Prevalence of Reintubation Within 24 Hours of Extubation in Bronchiolitis: Retrospective Cohort Study Using the Virtual Pediatric Systems Database

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OBJECTIVES: High-flow nasal cannula and noninvasive positive pressure ventilation are used to support children following liberation from invasive mechanical ventilation. Evidence comparing extubation failure rates between patients randomized to high-flow nasal cannula and noninvasive positive pressure ventilation is available for adult and neonatal patients; however, similar pediatric trials are lacking. In this study, we employed a quality controlled, multicenter PICU database to test the hypothesis that high-flow nasal cannula is associated with higher prevalence of reintubation within 24 hours among patients with bronchiolitis.

DESIGN: Secondary analysis of a prior study utilizing the Virtual Pediatric Systems database.

SETTING: One-hundred twenty-four participating PICUs.

PATIENTS: Children less than 24 months old with a primary diagnosis of bronchiolitis who were admitted to one of 124 PICUs between January 2009 and September 2015 and received invasive mechanical ventilation.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Among 759 patients, median age was 2.4 months (1.3–5.4 mo), 41.2% were female, 39.7% had greater than or equal to 1 comorbid condition, and 43.7% were Caucasian. Median PICU length of stay was 8.7 days (interquartile range, 5.8–13.7 d) and survival to PICU discharge was 100%. Median duration of intubation was 5.5 days (3.4–9.0 d) prior to initial extubation. High-flow nasal cannula was used following extubation in most (656 [86.5%]) analyzed subjects. The overall prevalence of reintubation within 24 hours was 5.9% (45 children). Extubation to noninvasive positive pressure ventilation was associated with greater prevalence of reintubation than extubation to high-flow nasal cannula (11.7% vs 5.0%; $p = 0.016$) and, in an a posteriori model that included Pediatric Index of Mortality 2 score and comorbidities, was associated with increased odds of reintubation (odds ratio, 2.43; 1.11–5.34; $p = 0.027$).

CONCLUSIONS: In this secondary analysis of a multicenter database of children with bronchiolitis, extubation to high-flow nasal cannula was associated with a lower prevalence of reintubation within 24 hours compared with noninvasive positive pressure ventilation in both unmatched and propensity-matched analysis. Prospective trials are needed to determine if post-extubation support modality can mitigate the risk of extubation failure.

KEY WORDS: bronchiolitis; high-flow nasal cannula; noninvasive ventilation; pediatric

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Extubation failure occurs in approximately 6–10% of patients within 72 hours of initial liberation from mechanical ventilation (MV) (1–3) and is associated with longer length of stay (LOS), higher costs, and increased morbidity and mortality in adults and children (4–6). Treatments that affect the risk of extubation failure, such as the modality of post-extubation respiratory support, could therefore influence clinical outcomes. Both high-flow nasal cannula (HFNC) and noninvasive positive pressure ventilation (NIPPV) are used to support children following liberation from invasive MV (7). In neonates and adults, there is no definitive difference in reintubation rate between subjects randomized to either one of the two modalities after extubation, but no similar data exist for critically ill children (8–11).

Such prospective randomized controlled trials in the pediatric population are particularly challenging due to lower volume of mechanically ventilated patients and greater disease heterogeneity. Alternatively, large multicenter databases can enable analyses of a large cohort of critically ill children with a single condition to inform both clinical practice and the design of subsequent prospective trials. We recently studied a large multicenter database of PICU patients with bronchiolitis and reported that initial use of NIPPV was associated with higher subsequent use of invasive MV compared with initial support with HFNC, even after adjusting for illness severity and comorbidities (12). Bronchiolitis is also a promising model for the evaluation of post-extubation respiratory support because of its high prevalence and because both HFNC and NIPPV are commonly used (7). However, no study has yet evaluated associations between these modes of respiratory support and need for reintubation among PICU patients with bronchiolitis. In this study, we aimed to employ a quality controlled, multicenter PICU database to test the hypothesis that HFNC is associated with higher prevalence of reintubation within 24 hours among patients with bronchiolitis.

MATERIALS AND METHODS

This study was reviewed and approved by the Institutional Review Board of University Hospitals of Cleveland and the review board for the Virtual Pediatric Systems (VPS), LLC (Los Angeles, CA). This study was not externally funded.

Study Design

This is a secondary analysis of a previously reported retrospective database study (12). Briefly, the VPS, LLC database was queried for PICU patients less than 24 months old with a primary diagnosis of bronchiolitis who were admitted to one of 124 PICUs from January 2009 to September 2015 and received invasive MV. Patients who received HFNC or NIPPV support immediately post-extubation were identified using the "stop" time for MV and the "start" time for HFNC or NIPPV and included in this secondary analysis. As previously described in the initial study using this dataset, NIPPV was defined as bilevel positive airway pressure or continuous positive airway pressure. Data collected include included weight, age, race, nonprimary diagnoses, Pediatric Index of Mortality (PIM) 2 score, respiratory support modalities, and survival to PICU discharge. Race was categorized as Caucasian, African American, Hispanic, or other. PIM 2 score is shown as calculated risk of death in percentage form.

Outcomes and Statistical Analysis

The primary outcome was reinsertion of an endotracheal tube within 24 hours of initial extubation (3, 10, 13). The secondary outcome was PICU LOS. Demographics, PIM 2 scores, comorbid conditions, and outcomes were compared between the two treatment groups using the chi-square test for categorical variables and Wilcoxon rank-sum for continuous variables. Other variables associated with outcomes were similarly evaluated using chi-square, Wilcoxon rank-sum, or Spearman correlation and included in multivariate models if loosely associated with the outcome ($p < 0.10$). A posteriori, multivariate models with forced inclusion of PIM 2 score and comorbidities were created to adjust for illness severity and conditions known to be associated with unfavorable courses of bronchiolitis (14, 15). To minimize the effect of site-specific practice, data were analyzed using generalized estimating equations. Finally, HFNC patients were matched to NIPPV patients by propensity-score matching using the MatchIt package (R software; R Foundation for Statistical Computing, Vienna, Austria) by the nearest method with the ratio of 2:1. The matching was based on age, gender, weight, any significant comorbidity, PIM 2 score, and the duration of intubation. Matched HFNC patients and NIPPV patients were then

compared as above, including a multivariate logistic regression model. All the analyses were performed in SigmaPlot (version 12.5; Systat Software, San Jose, CA) or R software (version 4.0.0; R Foundation for Statistical Computing). Data are shown as *n* (%), median (interquartile range), and odds ratio (95% CI).

RESULTS

A total of 1,793 children with bronchiolitis who received MV were identified in the original study database, 28 (1.6%) of whom died prior to extubation. Of the 1,765 children (98.4%) who underwent extubation, 783 (43.7%) were immediately supported by HFNC or NIPPV and were eligible for inclusion in this analysis. Records for the immediate post-extubation period were incomplete for 24 patients who were thus excluded from analysis. Among the 759 children included in the analysis, the median age was 2.4 months (1.3–5.4 mo), 41.2% were female, 39.7% had greater than or equal to 1 comorbid condition, and 43.7% were Caucasian (**Table 1**). Median duration of MV was 5.5 days (3.4–9.0 d) prior to the initial extubation. Six patients, all of whom were reintubated, received tracheostomies during the admission. Median PICU LOS was 8.7 days (5.8–13.7 d) and survival to PICU discharge was 100%.

HFNC was used following extubation in most (656 [86.5%]) analyzed subjects. Age, weight, race, PIM 2 scores, and duration of MV prior to extubation were similar between patients receiving HFNC after extubation and those receiving NIPPV (Table 1). Half (50.5%) of NIPPV subjects were female and 39.8% of HFNC subjects were female ($p = 0.052$). Both cardiovascular (22.3% vs 13.4%; $p = 0.026$) and pulmonary (10.7% vs 3.0%; $p < 0.001$) comorbidities were more common among children treated with NIPPV compared with children treated with HFNC.

The overall prevalence of reintubation within 24 hours was 5.9% (45 children). Extubation to NIPPV was associated with greater rate of reintubation than extubation to HFNC (11.7% vs 5.0%; $p = 0.016$). Age, weight, PIM 2 score, gender, race, and comorbid status were not associated with reintubation (**Table 2**). No variables met our a priori criteria for inclusion in the multivariate model for reintubation. In the a posteriori model that included PIM 2 score and comorbidities, NIPPV was associated with reintubation (OR, 2.43; 1.11–5.34; $p = 0.027$) (**Table 3**), but PIM 2 and comorbidities were not. In the propensity-matched analysis, age, weight, PIM 2 score, gender, race, comorbidities, and duration of MV did not differ significantly between groups (**Table 4**). In the multivariate logistic regression model of matched subjects, use of NIPPV was associated with reintubation (OR, 2.99; 1.20–7.42; $p = 0.018$), but the two other included independent variables—comorbidities (0.81 [0.32–2.03]; $p = 0.652$) and PIM 2 score (1.31 [0.85–2.03]; $p = 0.227$)—were not.

Median PICU LOS was nearly 1 week longer in those patients who were reintubated within 24 hours (15.8 d [10.0–25.5 d] vs 8.6 d [5.8–13.3 d]; $p < 0.001$). Gender and comorbidities, were also significantly associated with longer LOS (**Table 5**), as was duration of MV ($\rho = 0.852$; $p < 0.001$). Patient weight was significantly associated with LOS ($\rho = -0.108$; $p = 0.003$), but age ($\rho = -0.001$; $p = 0.970$) and PIM 2 score ($\rho = 0.040$; $p = 0.270$) were not. After adjusting for covariates, reintubation was associated with longer PICU LOS ($\beta = 7.23$; 95% CI, 5.63–8.84), as were PIM 2 score, duration of MV, cardiovascular comorbidities, and pulmonary comorbidities (**Table 6**).

DISCUSSION

In this secondary analysis of a multicenter database, extubation to NIPPV was associated with a two-fold higher rate of reintubation within 24 hours when compared with HFNC, even after adjusting for comorbidities and PIM 2 scores. This suggests that HFNC may be a superior way to support children with bronchiolitis following extubation, but our study should primarily be interpreted as hypothesis-generating; prospective trials are needed to evaluate the causality of this association and better adjust for both measured and unmeasured confounders. Given that nearly half of all subjects in the original database were extubated to either HFNC or NIPPV and that reintubation was associated with a 7-day increase in PICU LOS in our analysis, such studies are urgently needed.

Although we found that HFNC is associated with less reintubation in both unmatched and propensity-matched analysis, we cannot conclude that HFNC is superior to NIPPV in preventing extubation failure due to the inherent limitations of database studies, including the possibility that our findings are due to chance as the 95% CI does approach equivalence. However, database studies are well equipped to describe current practices, and we found that HFNC is used more commonly than NIPPV immediately following extubation

TABLE 1.
Characteristics of Patients With Bronchiolitis Extubated to High-Flow Nasal Cannula and Noninvasive Positive Pressure Ventilation

Characteristic	All (*n* = 759)	High-Flow Nasal Cannula (*n* = 656; 86.5%)	Noninvasive Positive Pressure Ventilation (*n* = 103; 13.5%)	*p*
Age (mo), median (IQR)	2.4 (1.3–5.4)	2.4 (1.2–5.4)	2.7 (1.6–5.5)	0.119
Weight (kg), median (IQR)	4.7 (3.6–6.8)	4.7 (3.5–6.7)	4.8 (3.6–6.9)	0.740
Pediatric Index of Mortality 2 score, median (IQR)	0.8 (0.7–1.3)	1.0 (0.7–1.6)	0.9 (0.8–1.5)	0.798
Gender, *n* (%)				0.052
Male	446 (58.8)	395 (60.2)	51 (49.5)	
Female	313 (41.2)	261 (39.8)	52 (50.5)	
Race, *n* (%)				0.380
Caucasian	332 (43.7)	283 (43.1)	49 (47.6)	
African American	145 (19.1)	130 (19.8)	15 (14.6)	
Hispanic	86 (11.4)	71 (10.8)	15 (14.6)	
Other	196 (25.8)	172 (26.2)	24 (23.3)	
Comorbidities, *n* (%)	301 (39.7)	248 (37.8)	53 (51.5)	0.012
Cardiovascular	111 (14.6)	88 (13.4)	23 (22.3)	0.026
Genetic	30 (4.0)	26 (4.0)	4 (3.9)	0.816
Prematurity	148 (19.5)	123 (18.8)	25 (24.3)	0.238
Immunologic	20 (2.6)	18 (2.7)	2 (1.9)	0.887
Neurologic	82 (10.8)	71 (10.8)	11 (10.7)	0.899
Pulmonary	31 (4.1)	20 (3.0)	11 (10.7)	< 0.001
Duration of mechanical ventilation prior to extubation (d), median (IQR)	5.5 (3.4–9.0)	5.5 (3.5–8.9)	5.9 (2.8–9.9)	0.994

IQR = interquartile range.

of children with bronchiolitis. The observed rate of post-extubation HFNC use (86.5%) was nearly identical to the rate of initial HFNC use in children with bronchiolitis in the VPS network we previously reported (85.6%) (12). Pediatric intensivists may prefer HFNC because it has a better-tolerated patient interface, minimizes gastric insufflation, improves clearance of secretions, has lower costs, and avoids of the effects of positive airway pressure on the right ventricle (16–18). HFNC can reduce the effort of breathing for children with bronchiolitis by clearing carbon dioxide out of physiologic dead space, providing a reservoir of well oxygenated gas for inspiration, and promoting a modest amount of positive airway pressure (18–22).

Subjects in the two treatment groups had similar ages, demographics, and PIM 2 scores, but NIPPV use was associated with pulmonary and cardiac comorbidities. Cardiac surgical patients are one cohort in which post-extubation HFNC and NIPPV have been compared in children. In 49 propensity-matched pairs of

TABLE 2.
Characteristics of Patients Reintubated and Not Reintubated

Characteristic	Reintubated Within 24 hr (*n* = 45; 5.9%)	Not Reintubated Within 24 hr (714; 94.1%)	*p*
Initial post-extubation modality, *n* (%)			0.016
High-flow nasal cannula	33 (5.0)	623 (95.0)	
Noninvasive positive pressure ventilation	12 (11.7)	91 (88.3)	
Age (mo), median (IQR)	2.1 (1.2–3.9)	2.5 (1.3–5.4)	0.381
Weight (kg), median (IQR)	4.3 (3.6–6.4)	4.7 (3.5–6.9)	0.500
Pediatric Index of Mortality 2 score (%), median (IQR)	0.9 (0.8–1.1)	0.9 (0.7–1.4)	0.546
Gender, *n* (%)			0.218
Male	23 (7.3)	290 (92.7)	
Female	22 (4.9)	424 (95.1)	
Race, *n* (%)			0.687
Caucasian	17 (5.1)	315 (94.9)	
African American	8 (5.5)	137 (94.5)	
Hispanic	5 (5.8)	81 (94.2)	
Other	15 (7.7)	181 (92.3)	
Comorbidities, *n* (%)			
Cardiovascular	6 (5.4)	105 (94.6)	0.972
Genetic	0 (0.0)	30 (100)	0.313
Prematurity	10 (6.8)	138 (93.2)	0.778
Immunologic	1 (5.0)	19 (95)	0.763
Neurologic	7 (8.5)	75 (91.5)	0.417
Pulmonary	4 (12.9)	27 (87.1)	0.197

IQR = interquartile range.

infants convalescing from cardiac surgery, there was no difference in extubation failure, but NIPPV was associated with slower weaning to room air, longer hospital LOS, and higher resource utilization (23). Our dataset was not large enough to support analyses of individual subgroups like cardiac patients, but future analyses of cardiac-specific databases may be warranted.

There are no prospective randomized trials comparing HFNC and NIPPV in critically ill children. In adults, use of HFNC was not inferior to NIPPV in patients at high risk of reintubation (10), and outcomes may be optimal by combining the two modalities (11). Similarly, in neonates, HFNC was found to be as efficacious as CPAP as a mode of respiratory support following extubation (8). A randomized trial comparing HFNC to standard oxygen in critically ill children found that HFNC significantly reduced extubation failure rates to 4%, although generalizability is limited by the high failure rate in the standard oxygen therapy group (22%) (24). Given the challenges inherent to a trial of HFNC versus NIPPV in children undergoing extubation, analyses such as ours may be the best data

TABLE 3.
Multivariate Analysis: Extubation Failure

Characteristic	OR (95% CI)	*p*
Noninvasive positive pressure ventilation	2.43 (1.11–5.34)	0.027
Comorbidities		
Cardiovascular	0.71 (0.26–1.91)	0.491
Prematurity	1.06 (0.56–2.01)	0.863
Immunologic	0.86 (0.11–6.58)	0.882
Neurologic	1.81 (0.71–4.56)	0.212
Pulmonary	2.11 (0.48–9.25)	0.321
Pediatric Index of Mortality 2 score	1.14 (0.83–1.57)	0.411

OR = odds ratio.
Use of noninvasive positive pressure as initial mode of respiratory support following extubation.

clinicians have despite their limitations. If a trial were to be undertaken, the rates of reintubation that we observed would mean that a sample size of approximately 500 children (250/group) would be needed.

Our findings are likely generalizable to patients with bronchiolitis at non-VPS centers given that our data come from over 100 centers and our patient demographics are similar to those previously reported in other cohorts of children with critical bronchiolitis (25–27). Although our data may be less applicable to children with other conditions, our observed reintubation rate is similar to what has been reported in children less than 24 months, as well as similar to those with neurologic disease, sepsis, or pneumonia (3, 28, 29), suggesting generalizability beyond bronchiolitis.

Our observed association between reintubation and prolonged ICU LOS has been previously reported (3). Effectively reducing extubation failure can lower both ICU and hospital LOS, greatly reduce hospital costs, and potentially reduce mortality (30–32). Reintubation leads to more MV days which often include invasive monitoring, therefore increasing the risk for associated hospital infections such as ventilator-associated infections and central line-associated infections (31).

Strengths of this study include the large cohort of children with a single disease cared for at many centers. The HFNC and NIPPV groups had similar patient

TABLE 4.
Characteristics of Patients With Bronchiolitis Extubated to High-Flow Nasal Cannula and Noninvasive Positive Pressure Ventilation Included in Propensity-Matched Analysis

Characteristic	High-Flow Nasal Cannula (*n* = 206)	Noninvasive Positive Pressure Ventilation (*n* = 103)	*p*
Age (mo), median (IQR)	2.2 (1.1–4.95)	2.7 (1.6–5.5)	0.081
Weight (kg), median (IQR)	4.5 (3.4–6.7)	4.8 (3.6–6.9)	0.465
Pediatric Index of Mortality 2 score, median (IQR)	1.0 (0.8–1.6)	0.9 (0.8–1.5)	0.383
Gender, *n* (%)			0.056
Male	127 (61.7)	51 (49.5)	
Female	79 (38.3)	52 (50.5)	
Race, *n* (%)			0.326
Caucasian	87 (42.2)	49 (47.6)	
African American	44 (21.4)	15 (14.6)	
Hispanic	21 (10.2)	15 (14.6)	
Other	54 (26.2)	24 (23.3)	
Comorbidities, *n* (%)	81 (39.3)	53 (51.5)	0.056
Duration of mechanical ventilation prior to extubation (d), median (IQR)	5.7 (3.6–9.0)	5.9 (2.8–9.9)	0.745

IQR = interquartile range.

TABLE 5.
Univariate Analysis: PICU Length of Stay

Characteristic	*n*	PICU Length of Stay (d)	*p*
Reintubation			< 0.001
Yes	45	15.8 (10.0–25.5)	
No	714	8.6 (5.8–13.3)	
Gender			0.008
Male	446	8.3 (5.5–13.2)	
Female	313	9.8 (6.2–14.7)	
Race			0.441
Caucasian	196	8.7 (5.9–13.9)	
African American	332	9.9 (5.9–14.8)	
Hispanic	145	8.4 (5.3–13.2)	
Other	86	8.6 (5.6–13.3)	
Comorbidities			
Cardiovascular			< 0.001
Yes	111	12.5 (6.2–17.0)	
No	648	8.6 (5.8–13.2)	
Genetic			0.033
Yes	30	13.0 (8.0–16.5)	
No	729	8.7 (5.8–13.7)	
Prematurity			0.003
Yes	148	10.3 (6.8–15.7)	
No	611	8.7 (5.5–13.4)	
Immunologic			0.001
Yes	20	13.9 (10.1–26.4)	
No	739	8.7 (5.8–13.7)	
Neurologic			0.984
Yes	82	9.9 (4.1–16.2)	
No	677	8.7 (5.9–13.5)	
Pulmonary			< 0.001
Yes	31	15.4 (12.5–28.5)	
No	728	8.7 (5.8–13.4)	

If corrected for multiple comparisons, the *p* cutoff for statistical significance is 0.006.

TABLE 6.
Multivariate Analysis: PICU Length of Stay

Characteristic	Coefficient (95% CI)
Reintubation	7.23 (5.63–8.84)
Weight (kg)	0.03 (–0.13 to 0.18)
Male	–0.24 (–1.01 to 0.53)
Comorbidities	
Cardiovascular	1.41 (0.26–2.57)
Genetic	–0.12 (–2.20 to 1.95)
Prematurity	–0.90 (–1.90 to 0.10)
Immunologic	2.01 (–0.37 to 4.39)
Pulmonary	3.76 (1.77–5.75)
Pediatric Index of Mortality 2 score	0.56 (0.15–0.98)
Duration of mechanical ventilation (d)	1.15 (1.08–1.21)

characteristics and PIM 2 scores, although PIM 2 scores may not be the ideal measure of bronchiolitis severity given the low mortality and the presence of both "MV" and "bronchiolitis" as variables within the score (12). Our study had several limitations and is best interpreted as a description of current practices that can be used to generate hypotheses. First, we were limited by the variables available in the database. Some markers of illness severity, such as work of breathing scores (e.g., Wood-Downes score), hypoxemia, hypercarbia, dyspnea, and encephalopathy, are not adequately captured in the VPS database, so we were only able to adjust our analyses for the available risk factors for severe bronchiolitis such as age, comorbid status, and weight. Our findings may have been different, if we were able to reduce inherent bias, by adjusting for, or propensity-score matching, based upon additional pertinent confounders. We were also not able to evaluate the impacts of physician preference, equipment availability, prior support modality, and tolerance of interface. Similarly, we were not able to examine the indication for reintubation (e.g., upper airway obstruction vs "true extubation failure" from neuromuscular, respiratory, or cardiac insufficiency). Again, even though we found that HFNC was associated with reduced reintubation, only appropriately designed prospective trials can

establish if one mode is truly superior. Second, database studies are inherently at risk of inaccurate data entry. However, the VPS database has been used for many retrospective observational studies of critically ill children and uses strict quality control measures to reduce data entry errors (33–35). Third, we were not able to evaluate cointerventions such as sedation to facilitate compliance with NIPPV (36, 37), use of corticosteroids to reduce extubation failure (38–40), occurrence of accidental/unplanned extubation (41), and others that may have impacted our findings. Fourth, we did not calculate a sample size a priori, and it is possible that our analyses may be underpowered. Fifth, it is possible that other children received HFNC or NIPPV promptly after extubation but were not included in our analyses. We intentionally used conservative definitions to identify children receiving HFNC or NIPPV after extubation, including a "start time" that was the same as the endotracheal intubation "end time." This makes our inclusion criteria as specific as possible at the possible cost of reducing the size of our cohort. It also precludes valid comparisons against the 982 subjects who were extubated who did not have immediate HFNC or NIPPV usage recorded, as some of these children may have been misclassified.

CONCLUSIONS

In this secondary analysis of a multicenter database of children with bronchiolitis, extubation to HFNC was associated with a lower prevalence of reintubation within 24 hours compared with NIPPV in both unmatched and propensity-matched analysis. HFNC may be a more effective means of post-extubation respiratory support than NIPPV, but only prospective trials can determine if the post-extubation support modality can mitigate the risk of extubation failure. Given the common use of HFNC and NIPPV after extubation and the strong association between reintubation and unfavorable clinical outcomes, such trials are urgently needed.

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