs 4.2 d [2.7–8.9 d]; $p < 0.001$).

CONCLUSIONS AND RELEVANCE: In this single-center, retrospective cohort study, compared with children with ARF-PARDS who received late EN, those who received early EN demonstrated a reduced odds of subsequent diagnosis of PARDS, and an unadjusted reduction in PICU LOS when compared with delayed EN. Prospective studies should be designed to confirm these findings.

KEY WORDS: acute lung injury; enteral nutrition; length of stay; respiratory distress syndrome; retrospective studies

Provision of enteral nutrition (EN) to critically ill children is associated with improved hospital outcomes, including decreased length of stay (LOS) and shorter duration of mechanical ventilation (MV) across a wide spectrum of disease processes, including pediatric acute respiratory distress syndrome (PARDS) (1–9). Proposed mechanisms of EN benefits in PARDS include maintenance of healthy gut mucosa and subsequent reductions

DOI: 10.1097/CCE.0000000000000856

KEY POINTS

Question: For children "at-risk" for PARDS, is early enteral nutrition within 48 hours of PICU admission associated with a reduction in subsequent diagnosis of PARDS?

Findings: this single-center retrospective cohort study, initiation of early enteral nutrition was associated with an adjusted 75% reduction in the odds of a subsequent PARDS diagnosis.

Meaning: Early enteral nutrition in this cohort may be associated with a reduction in subsequent PARDS diagnosis, but prospective studies are needed to elucidate this potential association.

of pro-inflammatory signaling, bacterial translocation, and immune dysfunction that accompany intestinal epithelium dysfunction (10, 11). Furthermore, multicenter retrospective studies of heterogenous PICU populations have previously demonstrated an association between early EN and improved survival (6, 8). Consensus guidelines from the American Society for Parental and Enteral Nutrition, Society of Critical Care Medicine, and European Society of Pediatric and Neonatal Intensive Care recommend early EN, generally defined as feed initiation within 24–48 hours of admission to the PICU (12, 13).

Despite the potential benefits of feeding as a low-cost, low-risk intervention, the application of nutrition as a primary therapy in PARDS remains largely unstudied (14). Because of the high prevalence, morbidity, and mortality of PARDS, identifying effective preventative and therapeutic strategies is a high priority (15). The Pediatric Acute Lung Injury Consensus Conference (PALICC) defined children "at-risk" for PARDS (ARF-PARDS), with a goal to identify a subset of children with hypoxic respiratory failure who could benefit from targeted prevention measures (16). To date, there have been no studies describing the relationship between feeding practices and PICU outcomes in children meeting the PALICC ARF-PARDS criteria. Therefore, the objective of this single-center study was to describe current feeding practices in a cohort of children meeting ARF-PARDS criteria within 48 hours of PICU admission. We hypothesized that initiation of early EN within 48 hours of admission to the PICU would be associated with a reduction in subsequent diagnosis of PARDS and a reduced PICU LOS when compared with children whose EN was delayed.

MATERIALS AND METHODS

This was a single-center, electronic health record (EHR)-based retrospective study conducted at University Hospital Rainbow Babies & Children's Hospital in Cleveland, OH, a quaternary referral children's hospital. Institutional review board approval was obtained on February 16, 2019 (Submission number STUDY20190462) for our study entitled "Current Nutritional Support in Children Meeting the At Risk for Pediatric Respiratory Distress Syndrome (ARF-PARDS) Criteria." Procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975. Due to the retrospective, EHR-based nature of our study, informed consent was not obtained nor necessary. We queried the local Virtual PICU Systems (VPS) database (Virtual Pediatric Systems, LLC, Los Angeles, CA) to identify children less than or equal to 18 years old admitted to our PICU between January 2017 and December 2018 with acute respiratory failure, defined as receiving high-flow nasal cannula (HFNC), continuous positive airway pressure, bilevel positive airway pressure, or MV during their PICU stay. Respiratory support and oxygenation indices were reviewed in 8-hour intervals, beginning at PICU admission. Children who met the 2015 PALICC definition for ARF-PARDS (**Supplemental Table 1**, http://links.lww.com/CCX/B138) within 48 hours of PICU admission were eligible for study inclusion. A chest radiograph obtained within 48 hours of PICU admission required an attending radiologist read consistent with new parenchymal disease (e.g., "new interstitial infiltrate," "scattered patchy opacities"). Images read as "hyperinflation" or "peri-bronchial thickening," for example, did not qualify (17). Children who were postoperative surgical patients or those with primary cardiac diagnoses were excluded. Additional exclusion criteria included chronic respiratory failure (defined as tracheostomy and/or ventilation-dependence at home), total parenteral nutrition-dependence, meeting criteria for PARDS at PICU admission, repeat patient encounter within the study period, and incomplete study

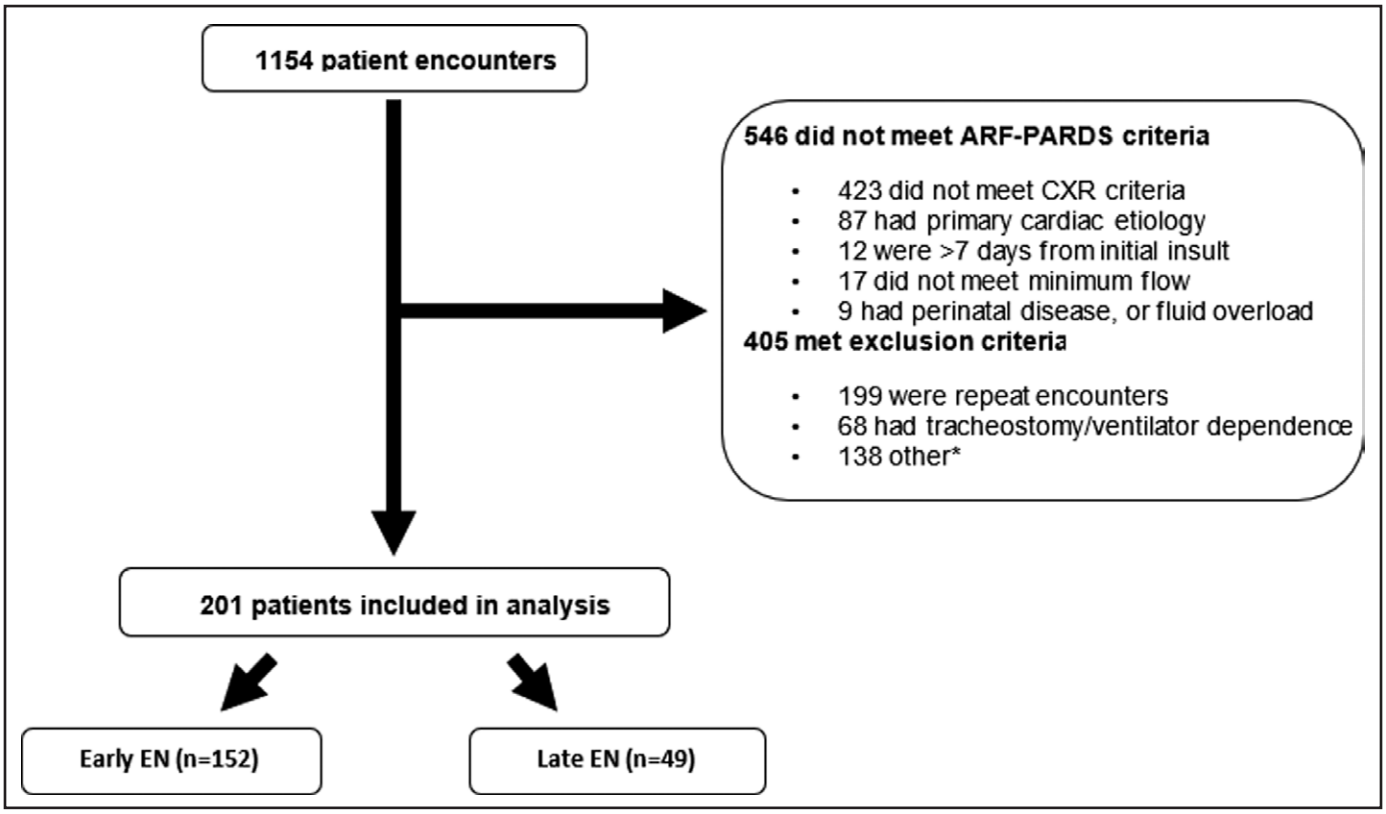

Figure 1. Patient selection. *Pediatric acute respiratory distress syndrome at admission, total parenteral nutrition-dependent, missing data. ARF-PARDS = at-risk for pediatric acute respiratory distress syndrome, CXR = chest radiograph, EN = enteral nutrition.

records (**Fig. 1**). Subsequent PARDS was diagnosed using PALICC criteria PARDS (**Supplemental Table 2**, http://links.lww.com/CCX/B138).

The VPS database was queried for patient age, sex, race, weight, height, PICU LOS, Pediatric Risk of Mortality (PRISM) III score, primary admission diagnosis, mortality, and duration of respiratory support modalities. We then used the electronic medical record (Allscripts Systems, Allscripts Healthcare Solutions, Chicago, IL) to collect additional clinical data including chest radiograph results, nutritional data, respiratory support settings, and oxygenation indices. Race was categorized as Black, White, or "other," which included Asian and mixed-race children. Primary diagnoses were categorized as pneumonia, bronchiolitis, asthma, sepsis, influenza, or "other," which included upper airway obstruction and trauma.

Nutritional data were collected in 8-hour intervals until discharge from PICU, death, or up to 14 days from PICU admission, whichever occurred first. "Early" EN was defined as initiation of any EN by mouth, nasogastric tube, or gastrotomy tube within 48 hours of PICU admission. Children remained in the early EN group regardless of whether EN was paused or stopped after initiation. Initiation of EN after 48 hours from admission was classified as "Delayed" EN.

Mann-Whitney *U* or chi-square tests were used, as appropriate, to compare demographics, clinical characteristics, and hospital outcomes including subsequent diagnosis of PARDS and PICU LOS between children receiving early versus delayed EN. The primary outcome of interest was subsequent diagnosis of PARDS during the PICU stay. Variables that differed between subjects who did and did not progress to PARDS in univariate analysis ($p < 0.05$) were included in the multivariate logistic regression model of subsequent PARDS. Continuous data were presented as medians with interquartile ranges. Categorical data were presented as numbers and percentages. Odds ratios (ORs) are presented with 95% CIs. A two-sided p value of less than 0.05 was considered statistically significant. All analyses were conducted using IBM SPSS Statistics, Version 27 (IBM, Armonk, NY).

RESULTS

In this study, 1,154 nonsurgical patients less than or equal to 18 years old were admitted to our PICU with

acute respiratory failure between January 2017 and December 2018. Over 80% (n = 953) were excluded, most often for not meeting the ARF-PARDS criteria (n = 602), leaving a study cohort of 201 children (Fig. 1). Of these, 152 (75.6%) received EN within 48 hours of PICU admission (early EN), while the remaining 49 children (24.4%) received delayed EN. Demographics and anthropomorphic measurements were similar between the two groups (**Table 1**). The most common admission diagnoses were pneumonia, bronchiolitis, and asthma. Overall mortality was low (< 1%) with only two deaths, both of whom were in the delayed EN group and progressed to PARDS. Compared with the delayed EN group, children receiving early EN had lower PRISM III scores (0 [0–2] vs 1 [0–5]; $p < 0.001$). There were differences in the maximum respiratory support received between the two groups. Children in the early EN group were treated with HFNC more often (77% vs 49%), while children in the delayed EN group required MV more often (28.6% vs 9.9%).

Our primary outcome was subsequent diagnosis of PARDS during the PICU stay. Overall, 21.4%

TABLE 1.

Demographics, Clinical Characteristics, and Hospital Outcomes of a Cohort of Children Meeting "At-Risk" for Pediatric Acute Respiratory Distress Syndrome Criteria, by Feeding Status

Variable	Early EN (n = 152)	Delayed EN (n = 49)	p
Age, mo	18.0 (7.0–69.8)	23.0 (4.5–90.0)	0.612
Female	72 (47.4)	25 (51.0)	0.656
Weight, kg	10.8 (7.2–20.4)	12.8 (6.1–31.6)	0.722
Height, cm[a]	78.0 (61.8–108.0)	84.5 (59.0–122.4)	0.587
Race[b]			0.517
Black	78 (51.3)	21 (42.8)	
White	56 (36.8)	24 (49.0)	
Other	13 (8.6)	3 (6.1)	
Primary diagnosis			0.168
Bronchiolitis/respiratory syncytial virus	52 (34.2)	12 (42.9)	
Pneumonia	35 (23.0)	14 (28.6)	
Asthma	24 (15.8)	5 (10.2)	
Sepsis	10 (6.6)	8 (16.3)	
Influenza	9 (6.0)	1 (2.0)	
Other	22 (14.5)	9 (18.4)	
Pediatric Risk of Mortality III score	0 (0–2)	1 (0–5)	< 0.001
Maximum respiratory support			0.001
High-flow nasal cannula	117 (77.0)	24 (49.0)	
Continuous positive airway pressure	4 (2.6)	3 (6.1)	
Bilevel positive airway pressure	16 (10.5)	8 (16.3)	
Invasive mechanical ventilation	15 (9.9)	14 (28.6)	
Subsequent diagnosis of pediatric acute respiratory distress syndrome, yes	23 (15.1)	20 (40.8)	< 0.001
PICU length of stay, d	2.2 (1.5–3.4)	4.2 (2.7–8.9)	< 0.001

EN = enteral nutrition.

[a]Missing data on seven patients in early EN group and one patient in delayed EN group.

[b]Missing data on three patients in early EN group.

Data are presented as median (interquartile range) or n (%), as appropriate.

(n = 43) of children developed PARDS. Children receiving early EN were subsequently diagnosed with PARDS less often than children receiving delayed EN (15.1% [23/152] vs 40.8% [20/49]; $p < 0.001$). There were differences in age, weight, height, primary diagnoses, severity of illness score, and feeding practices between children who did and did not develop PARDS (**Table 2**). After adjusting for these demographics and clinical factors including PRISM III, early EN remained associated with a reduction in the odds of subsequent diagnosis of PARDS (adjusted OR, 0.24; 95% CI, 0.10–0.58; $p = 0.002$) (**Table 3**). Early EN was also associated with an unadjusted reduction in PICU LOS when compared with delayed EN (2.2 vs 4.2 d; $p < 0.001$).

DISCUSSION

In this cohort of children "at-risk" for PARDS based on the 2015 PALICC criteria, initiation of EN within 48 hours of PICU admission was associated with a 75% reduction in the odds of a subsequent PARDS diagnosis. Although provision of early EN was at the discretion of individual providers, this association was preserved after adjusting for confounders, including illness severity (PRISM III) and primary diagnosis. Early EN was also associated with shorter PICU LOS in unadjusted analyses. Although the study methodology and risk of bias temper our results, overall our findings support the design of future prospective studies examining early EN as a potential therapy for critically ill children with acute hypoxemic respiratory failure.

The association between early EN and improved outcomes has been shown in both general PICU populations and specifically in respiratory failure; however, the potential benefits in children categorized as at-risk for PARDS have not been previously demonstrated in the literature (1–9). Because of the high morbidity and mortality associated with PARDS, identifying

TABLE 2.
Demographics and Clinical Characteristics Associated With Subsequent Diagnosis of Pediatric Acute Respiratory Distress Syndrome

Variable	Subsequent Diagnosis of PARDS (n = 43)	No Subsequent Diagnosis of PARDS (n = 158)	p
Age, mo	90.0 (22.0–169.0)	15.0 (6.0–48.5)	< 0.001
Female	18 (41.9)	79 (50.0)	0.344
Weight, kg	30.0 (10.2–51.5)	9.9 (6.8–16.8)	< 0.001
Height, cm[a]	106.0 (73.5–157.4)	75.0 (60.0–101.3)	< 0.001
Race[b]			0.642
Black	20 (46.5)	79 (51.0)	
White	20 (46.5)	60 (38.7)	
Other	2 (4.7)	14 (9.0)	
Primary diagnosis			0.032
Bronchiolitis/respiratory syncytial virus	6 (14.0)	58 (36.7)	
Pneumonia	11 (25.6)	38 (24.1)	
Asthma	8 (18.6)	21 (13.3)	
Sepsis	8 (18.6)	10 (6.3)	
Influenza	2 (4.7)	8 (5.1)	
Other	8 (18.6)	23 (14.6)	
Pediatric Risk of Mortality III	1 (0–6)	0 (0–2)	< 0.001
Early enteral nutrition, yes	23 (53.5)	129 (81.6)	< 0.001

PARDS = pediatric acute respiratory distress syndrome.
[a]Missing data for four patients in both groups.
[b]Missing data for three patients in no subsequent diagnosis of PARDS group.
Data are presented as median (interquartile range) or *n* (%), as appropriate.

TABLE 3.
Adjusted Odds of Subsequent Diagnosis of Pediatric Acute Respiratory Distress Syndrome in a Cohort of Children Meeting "At-Risk" for Pediatric Acute Respiratory Distress Syndrome Criteria

Variable	β Coefficient	OR (95% CI)	*p*
Early EN (vs late EN)	−1.412	0.24 (0.10–0.58)	0.002
Age, mo	0.007	1.00 (0.99–1.02)	0.333
Weight, kg	0.031	1.03 (0.88–1.14)	0.107
Height, cm[a]	−0.007	0.99 (0.96–1.02)	0.621
Primary diagnosis			
Bronchiolitis/ respiratory syncytial virus	Reference		
Influenza	0.945	2.57 (0.39–17.08)	0.328
Asthma	−0.022	0.98 (0.20–4.72)	0.978
Pneumonia	0.111	1.12 (0.32–3.93)	0.862
Sepsis	1.156	3.18 (0.59–17.17)	0.179
Other	0.176	1.19 (0.28–5.14)	0.813
Pediatric Risk of Mortality III	0.003	1.00 (0.88–1.14)	0.961

EN = enteral nutrition, OR = odds ratio.
[a]Missing data on eight patients.

potential preventative therapies is important. Several large, multicenter, retrospective studies have demonstrated decreased odds of mortality among heterogeneous populations of critically ill children receiving early EN, compared with those receiving delayed EN (6, 8). Others still have found a similar association in mechanically ventilated children with acute respiratory distress syndrome (4, 18). While both children who died in our study received delayed EN, overall mortality was too low (< 1%) to make any inferences regarding the benefits of early EN in decreasing mortality risk. Children receiving early EN in our cohort had a median PICU LOS 2 days shorter than children receiving late EN. Previous studies examining the association between LOS and timing of EN initiation in children with acute respiratory failure have suggested an inconsistent benefit of early EN, with some demonstrating a reduced PICU LOS (19, 20), while others found no difference at all (21). These inconsistencies highlight the need to design prospective studies with protocolized nutrition delivery to better understand the potential benefits of this therapy in children with acute respiratory failure.

In univariate analysis, we found younger age, smaller size (weight and height), lower severity of illness, and early EN to all be associated with lower rate of subsequent PARDS diagnosis in a cohort of children meeting ARF-PARDS criteria. In multivariate analysis, however, early EN was the only factor associated with decreased odds of subsequent PARDS. There is prior evidence to suggest an association between EN and improved patient outcomes for children in acute hypoxic respiratory failure (22–24). The nutritive benefits of food in a critically ill child with altered metabolism are well described and inform current practice guidelines (14). Targeted provision of protein, calories, and micronutrients may serve to attenuate the often-deleterious effects of pathologic catabolism during critical illness. But there is also emerging evidence suggesting that gut dysfunction has a direct role in the development of a pro-inflammatory state such as in PARDS (10, 11). Because the gastrointestinal tract is a primary lymphoid organ and major component of the immune system, intestinal barrier dysfunction can cause bacterial translocation and the release and upregulation of systemic inflammatory mediators, potentially causing or exacerbating multisystem organ dysfunction, including respiratory failure (10, 11, 14). The potential to modulate the intestinal immune system and reduce downstream inflammatory signaling in the lung through maintenance of the intestinal epithelial barrier is an area of active investigation. For now, judicious use of EN remains a promising therapeutic means of preventing intestinal epithelial barrier dysfunction, although the key constituents and minimal critical volume (so called "trophic feeds") is not yet known (14, 22–24). The role EN plays within these complex immune interactions may potentially explain the improved outcomes seen in children with respiratory failure, including in our study.

Over one-fifth (21.4%) of children meeting ARF-PARDS criteria in our study developed PARDS during their PICU stay, a rate similar to the multicenter, international PARDS Incidence and Epidemiology (PARDIE) substudy (25). While our observed 4.7% mortality rate for ARF-PARDS children who then developed PARDS was much lower than the 21.2% mortality rate reported in the PARDIE substudy, this may reflect our single-center design and our exclusions of

patients with PARDS at admission, surgical disease and cardiac disease (25, 26). The morbidity and mortality associated with PARDS, a disease that currently has no specific treatment, makes identifying preventative and therapeutic measures of high importance.

There are several limitations to this study. First, its retrospective, single-center design and small sample size limits generalizability and can at best identify an association between feeding practices and clinical outcomes. Second, decisions regarding respiratory support were at the clinician's discretion, creating the potential for biased over inclusion of children with relatively mild respiratory illness into our study cohorts. While PRISM III scoring was incorporated to control for differences in illness severity, its validity for use in children at-risk for PARDS is unknown, despite previous utilization in predicting mortality in children with PARDS (27, 28). Therefore, the score may not be ideally suited to adjust for illness severity in our population, particularly given the overall low scores and low reported mortality. Likewise, a feeding protocol was not used and therefore risk factors and clinical variables that may have influenced the decision to delay EN were neither controlled nor elucidated. Ultimately, the uncertainty around whether early EN was related to improved outcomes, or just a marker of lower illness severity must be recognized. Third, the lack of granular nutritional data within the EHR limited our ability to address additional confounders, including timing and route of EN, percentage of goal calories reached, and feeding interruption, intolerance, or feeding-associated complications. Last, we choose to limit our study years to the pre-COVID-19 pandemic era to limit confounding and loss of generalizability but feeding practices may have changed since that time.

CONCLUSIONS

This is the first study to describe the feeding practices in children meeting the 2015 PALICC at-risk for PARDS definition. In this single-institution cohort, early EN was associated with a significant reduction in the odds of subsequent diagnosis of PARDS as well as a reduced PICU LOS, when compared with delayed EN. Future larger and prospective studies are needed to verify these results and determine how best to tailor the provision of early EN to those children at-risk for progression to PARDS. Additional factors such as optimal route, method for caloric advancement, and individualized nutritional goal constitute areas in need of further investigation (29, 30).

1 *Division of Critical Care Medicine, Department of Anesthesiology Critical Care, Children's Hospital of Los Angeles, Los Angeles, CA.*

2 *University of Southern California, Los Angeles, CA.*

3 *Division of Critical Care, Department of Pediatrics, University Hospitals Rainbow Babies & Children's Hospital, Cleveland, OH.*

4 *Case Western Reserve University School of Medicine, Cleveland, OH.*

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccejournal).

The authors have disclosed that they do not have any potential conflicts of interest.

For information regarding this article, E-mail: tpei@chla.usc.edu

This work was performed at University Hospitals Rainbow Babies & Children's Hospital, Cleveland, OH.

REFERENCES

1. Bağci S, Keleş E, Girgin F, et al: Early initiated feeding versus early reached target enteral nutrition in critically ill children: An observational study in paediatric intensive care units in Turkey. *J Paediatr Child Health* 2018; 54:480–486
2. Briassoulis G, Zavras N, Hatzis T: Malnutrition, nutritional indices, and early enteral feeding in critically ill children. *Nutrition* 2001; 17:548–557
3. Gottschlich MM, Jenkins ME, Mayes T, et al: The 2002 clinical research award. An evaluation of the safety of early vs delayed enteral support and effects on clinical, nutritional, and endocrine outcomes after severe burns. *J Burn Care Rehabil* 2002; 23:401–415
4. Mehta NM: Early enteral nutrition in the PICU: Should we trust our gut? *Pediatr Crit Care Med* 2015; 16:786–789
5. Mehta NM, Bechard LJ, Cahill N, et al: Nutritional practices and their relationship to clinical outcomes in critically ill children--an international multicenter cohort study*. *Crit Care Med* 2012; 40:2204–2211
6. Mikhailov TA, Kuhn EM, Manzi J, et al: Early enteral nutrition is associated with lower mortality in critically ill children. *JPEN J Parenter Enteral Nutr* 2014; 38:459–466
7. Sánchez C, López-Herce J, Carrillo A, et al: Early transpyloric enteral nutrition in critically ill children. *Nutrition* 2007; 23:16–22
8. Srinivasan V, Hasbani NR, Mehta NM, et al: Early enteral nutrition is associated with improved clinical outcomes in critically ill children: A secondary analysis of nutrition support in the heart and lung failure-pediatric insulin titration trial. *Pediatr Crit Care Med* 2020; 21:213–221

9. Venter M, Rode H, Sive A, et al: Enteral resuscitation and early enteral feeding in children with major burns--effect on McFarlane response to stress. *Burns* 2007; 33:464–471
10. Feng Y, Ralls MW, Xiao W, et al: Loss of enteral nutrition in a mouse model results in intestinal epithelial barrier dysfunction. *Ann N Y Acad Sci* 2012; 1258:71–77
11. Fukatsu K, Zarzaur BL, Johnson CD, et al: Enteral nutrition prevents remote organ injury and death after a gut ischemic insult. *Ann Surg* 2001; 233:660–668
12. Mehta NM, Skillman HE, Irving SY, et al: Guidelines for the provision and assessment of nutrition support therapy in the pediatric critically ill patient: Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition. *Pediatr Crit Care Med* 2017; 18:675–715
13. Tume LN, Valla FV, Joosten K, et al: Nutritional support for children during critical illness: European Society of Pediatric and Neonatal Intensive Care (ESPNIC) metabolism, endocrine and nutrition section position statement and clinical recommendations. *Intensive Care Med* 2020; 46:411–425
14. Wilson B, Typpo K: Nutrition: A primary therapy in pediatric acute respiratory distress syndrome. *Front Pediatr* 2016; 4:108
15. Wong JJ, Jit M, Sultana R, et al: Mortality in pediatric acute respiratory distress syndrome: A systematic review and meta-analysis. *J Intensive Care Med* 2019; 34:563–571
16. Pediatric Acute Lung Injury Consensus Conference Group: Pediatric acute respiratory distress syndrome: Consensus recommendations from the pediatric acute lung injury consensus conference. *Pediatr Crit Care Med* 2015; 16:428–439
17. Slain KN, Rotta AT, Martinez-Schlurmann N, et al: Outcomes of children with critical bronchiolitis meeting at risk for pediatric acute respiratory distress syndrome criteria. *Pediatr Crit Care Med* 2019; 20:e70–e76
18. Wong JJ, Han WM, Sultana R, et al: Nutrition delivery affects outcomes in pediatric acute respiratory distress syndrome. *JPEN J Parenter Enteral Nutr* 2017; 41:1007–1013
19. Haney A, Burritt E, Babbitt CJ: The impact of early enteral nutrition on pediatric acute respiratory failure. *Clin Nutr ESPEN* 2018; 26:42–46
20. Slain KN, Martinez-Schlurmann N, Shein SL, et al: Nutrition and high-flow nasal cannula respiratory support in children with bronchiolitis. *Hosp Pediatr* 2017; 7:256–262
21. Tripathi S, Kaur H, Varayil JE, et al: Effects of enteral nutrition on clinical outcomes among mechanically ventilated and sedated patients in the pediatric intensive care unit. *Signa Vitae* 2015; 10:131–148
22. Iyer R, Bansal A: What do we know about optimal nutritional strategies in children with pediatric acute respiratory distress syndrome? *Ann Transl Med* 2019; 7:510–510
23. Keim G, Thomas NJ: Can we prevent the progression to pediatric acute respiratory distress syndrome? Let's start with identifying those "at risk." *Pediatr Crit Care Med* 2019; 20:204–205
24. Valentine SL, Nadkarni VM, Curley MA, et al: Nonpulmonary treatments for pediatric acute respiratory distress syndrome: Proceedings from the pediatric acute lung injury consensus conference. *Pediatr Crit Care Med* 2015; 16(5 Suppl 1):S73–S85
25. Shein SL, Maddux AB, Klein MJ, et al: Epidemiology and outcomes of critically ill children at risk for pediatric acute respiratory distress syndrome: A pediatric acute respiratory distress syndrome incidence and epidemiology study. *Crit Care Med* 2022; 50:363–374
26. Khemani RG, Smith L, Lopez-Fernandez YM, et al: Paediatric acute respiratory distress syndrome incidence and epidemiology (PARDIE): An international, observational study. *Lancet Respir Med* 2019; 7:115–128
27. Zimmerman JJ, Akhtar SR, Caldwell E, et al: Incidence and outcomes of pediatric acute lung injury. *Pediatrics* 2009; 124:87–95
28. Flori H, Dahmer MK, Sapru A, et al: Comorbidities and assessment of severity of pediatric acute respiratory distress syndrome: Proceedings from the pediatric acute lung injury consensus conference. *Pediatr Crit Care Med* 2015; 16(5 Suppl 1):S41–S50
29. Brown AM, Carpenter D, Keller G, et al: Enteral nutrition in the PICU: Current status and ongoing challenges. *J Pediatr Intensive Care* 2015; 4:111–120
30. Tume LN, Valla FV, Floh AA, et al: Priorities for nutrition research in pediatric critical care. *JPEN J Parenter Enteral Nutr* 2019; 43:853–862