Progression of Respiratory Support Following Pediatric Extubation

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Author Contributions:
JK and SA were the leaders of this project and were involved in the conception and design of the project, reviewing the available pertinent literature, data collection, drafting the initial draft of the manuscript, and final approval of the manuscript.

MF, AT, and RL were involved in the conception and design of the project, met regularly with the project leaders to review preliminary data and plan re-education efforts, performed critical revisions of the manuscript, and granted final approval of the manuscript.

JS was involved in the statistical analysis of all collected data and assisted in producing the results that were responsible for the tables and figures used in this manuscript. He performed critical revisions of the manuscript and granted final approval of the manuscript.

Abbreviations:

BiPAP	Bilevel positive airway pressure
BPD	Bronchopulmonary dysplasia
CPAP	Continuous positive airway pressure
HFNC	High-flow nasal cannula
IMV	Invasive mechanical ventilation
LOS	Length of stay
NC	Nasal Cannula
NIPPV	Non-invasive positive pressure ventilation
PICU	Pediatric intensive care unit
PIM3	Pediatric index of mortality 3
PRISM3	Pediatric risk of mortality score 3
RA	Room air

Abstract:

Objectives: High-flow nasal cannula (HFNC) and non-invasive positive pressure ventilation (NIPPV) have become ubiquitous in contemporary pediatric intensive care units (PICUs). Practice patterns associated with the use of these modalities have not been well described. In this study, we aimed to describe the use of HFNC and NIPPV in children after extubation and analyze the progression of usage in association with patient factors. Our secondary aim was to describe interventions used for post-extubation stridor.

Design: Single-center retrospective cohort study.

Setting: A 36-bed quaternary medical-surgical PICU.

Patients: Mechanically ventilated pediatric patients admitted between April 2017 and March 2018. Exclusions were patients in the cardiac ICU, patients requiring a tracheostomy or chronic ventilator support, and patients with limited resuscitation status.

Interventions: None.

Measurements and Main Results: Data regarding respiratory modality use was collected for the first 72 hours after extubation. There were 427 patients included in the analysis; 51 (11.9%) patients were extubated to room air (RA), 221 (51.8%) to nasal cannula (NC), 132 (30.9%) to HFNC, and 23 (5.4%) to NIPPV. By 72 hours, 314 (73.5%) patients were on RA, 52 (12.2%) on NC, 29 (6.8%) on HFNC, 8 (1.9%) on NIPPV, and 24 (5.6%) were re-intubated. HFNC was the most utilized respiratory modality for post-extubation stridor. Multivariate analysis demonstrated that longer duration of invasive mechanical ventilation increased the odds of initial HFNC and NIPPV use, and a diagnosis of cerebral palsy increased the odds of escalating from HFNC to NIPPV in the first 24 hours post-extubation.

Conclusions: HFNC is commonly utilized immediately after pediatric extubation and the development of post-extubation stridor; however, its usage sharply declines over the following 72 hours. Larger multi-center trials are needed to identify high-risk patients for extubation failure that might benefit the most from prophylactic use of HFNC and NIPPV after extubation.

Introduction:

Half of children admitted to pediatric intensive care units (PICUs) require invasive mechanical ventilation (IMV) [1, 2]. This life saving intervention has its own risk of ventilator-associated pneumonia, ventilator-induced lung injury, ventilator-induced diaphragmatic dysfunction, and the complications that arise from exposure to sedatives and narcotics [3, 4]. To minimize these complications, many institutions are implementing standardized extubation readiness protocols where patients are screened daily and advanced to daily extubation readiness testing when certain screening criteria are met. This has proven effective in reducing variation of extubation readiness assessment, as well as reducing extubation failure rates [5, 6].

Extubation failure is also associated with increased duration of IMV, longer PICU length of stay (LOS), and higher mortality [7-10]. Adult ventilator liberation guidelines strongly recommend prophylactic use of NIPPV to prevent extubation failure in high-risk populations [11, 12]. In the last decade, HFNC and NIPPV have become more popular respiratory support modalities to manage a wide range of respiratory pathologies in PICUs, which has led to a reduction in intubation rates and PICU LOS [13-19]. There have been pediatric studies that utilize pre-extubation risk factors for extubation failure to determine which patients may benefit from increased respiratory support upon extubation [20]; however, strong evidence for the

prophylactic use of HFNC and NIPPV to prevent extubation failure is still lacking in pediatric populations leading to variation of practice in using these modalities [21-24].

Commonly cited causes of extubation failure include upper airway obstruction, pulmonary insufficiency, muscular weakness, cardiac dysfunction, and neurologic impairment [25-28], with upper airway obstruction being the most common cause. Pediatric critical care providers may utilize respiratory support modalities like HFNC and NIPPV in addition to nebulized racemic epinephrine, nebulized or intravenous steroids, and Heliox in order to avoid re-intubation [29, 30].

The aim of this study was to describe the usage of HFNC and NIPPV in children after extubation, in addition to describing the progression of HFNC and NIPPV use and patient factors associated with the use of these modalities. We hypothesized that initial respiratory modality use was influenced by pre-extubation risk factors for extubation failure such as younger age, duration of IMV, and risk factors for post-extubation stridor. Our secondary aim was to describe interventions performed by providers after the development of post-extubation stridor.

Materials and Methods:

All mechanically ventilated children up to 18 years of age admitted to Riley Hospital for Children PICU between April 2017 and March 2018 were included in this retrospective cohort study. Riley Hospital is a quaternary Children's hospital with annual PICU admission of 2500 patients. Patients admitted to the cardiac ICU, with a tracheostomy, on chronic ventilator support, with limited resuscitation status, and who died prior to extubation attempt were excluded. Data regarding respiratory modality and interventions performed after the

development of post-extubation stridor were collected for the first 72 hours after first extubation attempt. Data was extracted from electronic medical records (Cerner, Kansas City, MO, USA) and input into RedCap database (Vanderbilt University, Nashville, TN, USA). Data regarding patients' demographics, severity of illness, PICU and hospital LOS, and mortality were extracted from Virtual PICU Systems database (VPS, LLC, Los Angeles, CA). The study was approved by the Indiana University Institutional Review Board.

Definitions

HFNC was defined as using heated humidified circuit, Optiflow by Fisher and Paykel Healthcare (Auckland, New Zealand), regardless of the flow rate. The initial flow rates post-extubation were determined by the treating physician. NIPPV was defined as continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP). NIPPV was delivered via nasal interface or full facemask. Extubation failure was defined as re-intubation within 48 hours of first extubation attempt. Post-extubation stridor was defined as the development of stridor leading to increased work of breathing that required provider intervention as documented in electronic medical records. Respiratory insufficiency was defined as the development of hypoxia or hypercarbia as determined by the treating physician, or evidence of respiratory distress such as tachypnea, grunting, or use of accessory muscles that required intervention. Cardiac dysfunction was defined as hemodynamic instability that required re-intubation. Neurologic impairment was defined as inability to protect airway excluding stridor and respiratory insufficiency, or otherwise clearly documented that re-intubation was performed for neurological reasons. All other reasons

of extubation failure were recorded as unspecified. IMV duration was divided into 4 categories: less than 24 hours, 1 to 7 days, 8 to 14 days, and more than 14 days.

Extubation Readiness Testing

Our daily extubation readiness testing is described in detail in our previous publication [5]. If the patient passed pressure support/CPAP trial of 8/5 for two hours, the patient is deemed appropriate for a trial of extubation that day. The time of extubation and respiratory modality used post-extubation was decided by the treating physician.

Statistical Analysis

Data was exported from RedCap database and then analyzed using SAS v9.4 (SAS Institute, Cary, NC, USA). Values were reported as medians and 25^{th}, 75^{th} interquartile ranges (IQRs) for continuous variables, and frequencies and percentages for categorical variables. Kruskal-Wallis was used for continuous variables and Fisher's Exact test or Chi-Square test were used for categorical variables as appropriate. Multivariate analysis was conducted to study the effect of clinical variables on initial respiratory modality use, the progression of respiratory modality use after extubation, and the rate of extubation failure. All statistical analyses were made considering a significance level of 5%. Sankey diagrams were produced by members of the Luddy School of Informatics, Computing, and Engineering, Indiana University, Indianapolis, Indiana.

Results:

There were 705 mechanically ventilated patients admitted to our PICU between April 2017 and March 2018. A total of 278 patients were excluded: 231 had a tracheostomy tube or were on chronic ventilator support, 35 patients had limited code status, and 12 patients died without an extubation attempt. The included 427 patients had a median age of 40 months (IQR 9, 134). Most patients were intubated for a respiratory etiology (38.6%), followed by injury/poisoning etiology (19%), and neurological etiology (14.5%). The patients' demographics are summarized in Table 1. Isolating for patients admitted post-operatively, 36.8% (43/117) were intubated for a respiratory etiology, 14.5% (17/117) had an injury/poisoning etiology, and 9.4% (11/117) had a neurologic etiology.

Respiratory Modality Use After Extubation

Initial respiratory support choice was influenced by the duration of IMV as shown in Table 2. For the total cohort, 30.9% (132/427) of patients were extubated to HFNC with a median flow rate of 1.0 L/kg/min (IQR 0.5, 1.4), but only 13.1% (56/427) and 12.2% (52/427) remained on HFNC by 48 hours and 72 hours respectively (Figure 1). Similarly, 5.4% (23/427) of the patients were extubated to NIPPV, which decreased to 2.1% (9/427) and 1.9% (8/427) by 48 hours and 72 hours respectively (Figure 1). For our cohort, 8.3% (11/132) of patients extubated to HFNC required escalation to NIPPV and 13.0% (3/23) of patients extubated to NIPPV were able to de-escalate to HFNC in the first 24 hours. Among the patients extubated to NIPPV, 73.9% (17/23) were able to de-escalate respiratory support by 72 hours. All NIPPV were BiPAP except for 2 patients supported with CPAP between 24 to 48 hours and 1 patient at 72 hours for the entire cohort.

Patients who were intubated for 8 to 14 days had a higher percentage of initial use of HFNC (67.3%; 37/55) and NIPPV (10.9%; 6/55) when compared to patients intubated for less than 24 hours and 1 to 7 days, p<0.0001 (Table 2). However, by 72 hours post-extubation, only 16.4% (9/55) of patients were on HFNC and 7.3% (4/55) required NIPPV (Supplemental figure 1-C). A similar pattern was noticed in patients intubated greater than 14 days, with initial HFNC use immediately after extubation of 70.6% (12/17) and NIPPV use of 11.8% (2/17), p<0.001 (Table 2). By 72 hours post-extubation, there were 23.6% (4/17) on HFNC and none on NIPPV (Supplemental figure 1-D).

In the multivariate analysis, duration of IMV was associated with higher initial use of HFNC (OR 1.01; 95% CI, 1.01-1.01; p<0.0001) and NIPPV (OR 1.01; 95% CI 1.00, 1.01; p=0.0382), and escalation from HFNC to NIPPV in first 24 hours (OR 1.02; 95% CI 1.00-1.03; p=0.0095) (Supplemental Tables 1, 2, and 4). Older age was associated with higher initial use of NIPPV after extubation (OR 1.02; 95% CI 1.01-1.04; p=0.0012) (Supplemental Table 2). A diagnosis of cerebral palsy was associated with escalation from HFNC to NIPPV in first 24 hours (OR 24.5; 95% CI 1.29-463.43; p=0.033) (Supplemental Table 4).

Extubation Failure and Interventions After the Development of Post-Extubation Stridor

Extubation failure was 4.9% (21/427) in our cohort. There were an additional 1.6% (7/427) of patients who were re-intubated for short procedures or operations after the initial extubation and were not counted as extubation failures. Extubation failure rate was 28.6% (2/7) in the patients who had unplanned extubations. The causes of extubation failure were upper airway obstruction (57.1%; 12/21), mixed cause (23.8%; 5/21), respiratory insufficiency (9.5%; 2/21),

cardiac dysfunction (4.8%; 1/21), and unspecified cause (4.8%; 1/21). There were 3 patients who had upper airway obstruction and respiratory insufficiency, and 2 who had upper airway obstruction and neurological impairment of the patients classified as mixed cause of extubation failure. Younger age and initial use of NIPPV after extubation were associated with a higher odds of extubation failure (OR 0.98, 95%CI 0.97-1.00, p=0.0415) and (OR 21.17, 95%CI 1.89-237.67, p=0.0134) respectively (Supplemental Table 5).

Of the patients who were extubated to HFNC, extubation failure rate was 22.2% (2/9) for patients intubated less than 24 hours, 6.8% (5/74) for patients intubated 1 to 7 days, 10.8% (4/37) patients for patients intubated 8 to 14 days, and 16.7% (2/12) for patients intubated greater than 14 days (Supplemental Figure 1A-D). In contrast, extubation failure rate was 8.7% (2/23) in patients extubated to NIPPV (Supplemental Figure 1A-D).

For our cohort, 26.7% (114/427) of patients developed post-extubation stridor. The most common interventions performed after the development of post-extubation stridor were nebulized racemic epinephrine (91.2%; 104/114), HFNC (59.6%; 68/114), and intravenous dexamethasone (51.8%; 59/114) (Figure 2). Patients received between 1 to 6 interventions for post-extubation stridor with a median of 2 (IQR 2, 3). Younger age and leak pressure greater than or equal to 20 cmH_2O were associated with an increased risk of developing post-extubation stridor (OR 0.99; 95%CI 0.98-1.00; p=0.0078) and (OR 2.93; 95%CI 1.5-5.74; p=0.0017) respectively (Supplemental Table 6).

Discussion:

To our knowledge, this is the first pediatric study to report respiratory modality progression after extubation. Traditionally, studies report the percentage of HFNC use, NIPPV use, and re-intubation rate in the first 48-hour after extubation attempt but don't delineate the flow of patients between different respiratory modalities over time. While some physicians believe that HFNC and NIPPV are over-utilized in our current era, some clinicians may utilize these modalities prophylactically with the goal to potentially prevent post-extubation respiratory distress, extubation failure, and allow for earlier liberation from IMV. However, more data is needed to inform guidelines to help clinicians decide which patients would benefit from these higher respiratory modalities to avoid potential risks like agitation, anxiety, aspiration, and pressure ulcers [31]. In general, pediatric studies fail to show a benefit of the prophylactic use of NIPPV over lower flow oxygen therapies such as nasal cannula in preventing re-intubation [20], but NIPPV could be beneficial in certain high-risk pediatric populations [32].

Our data shows a high usage of HFNC and NIPPV initially, but a drastic decline in the percentage of patients supported with HFNC and NIPPV by 72 hours. This trend of de-escalating respiratory support over the 72 hours post-extubation held across all duration of IMV subgroups. It could be argued that this is related to the improvement in patients' respiratory status, or it could potentially be related to over-utilization of HFNC and NIPPV. Comparing our results to published literature, our HFNC and NIPPV use post-extubation is comparable to other studies for general PICU patients, where the post-extubation HFNC use ranged from 21 to 36% and NIPPV use ranged from 7 to 14% [5, 33, 34].

Upper airway obstruction, as indicated by the development of post-extubation stridor, still remains the most common cause for extubation failure in the pediatric population ranging

between 5 to 22% [5, 8, 10]. We explored the relationship between the presence of stridor and the use of HFNC and NIPPV. In our cohort, HFNC was the most commonly used respiratory modality to support patients experiencing post-extubation stridor. This could be a factor as to why non-invasive respiratory modality use was initially high and then declined sharply. There was also an association between leak pressure greater than or equal to 20 cmH_2O and an increased odds of developing post-extubation stridor. This would support the inclusion of leak pressure measurement in the extubation readiness testing for pediatric patients.

Duration of IMV is associated with increased odds of extubation failure [7, 25, 35]. This may explain why we noticed increased use of HFNC and NIPPV in patients who are ventilated for more than 7 days. In patients who were intubated for 8 to 14 days, no patients extubated to NIPPV were re-intubated but 10.8% of those extubated to HFNC were re-intubated within 48 hours. While in patients who were intubated for greater than 14 days, 16.7% of patient extubated to HFNC were re-intubated within 48 hours and no patients extubated to NIPPV were re-intubated. In addition, our multivariate analysis demonstrated that younger patients and patients extubated to NIPPV had an increased odds of extubation failure. However, this was largely driven by only 2 patients extubated to NIPPV in the 1 to 7 days subgroup, which lead to a large confidence interval. It should be noted that HFNC and NIPPV use post-extubation was not randomized or protocolized at our institution, which makes it difficult to draw concrete conclusions. All this suggests that more aggressive initial respiratory support could potentially prevent extubation failure, but is not possible to conclude given the retrospective nature of this study.

NIPPV has been used to prevent extubation failure in patients with neuromuscular disease [36]. Our multivariate analysis demonstrated that a diagnosis of cerebral palsy increased the odds of progressing from HFNC to NIPPV in the first 24 hours. This result is congruent with the physiology in this patient population as they often have weakness in respiration or impaired lung function that would benefit from additional support [37]. However, it does not take into consideration the severity of cerebral palsy, nor did it consider other neuromuscular pathologies such as Duchenne's Muscular Dystrophy or acquired ICU myopathy.

Study Limitations and Implications

This study was limited due to its retrospective design. The respiratory modalities used after extubation reflect our local practices, which are not standardized and may not apply to other institutions. HFNC flow rates and NIPPV settings were also not standardized, which might be an important factor that influence progression of respiratory support and extubation failure rates. Clinicians' preference in the choice of respiratory modality use was not tracked in this study due to its retrospective design. However, similar patterns of HFNC and NIPPV use are noticed in recent pediatric studies. Our HFNC and NIPPV weaning practices could also differ from other PICUs as there is no current agreed-upon consensus in the literature [31].

Despite these limitations, the study demonstrates a clear progression of respiratory support as demonstrated in our Sankey diagrams that could serve as a potential reporting tools for future studies. In addition, this was a single-center study and it is possible that the sample size was too small to detect a difference in variables. A multi-center, prospective pediatric study

is needed to determine factors that could better predict the patient populations that would benefit from prophylactic use of higher respiratory support after extubation [23].

Conclusions:

HFNC and NIPPV are commonly utilized immediately after pediatric extubation and their use sharply declines over the course of 72 hours after extubation regardless of duration of invasive mechanical ventilation. Judicious use of non-invasive respiratory modalities might help mitigate respiratory distress and prevent re-intubation after the development of post-extubation stridor. Larger, multi-center pediatric studies are needed to identify high-risk patients that might benefit from prophylactic use of HFNC and NIPPV after extubation.

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Figure Legend:

Figure 1: Progression of Respiratory Modality Use in First 72 Hours Post-Extubation for the Whole Cohort (N=427)
RA: room air; NC: nasal cannula; HFNC: high-flow nasal cannula; NIPPV: noninvasive positive pressure ventilation; ETT: endotracheal tube

Figure 2: Intervention Used for Post-Extubation Stridor (N=114)
HFNC: high-flow nasal cannula; NIPPV: noninvasive positive pressure ventilation

Figure 1

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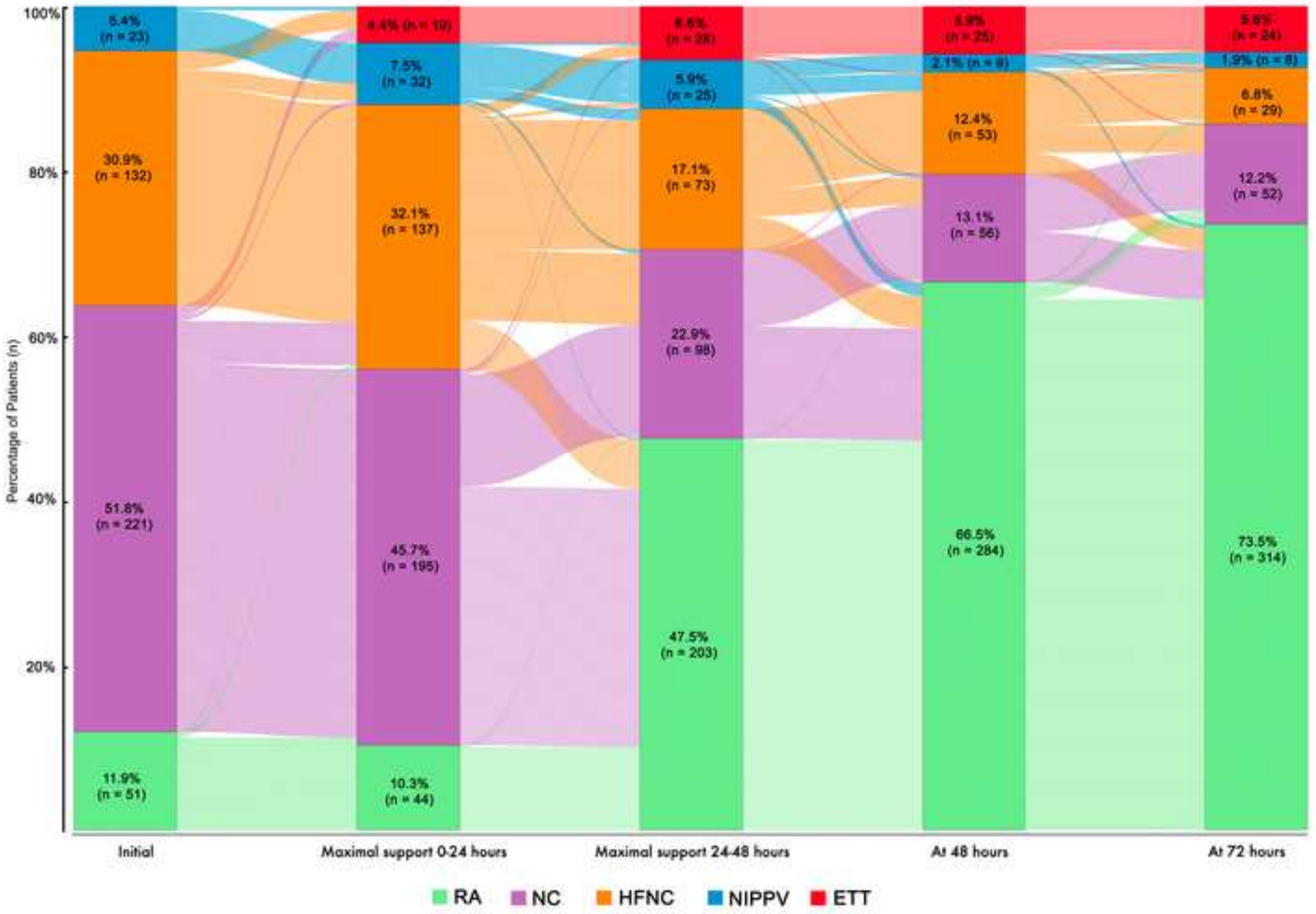

Figure 2

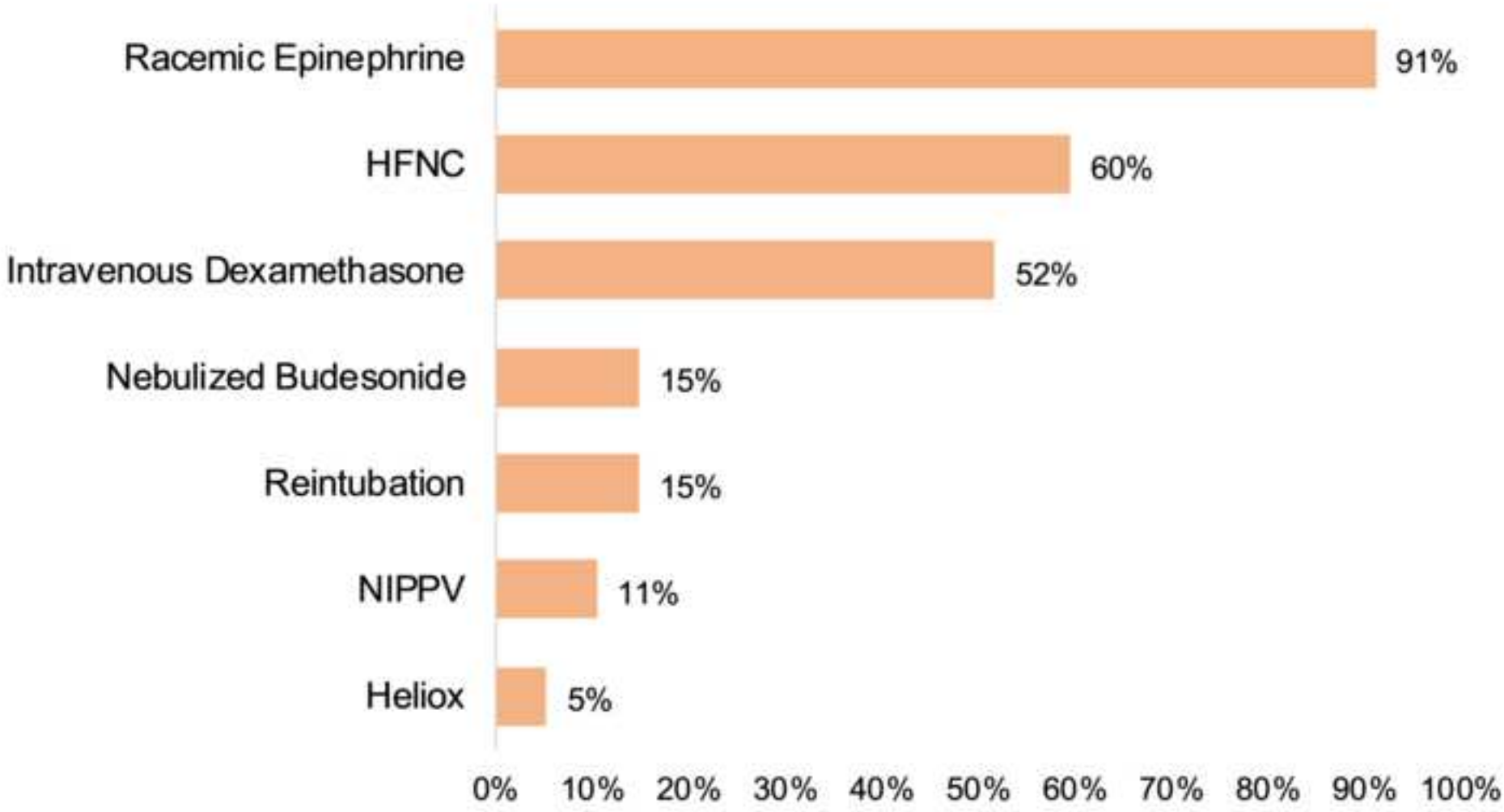

Table 1: Patient Demographics by Invasive Mechanical Ventilation Duration

Variable	All patients N=427	IMV <24 hours N=139	IMV 1-7 days N=216	IMV 8-14 days N=55	IMV >14 days N=17	p-value
Age in months	40 (9, 134)	74 (18, 166)	36 (5, 126)	29 (5, 96)	16 (7, 52)	0.0002
Age categories, N (%)						
0-12 months	123 (28.8)	24 (17.3)	75 (34.7)	18 (32.7)	6 (35.3)	0.0045
1-5 years	116 (27.2)	41 (29.5)	49 (22.7)	19 (34.6)	7 (41.2)	
6-11 years	80 (18.7)	26 (18.7)	41 (19.0)	11 (20.0)	2 (11.8)	
>11 years	108 (25.3)	48 (34.5)	51 (23.6)	7 (12.7)	2 (11.8)	
Female gender, N (%)	192 (45.0)	65 (46.8)	100 (46.3)	22 (40.0)	5 (2.94)	0.4671
Race/Ethnicity, N (%)						
Caucasian	314 (73.5)	107 (77.0)	157 (72.7)	36 (65.5)	14 (82.4)	0.2920
African American	75 (17.6)	23 (16.6)	40 (18.5)	10 (18.2)	2 (11.8)	
Hispanic	22 (5.2)	3 (2.2)	11 (5.1)	7 (12.7)	1 (5.9)	
Other	16 (3.8)	6 (4.3)	8 (3.7)	2 (3.6)	0 (0)	
PRISM III Score	3 (0, 7)	2 (0, 5)	3 (0, 7)	4 (0, 10)	5 (0, 13)	0.0387
PIM3 Score	1.7 (0.9, 3.7)	2.9 (1.0, 3.8)	1.2 (0.7, 3.4)	1.6 (0.7, 4.7)	1.5 (1.0, 3.8)	0.1544
PRISM probability of death (%)	0.6 (0.3, 1.8)	0.4 (0.2, 1.0)	0.7 (0.3, 2.2)	1.0 (0.5, 3.9)	1.0 (0.5, 4.2)	<0.0001
Primary illness categories, N (%)						
Respiratory	165 (38.6)	25 (18.0)	103 (47.7)	29 (52.7)	8 (47.1)	<0.0001
Injury/ Poisoning	81 (19.0)	44 (31.7)	30 (13.9)	6 (10.9)	1 (5.9)	
Neurological	62 (14.5)	35 (25.2)	24 (11.1)	2 (3.6)	1 (5.9)	
Infectious	48 (11.2)	5 (3.6)	31 (14.4)	12 (21.8)	0 (0)	
Hematology/Oncology	28 (6.6)	8 (5.8)	14 (6.5)	4 (7.3)	2 (11.8)	
Other	43 (10.1)	22 (15.8)	14 (6.5)	2 (3.6)	5 (29.4)	
Post-operative status, N (%)	117 (27.4)	56 (40.3)	50 (23.2)	4 (7.3)	7 (41.2)	<0.0001
Trauma status, N (%)	55 (12.9)	24 (17.3)	24 (11.1)	6 (10.9)	1 (5.9)	0.2705
Trisomy 21, N (%)	7 (1.6)	1 (0.7)	1 (0.5)	1 (1.8)	4 (23.5)	<0.0001
Bronchopulmonary dysplasia, N (%)	16 (3.8)	2 (1.4)	9 (4.2)	4 (7.3)	1 (5.9)	0.2338
Cerebral palsy, N (%)	21 (4.9)	5 (3.6)	13 (6.0)	2 (3.6)	1 (5.9)	0.7279

Data presented as median (25^{th}, 75^{th} IQR) or number (%)
IMV: invasive mechanical ventilation; PRISM3: pediatric risk of mortality score 3; PIM3: pediatric index of mortality 3

Table 2

Table 2: Clinical Outcomes by Mechanical Ventilation Duration

Variable	All patients N=427	IMV <24 hours N=139	IMV 1-7 days N=216	IMV 8-14 days N=55	IMV >14 days N=17	p-value
Length of IMV in hours	49 (19, 131)	13 (6, 19)	70 (43, 116)	212 (187, 248)	471 (404, 526)	<0.0001
Initial respiratory support, N (%)						
RA	51 (11.9)	33 (23.7)	17 (7.9)	1 (1.8)	0 (0)	<0.0001
NC	221 (51.8)	93 (66.9)	114 (52.8)	11 (20.0)	3 (17.7)	
HFNC	132 (30.9)	9 (6.5)	74 (34.3)	37 (67.3)	12 (70.6)	
NIPPV	23 (5.4)	4 (2.9)	11 (5.1)	6 (10.9)	2 (11.8)	
Close NIPPV in first 48 hours, N (%)	25 (5.9)	4 (2.9)	11 (5.1)	8 (14.6)	2 (11.8)	0.0113
Extubation failure, N (%)	21 (4.9)	2 (1.4)	13 (6.0)	4 (7.3)	2 (11.8)	0.0891
PICU LOS in days	5 (2, 9)	2 (1, 3)	5 (4, 8)	14 (11, 17)	26 (24, 34)	<0.0001
Hospital LOS in days	12 (6, 21)	5 (3, 10)	12.5 (8, 19)	23 (17, 34)	48 (33, 62)	<0.0001

Data presented as median (25th, 75th IQR) or number (%)
IMV: invasive mechanical ventilation; RA: room air; NC: nasal cannula; HFNC: high-flow nasal cannula; NIPPV: noninvasive positive pressure ventilation; LOS: length of stay