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Modifiable and Non-Modifiable Risk Factors for Tracheostomy in Preterm Infants

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ABSTRACT

Objective: To identify risk factors for tracheostomy among infants born < 33 week gestational age.

Methods: We conducted a retrospective matched case-control study of infants < 33 week gestation who underwent tracheostomy between 2000 and 2018 at a single level IV NICU. For each case, we identified two controls matched for gestational age ± 1 week and birthweight ± 100 g who were admitted during the same year. Records were reviewed for IMV duration, number of intubations/extubations, postnatal steroid exposure, BPD severity and other clinical factors. Odds ratios and 95% CI were calculated by a conditional logistic regression.

Results: The mean (SD) gestation of the cohort (30 tracheostomy cases; 60 controls) was 26.2 (2.2) week. Tracheostomies were performed at 158 d (127–183) of age and 48 week (44.6–55) post-menstrual age (PMA) following 92 d (64–134) IMV; median (IQR). Tracheostomy was indicated for severe BPD [N = 19(68%)], acquired airway obstruction [*N* = 4(14%)], or severe BPD with airway obstruction [*N* = 5(18%)]. Additional risk factors included male sex, outborn birth, intrauterine growth retardation, pulmonary hypertension, and sepsis. IMV duration and length of stay were longer, postnatal steroid exposure was more common and PMA at discharge was later for tracheostomy cases than controls. The number of intubations, extubations (planned and unplanned) and extubations adjusted for IMV duration were significantly higher in cases than controls. In the final logistic model, the number of unplanned extubations and steroid courses were independently associated with tracheostomy.

Conclusion: Strategies to minimize tracheostomy risk should target modifiable risk factors such as reducing unplanned extubations and limiting postnatal steroids in high-risk infants.

1 | Introduction

Tracheostomies are performed in 0.1%–3.5% of all newborns and 3.5% of preterm infants born at < 30 weeks [1, 2]. A recent study utilizing a national database of pediatric admissions in the United States demonstrated that the occurrence of extremely preterm infants with bronchopulmonary dysplasia (BPD) increased 17% and tracheostomy placement increased 31% from 2006 to 2012 [2], underscoring the importance of identifying risk factors and possible mitigation strategies to reduce these complications of prematurity. Neonatal tracheostomy indications include prolonged ventilation dependence secondary to BPD, congenital and acquired upper airway obstruction, neurologic disease, genetic syndromes, and craniofacial abnormalities [3]. At our institution, increased neonatal tracheostomy placement for anatomical obstruction was observed [4]. Risk factors for tracheostomy in the preterm population that have been previously identified include very low birthweight and gestational age, male sex, and the presence of a congenital anomaly

[5]. Preterm infants ≤ 28 weeks gestation with tracheostomies have associated comorbidities including severe chronic lung disease, retinopathy of prematurity, pulmonary hypertension (PH), intraventricular hemorrhage (IVH), poor growth requiring nutritional supplemental support via a nasogastric or gastrostomy tube [5, 6] and higher rates of death and neurodevelopmental impairment at 18–22 months compared to infants without tracheostomy placement [1, 5, 7, 8].

Although severe BPD is a major risk factor for tracheostomy in preterm infants, BPD has been defined by evolving criteria since it was first described in 1967 [9]. Updated BPD severity-based classifications [10–12] have recently been proposed to address changes in clinical management including increased noninvasive respiratory support with or without supplemental oxygen. According to these classification schemes, 40%–53% infants with Grade 3 BPD compared to 1% infants without BPD received a tracheostomy [13]. To better understand the underlying pathophysiology of BPD, infants with BPD have been classified into phenotypic subgroups based on the presence of moderate-severe parenchymal lung disease, PH, and large airway disease (tracheomalacia and/or bronchomalacia) [14]. Presence of two or more phenotypic components has been associated with an increased risk for tracheostomy [14].

Our long-term goal is to develop risk mitigation strategies to reduce tracheostomy placement rates. The aim of this single institution retrospective case-control study was to identify potential modifiable risk factors for tracheostomy in preterm infants < 33 weeks gestation. We hypothesized that unplanned extubations are a modifiable risk factor for tracheostomy in this population. In addition, we assessed changes in characteristics of preterm infants who received tracheostomies over an 18-year period.

2 | Methods

A single-center, retrospective matched case-control study was conducted at the University of Maryland Medical Center level IV NICU for the 18 year period 2000–2018. The University of Maryland institutional review board approved the study (HP-00083174). Waiver of consent was granted by institutional review board for retrospective chart review. Eligibility criteria included gestational age < 33 weeks, inborn or admission to the level IV NICU within 7 days after birth, and tracheostomy placement. Exclusion criteria included congenital airway anomalies or neurologic etiology for ventilator dependence. Two controls for each case were identified that were matched for gestational age ± 1 week, birth weight ± 100 grams, and admission to the NICU within the same year. Medical records were reviewed for baseline characteristics including race, NICU comorbidities, respiratory support, airway exam results, treatment with postnatal steroids, and presence and severity of BPD at 36 weeks post-menstrual age (PMA) using the 2019 Neonatal Research Network (NRN) classification [11]. Infants were classified at 36 weeks post-menstrual age (PMA) as no BPD if they were on no respiratory support or supplemental oxygen, mild (Grade 1) BPD if receiving ≤ 2 liters per minute (LPM) nasal canula (NC), moderate (Grade 2) BPD if receiving > 2 LPM NC or noninvasive positive pressure support, or severe BPD (Grade 3) if receiving invasive respiratory support [11]. A postnatal steroid course was any systemic steroid for 7 days or longer initiated at > 7 days of age for the prevention or treatment of BPD. Inhaled steroids and peri-extubation steroids were excluded.

During the study period, our NICU pulmonary hypertension screening protocol recommended obtaining a baseline echocardiogram at 4 weeks of age in infants requiring supplemental oxygen and subsequent echocardiograms every 4 weeks until 36 week PMA in infants with BPD and predischarge. Serial echocardiograms were reviewed by a single pediatric cardiologist for evidence of PH (e.g., tricuspid regurgitation, septal flattening, and right to left or bidirectional shunt at the atria, ventricular septal defect, or across a patent ductus arteriosus). Pulmonary hypertension cases were classified according to timing of presentation (< 4 weeks vs. ≥ 4 weeks postnatal age); presence at 36 weeks PMA or predischarge which ever came first; and PH phenotypes as described by Mirza et al [15].

The total number of intubation and extubation events (planned and unplanned) was recorded. An extubation event was classified as unplanned if the endotracheal tube was dislodged or unintentionally removed during invasive mechanical ventilation (IMV). The number of extubations was adjusted for IMV duration pre-tracheostomy for cases and for total IMV duration for controls. Specific data collected for tracheostomy cases included the timing of tracheostomy, duration of IMV pre-tracheostomy, and procedure indication.

2.1 | Statistical Analysis

Cases were compared to matched controls for clinical and ventilatory support variables. Since clinical management practices and rates of comorbidities may have changed over the 18 year period of the study, we compared infants who received tracheostomies in two periods (2000–2009 and 2010–2018). Statistical analysis included Student *t*-test and Wilcoxon rank sum test or Kruskal-Wallis test for normally and non-normally distributed continuous variables, respectively, and Fisher's exact test for categorical variables. Odds ratios with 95% confidence intervals were calculated using a conditional fixed-effects logistical regression. The statistical analyses were performed using Stata version 17.0 (StataCorp, College Station, TX).

3 | Results

3.1 | Comparison of Tracheostomy Cases in Two Cohorts

Of 74 newborns admitted to the University of Maryland NICU between January 2000 to December 2018 who received a tracheostomy, 30 (41%) met eligibilty criteria for study inclusion (Figure 1). Excluded tracheostomy patients included 16 who were > 1 week of life on admission and 28 who were born ≥ 33 weeks gestation. Characteristics of tracheostomy cases for the entire 18 years and within 2000–2009 (period 1) and 2010–2018 (period 2) epochs are presented in Table 1. Cases in the 2 periods were similar for gestational age, sex, race, Apgar scores, and antenatal steroid exposure. Comorbidities were similar between the groups except the frequency of culture-confirmed sepsis was lower and frequency of postnatal steroid

exposure and number of steroid courses were higher in cases during period 2 compared to period 1. All tracheostomy cases were classified with BPD at 36 week PMA with similar distribution of severity in the two time periods. Pulmonary hypertension was diagnosed in 70% of tracheostomy cases and was present in 43% cases at 36 week PMA. Postnatal steroids were utilized in 93% cases in the 2010-2018 period and 53% in the 2000–2009 period (Table 2). All cases in period 2 compared to two-thirds in period 1 had an airway exam completed before tracheostomy. Nine cases had airway obstruction with or without severe BPD (subglottic stenosis, [$N = 8$]; tracheal stenosis, [$N = 1$]). Only two cases had tracheomalacia/bronchomalacia documented before tracheostomy placement. There were no significant difference in IMV days, timing of tracheostomy [postnatal age (PNA) or PMA], length of stay, PMA at discharge, or survival to discharge between cases in the two periods (Table 2).

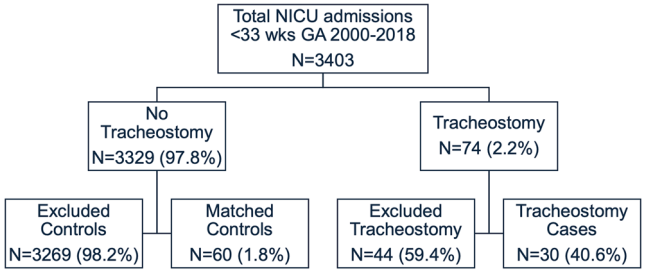

FIGURE 1 | Total NICU admissions < 33 weeks gestation between 2000 and 2018.

3.2 | Comparison of Tracheostomy Cases and Matched Controls

The mean (SD) gestation of the combined cohort (30 tracheostomy cases; 60 controls) was 26.2 (2.2) week and mean birthweight was 771 (243) g. The frequencies of male sex,

TABLE 1 | Comparison of demographics of tracheostomy cases in the 2 study periods.

Variable	Tracheostomy Cases 2000–2018 $N = 30$	Tracheostomy Cases 2000–2009 $N = 15$	Tracheostomy Cases 2010–2018 $N = 15$	p value
GA (week), mean ± SD	26.3 ± 2.4	26.2 ± 2.7	26.4 ± 2.0	0.78
BW (g), mean ± SD	768 ± 294	780 ± 380	755 ± 185	0.828
Female Sex, N (%)	9 (30)	7 (47)	2 (13)	0.109
Black race, N (%)	20 (67)	9 (60)	11 (73)	0.7
Outborn, N (%)	8 (27)	6 (40)	2 (13)	0.215
SGA, N (%)	10 (33)	5 (33)	5 (33)	1.00
Antenatal steroids, N (%)	23 (77)	10 (67)	13 (87)	0.390
C/S, N (%)	24 (80)	11 (73)	13 (87)	0.651
Apgar 1 min, mean ± SD	3.7 ± 2.6	3.9 ± 2.6	3.4 ± 2.7	0.611
Apgar 5 min, mean ± SD	6.2 ± 2.4	6.7 ± 1.9	5.7 ± 2.8	0.251
PDA medical Rx, N (%)	20 (67)	11 (73)	9 (60)	0.70
PDA ligation, N (%)	8 (27)	4 (27)	4 (27)	1.00
IVH > Grade 2, N (%)	5 (17)	2 (13)	3 (20)	1.00
BPD at 36 week PMA, N (%)	30 (100)	15 (100)	15 (100)	
Grade 0	0 (0)	0 (0)	0 (0)	0.099
Grade 1	4 (13)	4 (27)	0 (0)	
Grade 2	7 (23)	3 (8)	4 (27)	
Grade 3	19 (63)	8 (53)	11 (73)	
Pulmonary hypertension, N (%)	21 (70)	8 (53)	13 (87)	0.109
PH at 36 week PMA	9 (43)	3 (38)	6 (46)	1.00
PH phenotype				
Delayed pulmonary vascular transition	10 (48)	3 (38)	7 (54)	0.659
Late PH (> 4week)	11 (52)	5 (62)	6 (46)	
Sepsis, N (%)	19 (63)	14 (93)	5 (33)	0.002
NEC, N (%)	8 (27)	4 (27)	4 (27)	1.00
Gastrostomy tube placement	26 (87)	13 (87)	13 (87)	1.00

Abbreviations: BPD, bronchopulmonary dysplasia; BW, birth weight; C/S, Cesarean section; GA, gestational age; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus; PH, pulmonary hypertension; SGA, small for gestational age.

TABLE 2 | Comparison of respiratory variables of tracheostomy cases in the 2 study periods.

Variable	Tracheostomy Cases 2000–2018 $N = 30$	Tracheostomy Cases 2000–2009 $N = 15$	Tracheostomy Cases 2010–2018 $N = 15$	p value
Airway exam N (%)	25 (83)	10 (67)	15 (100)	0.042
Tracheostomy indication, N (%)				
Acquired airway obstruction	4 (14)	3 (23)	1 (7)	0.110
BPD	19 (68)	6 (46)	13 (86)	
Airway obstruction/BPD	5 (18)	4 (31)	1 (7)	
Postnatal steroids, N (%)	22 (73)	8 (53)	14 (93)	0.035
Postnatal steroid courses, median (range)	1 (0–7)	0 (0–2)	1 (0–7)	0.001
Pre-tracheostomy duration IMV (d), median (IQR)	92 (64–134)	93 (64–129)	91 (64–140)	0.950
Tracheostomy PNA (d), median (IQR)	158 (127–183)	157 (124–190)	158 (127–183)	0.678
Tracheostomy PMA (week), median (IQR)	47.7 (44.6–55)	46.4 (44.4–55)	49 (44.6–55)	0.678
LOS (d), median (IQR)	214 (176–266)	218 (131–264)	207 (176–307)	0.772
PMA discharge (week), median (IQR)	56.1 (50.0–64.6)	57 (46.2–63.4)	54.3 (50.6–67.1)	0.663
Survival, N (%)	24 (80)	12 (80)	12 (80)	1.00

Abbreviations: BPD, bronchopulmonary dysplasia; IMV, invasive mechanical ventilation; IQR, interquartile range LOS, length of stay; PMA, postmenstrual age.

TABLE 3 | Characteristics of preterm infants in combined cohorts with tracheostomy compared to matched controls.

Variable	Controls $N = 60$	Tracheostomy Cases $N = 30$	Odds Ratio	95% CI	p value
GA (week), mean ± SD	26.11 ± 2.08	26.32 ± 2.37	1.66	0.823–3.356	0.157
BW (g), mean ± SD	772.9 ± 216.9	767.6 ± 294.1	0.999	0.995– 1.003	0.826
Female Sex, N (%)	32 (53)	9 (30)	0.317	0.110–0.913	0.033
Black race, N (%)	34 (57)	20 (67)	1.49	0.614–3.612	0.378
Outborn, N (%)	6 (10)	8 (27)	5.62	1.14–27.8	0.034
SGA, N (%)	10 (17)	10 (33)	4	1.026–15.6	0.046
Antenatal steroids, N (%)	46 (77)	23 (77)	1.00	0.285– 3.503	1.00
C/S, N (%)	41(68)	24 (80)	1.830	0.637–5.261	0.262
Apgar 1 min, mean ± SD	3.9 ± 2.5	3.7 ± 2.6	0.956	0.801–1.140	0.615
Apgar 5 min, mean ± SD	6.5 ± 2.1	6.2 ± 2.4	0.930	0.739– 1.171	0.539
PDA, N (%)	40 (68)	22 (73)	1.424	0.437–4.639	0.558
PDA medical Rx, N (%)	29 (50)	20 (67)	2.774	0.839–9.165	0.094
PDA ligation, N (%)	8 (14)	8 (27)	2.147	0.726–6.348	0.167
IVH, N (%)	27 (46)	15 (50)	1.146	0.473–2.774	0.763
IVH > Grade 2, N (%)	6 (10)	5 (17)	1.667	0.509–5.461	0.399
BPD at 36 week PMA, N (%)	49 (82)	30 (100)	3.177	1.703–5.925	< 0.001
Grade 0	11 (18)	0 (0)			
Grade 1	23 (38)	4 (13)			
Grade 2	18 (30)	7 (23)			
Grade 3	4 (7)	19 (63)			
Death before 36 week PMA	4 (7)	0 (0)			
PH, N (%)	6 (10)	21 (70)	17.811	4.14–76.63	< 0.001
PH at 36 week PMA, N (%)	3 (5)	9 (30)	8.3	1.78–38.7	0.007
Sepsis, N (%)	19 (32)	19 (63)	9.026	1.994–40.86	0.004
NEC, N (%)	7 (12)	8 (27)	3.53	0.885– 14.093	0.074
Postnatal steroids, N (%)	14 (23)	22 (73)	10	2.9–34.2	< 0.001
Postnatal steroid courses, median (range)	0 (0–2)	1 (0–7)	3.16	1.52–6.58	0.002
Cumulative duration IMV, median (IQR)	35 (14.5–52)	151 (104–186)	1.069	1.013– 1.128	0.015
LOS (d), median (IQR)	89 (75–120)	214 (176–266)	1.059	1.009–1.111	0.019
PMA discharge, median (IQR)	38.7 (36.3–42.5)	56.1 (50.0–64.6)	1.624	1.016– 2.596	0.043
Survival, N (%)	54 (90%)	24 (80%)	0.420	0.114–1.542	0.191

Abbreviations: BW, birth weight; C/S, Cesarean section; GA, gestational age; PDA, patent ductus arteriosus; IMV, invasive mechanical ventilation; IQR, interquartile range; IVH, intraventricular hemorrhage; LOS, length of stay; NEC, necrotizing enterocolitis; PH, pulmonary hypertension; PMA, postmenstrual age; SGA, small for gestational age.

outborn status, intrauterine growth retardation, and culture-confirmed sepsis were higher in cases than controls (Table 3). The risk for severe BPD was threefold higher in cases than controls. The risk for pulmonary hypertension at any time point and at 36 week PMA was 17-fold and eightfold higher, respectively in cases than controls. Four of five (80%) controls and 19/21 (90%) cases with PH had moderate to severe BPD. Exposure to any postnatal steroids and number of steroid courses was significantly higher in cases than controls. There was no significant difference in incidence of patent ductus arteriosus (PDA), PDA treatment, IVH, or necrotizing enterocolitis. Duration of IMV, and length of stay was longer and PMA at discharge was later in cases than in controls. The frequency of gastrostomy tube placement was 6.5-fold higher in cases than controls (26 (87%) vs. 8 (13%), $p < 0.001$). There was no difference in survival to NICU discharge between the groups. The number of intubations, extubations (planned and unplanned) and extubations adjusted for IMV duration were significantly higher in cases than controls (Table 4). There was an increased risk for tracheostomy for each additional intubation (OR 2.06; 95% CI 1.38–3.09), any extubation (OR 2.05, 95% CI 1.37–3.07), planned extubation (OR 1.95; 95% CI 1.3–2.94), and unplanned

TABLE 4 | Comparison of number of extubations in tracheostomy cases and controls in combined cohorts.

Variable	Controls $N = 60$	Tracheostomy Cases $N = 30$	p value
Intubations, median (IQR)	3 (1–4)	8 (6–10)	< 0.001
Total Extubations, median (IQR)[a]	3 (1–4)	7 (6–10)	0.001
Unplanned Extubations, median (IQR)•	1 (0–2)	4 (2–7)	< 0.001
Planned Extubations, median (IQR)[a]	1 (1–2.5)	3 (2–4)	0.001
Total Extubations/IMVday, median (IQR)[b]	0.09 (0.05–0.167)	0.08 (0.06–0.125)	0.344
Unplanned Extubations/IMVday, median (IQR)[b]	0.02 (0–0.06)	0.05 (0.02–0.079)	0.0031
Planned Extubations/IMVday, median (IQR)[b]	0.059 (0.021–0.118)	0.026 (0.02–0.037)	0.0037

[a]Six controls were never intubated so total, planned, and unplanned extubations are based on 54 controls and 30 cases.
[b]Number of extubations were corrected for number of days of IMV (IMV/day) before tracheostomy for cases and total IMV for controls.

extubation (OR 1.82; 95% CI 1.3–2.5). Compared to tracheostomy cases with severe BPD, cases with airway obstruction had a higher number of intubations (7 (5–8) vs. 10 (7–13), median [IQR], $p = 0.021$). In contrast, the number of intubations, and planned and unplanned extubations adjusted for number of ventilation days was not statistically different among the BPD grades (Table 5).

3.3 | Logistic Model

Factors associated with tracheostomy in the univariate analyses (number unplanned extubations, number postnatal steroid courses, sepsis, PH at 36 week PMA, and severe BPD) were included in a stepwise conditional fixed effects logistic regression model. In the resulting model, the number of unplanned extubations (OR 1.6, 95% CI 1.2–2.2, $p = 0.005$) and postnatal steroids courses (OR 4.3, CI 1.3–14.4, $p = 0.019$) were each independently associated with tracheostomy.

4 | Discussion

This study describes modifiable and non-modifiable risk factors for neonatal tracheostomy to help identify high-risk infants and potentially lead to efforts to reduce overall placement. In agreement with prior studies [5, 6], male sex, small for gestational age (SGA), outborn status, severe BPD, pulmonary hypertension, sepsis, and prolonged ventilation were risk factors associated with tracheostomy placement in our population, indicating that smaller, sicker infants are at highest risk for tracheostomy. The current study highlights the contribution of the number of intubations and extubations, particularly unplanned extubations and exposure to multiple courses of postnatal steroids to risk for tracheostomy [5, 6, 16].

Currently, there is no decision tree or protocol for tracheostomy placement and the timing of the procedure is based on clinical judgment which can vary between institution and provider [17]. In the current study, tracheostomies were performed at greater than 3 months postnatal age at a post-term post-menstrual age. Timing is important as current literature demonstrates early tracheostomy placement, before 120 days of life, is associated with better neurodevelopmental outcomes [5]. This has been confirmed in a recent study demonstrating that preterm infants with BPD exposed to postnatal corticosteroids who had early tracheostomy ≤122 days had better cognitive outcomes at 2–3 years of age than corticosteroids-exposed infants with late tracheostomy [18]. However, timing of tracheostomy placement varies from 44 weeks to greater than 48 weeks PMA [19] with surveys demonstrating placement occurring for indications including airway malacia, PEEP ≥ 9-11, FiO2 ≥ 0.6, pCO2 > 75 mmHg, PMA > 44 weeks, and weight < 10%ile [20]. Strategies to develop an imaging-based clinical tool for early identification of infants with BPD who are likely to require tracheostomy [21], involvement of a multidisciplinary chronic lung disease team [16], and early goal of care discussions with parents [22] would facilitate timely interventions including tracheostomy.

Severe BPD is a known significant risk factor for tracheostomy placement and adverse respiratory outcomes in the first 2 years of life [6, 13, 23] with over two-thirds of our cohort having severe BPD as the indication for tracheostomy. One-third had a diagnosis of acquired airway obstruction (subglottic stenosis, tracheomalacia) upon airway examination with obstruction remaining a common indication for tracheostomy placement [4]. Tracheobronchomalacia (TBM) has been diagnosed in 50% of preterm infants < 32 week gestation by dynamic computed tomography [24] and 10%–48% of infants by bronchoscopy [25, 26]. It is likely that the rate of TBM was underestimated in our cohort since the presence of TBM was not assessed in all airway exams due to instability of many of the infants undergoing the procedure that may have precluded discontinuation of PEEP and spontaneous respiration needed to visualize TBM as well as variability in the practice patterns of the ENT and pediatric surgeons that performed the tracheostomies and lack of alternative imaging studies.

BPD-associated pulmonary hyptension (BPD-PH) was diagnosed in 70% of tracheostomy cases and was present at 36 weeks PMA in 43%. In the Children's Hospital Neonatal Consortium, 22% of infants < 32 weeks gestation were diagnosed with PH. PH is associated with invasive respiratory support at 36 week PMA, longer duration of ventilation and increased risk for tracheostomy and increased frequency of hospital readmissions [27]. BPD-PH is associated with higher mortality and morbidity including higher rates of gastrostomy tube feedings and higher health care costs [28]. Compared to non-PH infants, infants with BPD-PH experience adverse growth and neurodevelopmental outcomes at 18–24 months of age [29]. Longitudinal screening and individualized management of infants with PH may reduce the impact of this diagnosis on adverse respiratory outcomes [30].

TABLE 5 | Comparison of number of extubations by BPD severity in combined cohorts.

Variable	BPD severity				*p* value
	Grade 0 ($N = 11$)	Grade 1 ($N = 27$)	Grade 2 ($N = 25$)	Grade 3 ($N = 23$)	
Intubations, median (IQR)[a]	0 (0–2)	4 (2–5)	4 (3–7)	7 (5–10)	< 0.001
Total Extubations, median (IQR)[a]	0 (0–2)	4 (2–5)	4 (3–6)	7 (5–10)	< 0.001
Unplanned Extubations, median (IQR)[a]	0 (0–0)	2 (0–3)	2 (0–3)	2 (1–4)	0.001
Planned Extubations, median (IQR)[a]	0 (0–1)	2 (1–3)	2 (1–3)	3 (2–5)	< 0.001
Total Extubations/IMVday, median (IQR)[a,b]	0.11 (0.07–0.14)	0.12 (0.07–0.18)	0.08 (0.06–0.13)	0.08 (0.04–1.0)	0.069
Unplanned Extubations/IMVday, median (IQR)[a,b]	0 (0–0.07)	0.04 (0–0.07)	0.04 (0.02–0.08)	0.04 (0.01–0.06)	0.704
Planned Extubations/IMVday, median (IQR)[a,b]	0.067 (0.05–0.07)	0.06 (0.02–0.14)	0.04 (0.02–0.07)	0.026 (0.02–0.03)	0.082

[a]Excluded four controls who died before 36 week PMA.
[b]Number of extubations were corrected for number of days of IMV (IMV/day) before tracheostomy for cases and total IMV for controls.

Postnatal steroid use was associated with a 10-fold increased risk for tracheostomy placement. Steroid administration in tracheostomy patients increased from 53% in 2000–2010 to 93% in 2010–2018. Similar to our study, a study in Canada noted all tracheostomy patients received postnatal steroids between years 2013–2017 [31]. The lower usage during the earlier period likely reflects reduced steroid usage in the late 1990s and early 2000s due to concerns for adverse effects on neurodevelopment particularly cerebral palsy [32]. Specifically in 2002, the AAP recommended against routine use of steroids in treatment of chronic lung disease in citing concerns of impaired growth and adverse neurodevelopment [33]. However, a 2024 Cochrane review recommends dexamethasone initiation after 7 days of life to reduce chronic lung disease, combination of death and chronic lung disease, and need for future steroids, but the optimal dosing regimen remains debated [34]. It is difficult to determine whether repeat steroid exposure is simply an indicator of lung disease severity in the tracheostomy infants or whether repeated or cumulative steroid exposure has negative effects on the lung. However, infants who remain on invasive respiratory support despite repeated steroid courses, appear to be high risk for tracheostomy.

Premature neonates are at increased risk of infections due to compromised immune systems and multiple exposures [35]. Bacterial infections have been known to increase all-cause mortality, increased morbidity, and may also increase the probability of significant morbidity in the neonatal population [36]. In our study culture-positive sepsis occurred at two times the rate in tracheostomy cases compared to matched controls, consistent with increased morbidity risk. Strategies to reduce late onset infection rates including hand hygiene, early human milk supplementation, central line bundles and limiting usage, and antibiotic stewardship may have contributed to lower rates of sepsis in the second compared to first period of the study [35].

We demonstrated that the number of intubations and extubations are modifiable risk factors for tracheostomy placement with risk increased with each additional intubation and extubation event after adjustment for IMV duration and BPD severity. We demonstrated a twofold increase in risk for tracheostomy for each additional unplanned extubation. This is in agreement with Windsor et al [37] who observed that more than three failed extubation attempts was a risk factor for tracheostomy. Unplanned extubations remain one of the most common adverse events noted in the NICU [38]. Unplanned extubations are associated with prolonged ventilation with increased odds of BPD, need for tracheostomy, longer length of stay [38, 39], and increased healthcare costs [40].

Implementation of QI initiatives, PDSA cycles, unplanned extubation bundles, along with care standardization have reduced unplanned extubations [41, 42]. Multiple unplanned extubations increases the likelihood of multiple attempts per intubation event, airway trauma, and need for resuscitation [38, 42]. In our study, acquired airway obstruction occurred in one-third of tracheostomy cases and was associated with increased number of intubation events. This may be a result of repeated intubation attempt event trauma. There is a current knowledge gap of targeted unplanned extubation reduction efforts on tracheostomy placement.

This case control study identifies risk factors correlating with neonatal tracheostomy placement when compared to matched controls over an 18-year study period. Identification of correlated risk factors allows for targeted quality improvement initiatives for risk mitigation strategies. Limitations of this study included total duration which may introduce practice changes and provider bias over the 18-year span. Due to the retrospective nature of the study, we were unable to collect details on number of intubation attempts since this information was not reliably reported. We were not able to classify cases and controls by BPD phenotypes since airway exams were not done in all instances and appropriate imaging studies were not available. Another limitation is the lack of post-discharge information on survival and neurodevelopmental and respiratory outcomes. The generalizability is limited due to the small tracheostomy sample size and extended duration of a single center study. This case control study can help define correlated risk factors but causation cannot be concluded.

The infant tracheostomy population requires extensive family discussion and intense medical home involvement [22, 43]. Modifiable risk factors should be targeted for QI initiatives and counseling. Reducing intubation and extubation events, specifically unplanned extubations, should be targeted to reduce known medical comorbidities and reduce overall healthcare costs [40]. Additional studies are needed to assess the impact of QI initiatives on other specific risk factors, such as postnatal steroids and sepsis, feasibility of implementation of change, and the downstream effects on tracheostomy placement. Continued analysis of these factors will additionally help construct future protocols and decision-making tools for tracheostomy placement, family-medical team counseling, and long-term pediatric outcomes.

In summary, we have identified unplanned extubations and repeated postnatal steroid courses in extremely preterm infants supported by prolonged invasive mechanical ventilation as risk factors for tracheostomy placement that might be amendable to risk mitigation strategies.

Author Contributions

Brandon Dudeck: writing–original draft, writing–review and editing, conceptualization, investigation. **Elias W. Abebe:** investigation, writing–original draft. **Wendy Sun:** writing–review and editing, investigation, writing–original draft. **Peter R. Gaskin:** resources, writing–review and editing, investigation. **Rose M. Viscardi:** conceptualization, formal analysis, supervision, writing–original draft, writing–review and editing. **Eunsung Cho:** supervision, writing–review and editing, conceptualization, investigation, writing–original draft.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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