BRIEF REPORT

OPEN

First-Line Respiratory Support for Children With Hematologic Malignancy and Acute Respiratory Failure

Hassaan Asif, BS[1]

Jennifer L. McNeer, MD, MS[2]

Nancy S. Ghanayem, MD, MS[3]

John F. Cursio, PhD[4]

Jason M. Kane, MD, MS[3]

OBJECTIVES: To characterize trends in noninvasive ventilation (NIV) and invasive mechanical ventilation (IMV) use over time in children with hematologic malignancy admitted to the PICU with acute respiratory failure (ARF), and to identify risk factors associated with NIV failure requiring transition to IMV.

DESIGN: Retrospective cohort analysis using the Virtual Pediatric Systems (VPS, LLC) between January 1, 2010 and December 31, 2019.

SETTING: One hundred thirteen North American PICUs participating in VPS.

PATIENTS: Two thousand four hundred eighty children 0–21 years old with hematologic malignancy admitted to participating PICUs for ARF requiring respiratory support.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: There were 3013 total encounters, of which 868 (28.8%) received first-line NIV alone (NIV only), 1544 (51.2%) received first-line IMV (IMV only), and 601 (19.9%) required IMV after a failed NIV trial (NIV failure). From 2010 to 2019, the NIV only group increased from 9.6% to 43.1% and the IMV only group decreased from 80.1% to 34.2% ($p < 0.001$). The NIV failure group had the highest mortality compared with NIV only and IMV only (36.6% vs. 8.1%, vs. 30.5%, $p < 0.001$). However, risk-of-mortality (ROM) was highest in the IMV only group compared with NIV only and NIV failure (median Pediatric Risk of Mortality III ROM 8.1% vs. 2.8% vs. 5.5%, $p < 0.001$). NIV failure patients also had the longest median PICU length of stay compared with the other two study groups (15.2 d vs. 6.1 and 9.0 d, $p < 0.001$). Higher age was associated with significantly decreased odds of NIV failure, and diagnosis of non-Hodgkin lymphoma was associated with significantly increased odds of NIV failure compared with acute lymphoid leukemia.

CONCLUSIONS: For children with hematologic malignancy admitted to the PICU with ARF, NIV has replaced IMV as the most common initial therapy. NIV failure rate remains high with high-observed mortality despite lower PICU admission ROM.

KEYWORDS: endotracheal intubation; hematologic neoplasm; intensive care units; noninvasive ventilation; pediatric; respiratory failure

Pediatric patients with oncologic disease account for 4% of all PICU admissions but represent 11% of PICU mortality. Compared with children with solid tumors, children with hematologic malignancy have higher illness severity, infection rates, and PICU mortality. Many are admitted to the PICU with acute respiratory failure (ARF) requiring advanced respiratory support (1). Noninvasive ventilation (NIV) is increasingly used for the initial temporization and treatment of acute respiratory failure in the PICU (2). NIV has emerged as a means to stave-off invasive mechanical ventilation

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KEY POINTS

Question: How does the choice of first-line respiratory support in children with hematologic malignancy and acute respiratory failure (ARF) affect clinical outcomes?

Findings: In this retrospective cohort study across 113 PICUs, children with hematologic malignancy who failed a trial of noninvasive ventilation (NIV) and required invasive mechanical ventilation (IMV) had worse clinical outcomes compared with those requiring only NIV or only IMV, despite lower PICU admission risk of mortality.

Meaning: Careful attention should be paid to selection criteria for determining candidacy for NIV trial for children with hematologic malignancy in ARF due to disparities in outcomes relative to predicted risk of mortality.

(IMV) and avoid barotrauma, ventilator-associated events, and intubation-related complications (3). Adult oncology data suggest a survival benefit when NIV is first-line therapy in patients admitted to the ICU with ARF; however, data in children are lacking (4).

Immunocompromised children, including those with malignancy, admitted to the PICU with ARF requiring respiratory support have worse overall clinical outcomes compared with children with a functional immune system (5). The initial choice of respiratory support modality for patients with compromised immune function is not standardized and there is significant center-to-center variation in the choice of first-line modality (6, 7). Despite the suggested efficacy of NIV in pediatric patients with all-cause ARF admitted to the PICU, there is a paucity of recent data on NIV usage in pediatric oncology patients. It is unclear how NIV and IMV use have changed over time for children with hematologic malignancy admitted to the PICU with ARF. The purpose of this study was to investigate the rates of IMV and NIV use over time for pediatric patients with hematologic malignancy admitted to the PICU with ARF, and to identify risk factors associated with NIV failure.

MATERIALS AND METHODS

A retrospective cohort study of pediatric oncology patients admitted to participating PICUs between January 1, 2010, and December 31, 2019, with ARF was performed. Patients with hematologic malignancies were identified using codes from the *International Classification of Diseases*, ninth Revision (ICD-9) and ICD-10 corresponding to "malignant neoplasms of lymphoid, hematopoietic, and related tissue" (**Supplemental eTable 1** http://links.lww.com/CCX/B329). Only those admitted to a PICU with the diagnosis of ARF (ICD-10 = J96.X or ICD-9 = 518.XX) were included. Postoperative, planned, post-hematopoietic stem cell transplantation admissions and patients with chronic respiratory failure or tracheostomy before PICU admission were excluded. Only the first use of respiratory support during any PICU admission was analyzed. Deidentified data were obtained from the Virtual Pediatric Systems (VPS) database and included demographic, admission characteristics, respiratory support modality, diagnosis codes, risk-of-mortality (ROM) scores as measured by the Pediatric Index of Mortality (PIM) 2 and Third-Generation Pediatric Risk of Mortality (PRISM III), and clinical outcomes at PICU discharge (8–10).

NIV was defined as the use of continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP), or heated humidified high flow nasal cannula; IMV use was defined as endotracheal intubation and mechanical ventilation. Three study groups were created based on the respiratory support modality received. Patients who received IMV only or required IMV less than 2 hours after initiating NIV were grouped as "IMV only." Those who received more than 2 hours of NIV before IMV were grouped as "NIV failure." Two hours was chosen as the cutoff to allow for NIV usage in preparation for intubation after arrival at the PICU. Patients who received only NIV without IMV were grouped as "NIV only."

Trends in use over time were assessed by comparing annual rates of the three groups. Multivariable logistic regression analysis of factors associated with each of the study groups was performed to identify risks associated with each strategy. Specifically, two models were analyzed: one comparing the NIV failure and NIV only groups, and the second comparing the NIV failure and IMV only groups.

Age, race, oncologic diagnoses, PICU length of stay, mortality, and ROM scores were compared between study groups using chi-square tests. Median and range of continuous variables were compared using

Wilcoxon rank-sum tests. Logistic multivariable regression models were used to predict failure outcomes. Analyses were performed in SAS, version 9.4 (Cary, NC). The institutional review board at the University of Chicago exempted this study (IRB22-0116).

RESULTS

After application of inclusion and exclusion criteria, there were 3013 encounters across 113 PICUs. The largest study group was IMV only group (51.2%), followed by NIV only group (28.8%), and finally NIV failure group (19.9%) (**Table 1**). Median PIM 2 ROM was significantly higher in the IMV only group (6.1%) compared with the NIV only and NIV failure groups (4.6% and 4.7%, $p < 0.001$). Median PRISM III ROM was also significantly higher in the IMV only group (8.1%) compared with the NIV only and NIV failure groups (2.8% and 5.5%, $p < 0.001$). However, the NIV failure group had significantly higher observed PICU mortality compared with the NIV only and IMV only groups, respectively (36.6% vs. 8.1% and 30.5%, $p < 0.001$). The NIV failure group also had longer median PICU length of stay compared with the NIV only and IMV only groups (15.2 vs. 6.1 and 9.0 d, $p < 0.001$).

Compared with 2010, the percentage of NIV only encounters in 2019 increased from 9.6% to 43.1% (*p*

TABLE 1.
Characteristics of Individual PICU Encounters

Characteristics	Subcharacteristic	All Encounters (*n* = 3013)	NIV Only (*n* = 868)	IMV Only (*n* = 1544)	NIV Failure (*n* = 601)	*p*
Sex, *n* (%)	Female	1369 (45.4)	397 (45.7)	690 (44.7)	282 (46.9)	0.63
Age distribution, *n* (%)	0–23 mo	302 (10.0)	66 (7.6)	175 (11.3)	61 (10.1)	< 0.001
	2–5 yr	613 (20.4)	161 (18.6)	345 (22.3)	107 (17.8)	
	6–11 yr	738 (24.5)	204 (23.5)	379 (24.6)	155 (25.8)	
	12–17 yr	1016 (33.7)	312 (35.9)	495 (32.1)	209 (34.8)	
	18–21 yr	344 (11.4)	125 (14.4)	150 (9.7)	69 (11.5)	
Diagnosis, *n* (%)	Acute lymphoid leukemia	1628 (54.0)	436 (50.2)	887 (57.5)	305 (50.8)	< 0.001
	Acute myeloid leukemia	714 (23.7)	248 (28.6)	306 (19.8)	160 (26.6)	
	Chronic myeloid leukemia	31 (1.0)	10 (1.2)	13 (0.8)	8 (1.3)	
	Non-Hodgkin lymphoma	283 (9.4)	70 (8.1)	143 (9.3)	70 (11.7)	
	Hodgkin lymphoma	64 (2.1)	27 (3.1)	26 (1.7)	11 (1.8)	
	Burkitt lymphoma	65 (2.2)	16 (1.8)	35 (2.3)	14 (2.3)	
	Other	228 (7.6)	61 (7.0)	134 (8.7)	33 (5.5)	
Severity, median % (range)	PIM 2 ROM	5.1 (0.2–99.6)	4.6 (0.2–48.9)	6.1 (0.2–99.6)	4.7 (0.2–37.9)	< 0.001
	PRISM III ROM	5.0 (0.1–99.9)	2.8 (0.2–66.3)	8.1 (0.1–99.9)	5.5 (0.3–92.8)	< 0.001
Duration of respiratory Support	Days of NIV, median (range)	N/A	2.6 (0.0–72.0)	N/A	N/A	
	Days of NIV before IMV, median (range)	N/A	N/A	N/A	1.0 (0.1–53.2)	
	Days of IMV, median (range)	N/A	N/A	3.5 (0.03–135.7)	6.3 (0.03–71.7)	
Outcomes	PICU length of stay median days (range)	9.1 (0.1–248.1)	6.1 (0.11–115.8)	9.0 (0.1–248.2)	15.2 (0.5–115.8)	< 0.001
	Mortality, *n* (%)	761 (25.3)	70 (8.1)	471 (30.5)	220 (36.6)	< 0.001

IMV = invasive mechanical ventilation, NIV = noninvasive ventilation, PIM 2 = Pediatric Index of Mortality 2, PRISM III = Third-Generation Pediatric Risk of Mortality, ROM = risk-of-mortality.

< 0.001), and the percentage of IMV only encounters decreased from 80.1% to 34.2% ($p < 0.001$). There was an increase in the percentage of NIV failure encounters from 12.1% in 2012 to 22.1% in 2013, which was relatively stable for the remainder of the study period, ranging from a low of 19.2% in 2015 to a high of 22.7% in 2019 (**Fig. 1**). There was also notable center-to-center variation in first-line respiratory modality choice (**Supplemental eFig. 1**, http://links.lww.com/CCX/B329).

When stratified by survival to PICU discharge, median PIM 2 and PRISM III scores were higher in the nonsurvivor group (5.6% and 26.6%) compared with survivors (5.0% and 3.5%, $p < 0.001$) (**Supplemental eTable 2**, http://links.lww.com/CCX/B329). Study group distribution was significantly different between the survivors and nonsurvivors, with a higher percentage of IMV only or NIV failure in nonsurvivors, and a higher percentage of NIV only in survivors.

Based on the multivariable logistic regression analyses, compared with NIV only, increasing age was associated with significantly decreased odds of NIV failure.(**Supplemental eTable 3**, http://links.lww.com/CCX/B329) Likewise, higher PRISM III score, but not PIM2 score, was associated with significantly higher odds of NIV failure. Compared with acute lymphoid leukemia, non-Hodgkin lymphoma was the only cancer diagnosis significantly associated with odds of NIV failure.

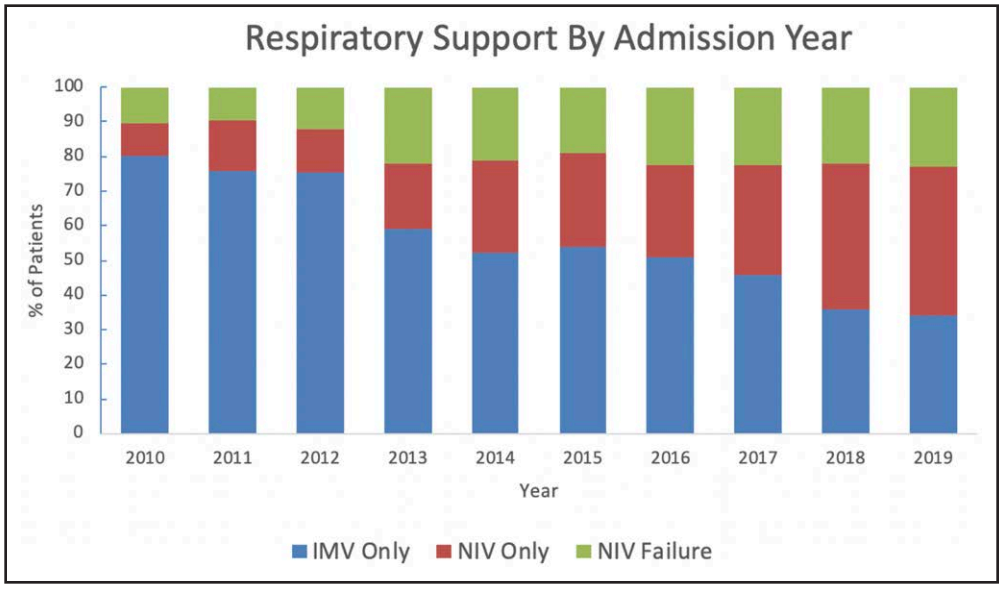

Figure 1. Percentage of patients in each study group by year. *Stacked bar* graph of respiratory support as a percentage of the total cohort over time. IMV = invasive mechanical ventilation, NIV = noninvasive ventilation.

DISCUSSION

Over the past decade, NIV has been replacing IMV as the first-line respiratory support for pediatric patients with hematologic malignancy admitted to the PICU with ARF, which is similar to other PICU cohorts with ARF (5, 11, 12). Also, we observed an initial increase in the percentage of NIV failure encounters which then remained stable between 2013 and 2019. Because patients with unsuccessful NIV had worse PICU outcomes compared with the other groups, these data raise concern about patient selection for first-line respiratory support. Additionally, patients with NIV failure had lower predicted ROM but higher observed mortality compared with the other groups, which could suggest unrecognized clinical factors that contribute to failure, such as iatrogenic positive pressure-induced lung injury with NIV, or a delay in initiation of IMV when clinically indicated. The higher-than-predicted mortality in the cohort of NIV failure patients identifies a target population for additional study identifying risk factors associated with poor outcomes.

These data reveal differences in clinical outcomes for critically-ill children with hematologic malignancy based on initial respiratory support. Previous data identified any IMV as an independent risk factor for mortality in children with various hemato-oncologic disease but did not include unsuccessful NIV in the analysis (13). Children who fail their NIV and require intubation have higher rates of PICU mortality compared with those who tolerate NIV or IMV alone. Similar findings have been described in adult ICU oncology patients where patients who failed NIV and required IMV had high mortality overall and specifically those who failed NIV and subsequently received IMV (71.3%) had the highest mortality compared with those receiving IMV only (61.5%) and NIV only (28.2%) (14, 15). Additionally there are data to suggest that use of CPAP

as a form of NIV may increase risk of IMV in pediatric patients with impaired immunity (16). Overall, any pediatric patient admitted to the PICU with ARF who fails NIV has worse outcomes than those who require only IMV (5–7, 14, 15, 17, 18). In our study, advancing age decreased odds of NIV failure, whereas a diagnosis of non-Hodgkin lymphoma increased odds of NIV failure. Specific non-Hodgkin lymphoma tumor subtype may have influenced this finding. Finally, these data suggest an association between failed NIV and increased mortality, and thus critical evaluation of patient candidacy for an NIV trial to stave-off IMV may be warranted.

This study has several limitations. First, the data from VPS may be subject to data entry errors, but strict quality control around data entry may ameliorate that risk. Additionally, respiratory support use before or after PICU admission is not captured by VPS. Furthermore, the IMV only group included patients with less than 2 hours of preintubation NIV to account for cases of planned intubation with NIV use only to temporize patients. Patient-specific physiologic variables (such as partial pressure of oxygen or CO_2) were not included in the multivariable regression due to a high percentage of missing data. PIM/PRISM risk of mortality scores are validated for the general PICU population and not specifically for those with hematologic malignancy and thus may not accurately capture PICU admission risk of mortality in this population. It is also important to note that both PIM/PRISM are coded at the time of PICU admission and thus patients whose disease state progresses despite critical care interventions may have lower initial predicted ROM than their ultimate mortality. Additionally, a database coding change with BiPAP designation occurred in the VPS dataset in 2012 which likely accounted for the sharp increase in NIV failure between 2012 and 2013. Finally, these results may not be generalizable to PICUs dissimilar to those participating in VPS.

CONCLUSIONS

NIV has become the most common first-line respiratory modality for pediatric patients with hematologic malignancy admitted to the PICU with ARF. NIV failure rates have remained elevated, with high mortality in those who fail a trial of NIV before IMV despite lower predicted mortality. Standardized and objective criteria for a trial of NIV may be prudent to avoid untoward outcomes in PICU patients with hematologic malignancies admitted with ARF.

1 Pritzker School of Medicine, University of Chicago, Chicago, IL.

2 Department of Pediatrics, Section of Pediatric Hematology/Oncology, University of Utah, Primary Children's Hospital, Salt Lake City, UT.

3 Department of Pediatrics, Section of Pediatric Critical Care Medicine, University of Chicago, Comer Children's Hospital, Chicago, IL.

4 Department of Public Health Sciences, University of Chicago, Chicago, IL.

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For information regarding this article, E-mail: jasonk@uchicago.edu

REFERENCES

1. Zinter MS, DuBois SG, Spicer A, et al: Pediatric cancer type predicts infection rate, need for critical care intervention, and mortality in the pediatric intensive care unit. *Intensive Care Med* 2014; 40:1536–1544
2. Alibrahim O, Rehder KJ, Miller AG, et al: Mechanical ventilation and respiratory support in the pediatric intensive care unit. *Pediatr Clin North Am* 2022; 69:587–605
3. Grieco DL, Maggiore SM, Roca O, et al: Non-invasive ventilatory support and high-flow nasal oxygen as first-line treatment of acute hypoxemic respiratory failure and ARDS. *Intensive Care Med* 2021; 47:851–866
4. Barreto LM, Ravetti CG, Athaíde TB, et al; Núcleo Interdisciplinar de Investigação em Medicina Intensiva (NIIMI): Factors associated with non-invasive mechanical ventilation failure in patients with hematological neoplasia and their association with outcomes. *J Intensive Care* 2020; 8:68
5. Kopp W, Gedeit RG, Asaro LA, et al; Randomized Evaluation of Sedation Titration for Respiratory Failure (RESTORE) Study Investigators: The impact of preintubation noninvasive ventilation on outcomes in pediatric acute respiratory distress syndrome. *Crit Care Med* 2021; 49:816–827
6. Lindell RB, Fitzgerald JC, Rowan CM, et al; National Emergency Airway Registry for Children (NEAR4KIDS) and

Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network: The use and duration of preintubation respiratory support is associated with increased mortality in immunocompromised children with acute respiratory failure. *Crit Care Med* 2022; 50:1127–1137

7. Rowan CM, Gertz SJ, McArthur J, et al; Investigators of the Pediatric Acute Lung Injury and Sepsis Network: Invasive mechanical ventilation and mortality in pediatric hematopoietic stem cell transplantation. *Pediatr Crit Care Med* 2016; 17:294–302
8. Wetzel RC: Pediatric intensive care databases for quality improvement. *J Pediatr Intensive Care* 2015; 5:81–88
9. Slater A, Shann F, Pearson G; Paediatric Index of Mortality (PIM) Study Group: PIM2: A revised version of the paediatric index of mortality. *Intensive Care Med* 2003; 29:278–285
10. Pollack MM, Patel KM, Ruttimann UE: PRISM III. An updated pediatric risk of mortality score. *Crit Care Med* 1996; 24:743–752
11. Ganu SS, Gautam A, Wilkins B, et al: Increase in use of noninvasive ventilation for infants with severe bronchiolitis is associated with decline in intubation rates over a decade. *Intensive Care Med* 2012; 38:1177–1183
12. Smith A, França UL, McManus ML: Trends in the use of noninvasive and invasive ventilation for severe asthma. *Pediatrics* 2020; 146:e20200534
13. García-Salido A, Mastro-Martínez I, Cabeza-Martín B, et al.: Respiratory failure in children with hemato-oncological diseases admitted to the PICU: A single-center experience. *J Pediatr Hematol Oncol* 2015; 37:449–454
14. Rathi NK, Haque SA, Nates R, et al: Noninvasive positive pressure ventilation vs invasive mechanical ventilation as first-line therapy for acute hypoxemic respiratory failure in cancer patients. *J Crit Care* 2017; 39:56–61
15. Liu J, Bell C, Campbell V, et al: Noninvasive ventilation in patients with hematologic malignancy: A retrospective study. *J Intensive Care Med* 2019; 34:197–203
16. Peters MJ, Agbeko R, Davis P, et al; SCARF Study Investigators and the Pediatric Intensive Care Society Study Group (PICS-SG): Randomized study of early continuous positive airways pressure in acute respiratory failure in children with impaired immunity (SCARF) ISRCTN82853500. *Pediatr Crit Care Med* 2018; 19:939–948
17. Molina R, Bernal T, Borges M, et al; EMEHU study investigators: Ventilatory support in critically ill hematology patients with respiratory failure. *Crit Care* 2012; 16:R133
18. Gristina GR, Antonelli M, Conti G, et al; GiViTI (Italian Group for the Evaluation of Interventions in Intensive Care Medicine): Noninvasive versus invasive ventilation for acute respiratory failure in patients with hematologic malignancies: A 5-year multicenter observational survey. *Crit Care Med* 2011; 39:2232–2239