Duration of and trends in respiratory support among extremely preterm infants

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ABSTRACT

Objective To evaluate annual trends in the administration and duration of respiratory support among preterm infants.

Design Retrospective cohort study.

Setting Tertiary neonatal intensive care units in the Canadian Neonatal Network.

Patients 8881 extremely preterm infants born from 2010 to 2017 treated with endotracheal and/or non-invasive positive pressure support (PPS).

Main outcome measures Competing risks methods were used to investigate the outcomes of mortality and time to first successful extubation, definitive extubation, weaning off PPS, and weaning PPS and/or low-flow oxygen, according to gestational age (GA). Cox proportional hazards and regression models were fitted to evaluate the trend in duration of respiratory support, survival and surfactant treatment over the study period.

Results The percentages of infants who died or were weaned from respiratory support were presented graphically over time by GA. Advancing GA was associated with ordinally earlier weaning from respiratory support. Year over year, infants born at 23 weeks were initially and definitively weaned from endotracheal and all PPS earlier (HR 1.06, 95% CI 1.01 to 1.11, for all outcomes), while survival simultaneously increased (OR 1.11, 95% CI 1.03 to 1.18). Infants born at 26 and 27 weeks remained on non-invasive PPS longer (HR 0.97, 95% CI 0.95 to 0.98 and HR 0.97, 95% CI 0.95 to 0.99, respectively). Early surfactant treatment declined among infants born at 24–27 weeks GA.

Conclusions Infants at the borderline of viability have experienced improved survival and earlier weaning from all forms of PPS, while those born at 26 and 27 weeks are spending more time on PPS in recent years. GA-based estimates of the duration of respiratory support and survival may assist in counselling, benchmarking, quality improvement and resource planning.

What is already known on this topic?

- Nearly all extremely preterm infants are treated with endotracheal and/or non-invasive positive pressure support.
- Avoidance of endotracheal ventilation in the delivery room and in the first days of life is being increasingly adopted in clinical practice.
- Treatment with non-invasive positive pressure support and less invasive surfactant administration, in lieu of endotracheal ventilation, may improve neonatal and neurodevelopmental outcomes.

What this study adds?

- This cohort study, including 8881 extremely preterm infants, considered the risk of mortality to delineate the total duration of respiratory support.
- Infants born at the borderline of viability experienced both improved survival and earlier weaning from all forms of positive pressure support in recent years.
- Gestational age-based estimates of the duration of respiratory support and mortality may assist in counselling, benchmarking, quality improvement and resource planning.

BACKGROUND

Over the past decade, advances in non-invasive positive pressure support (PPS) and greater understanding of the potential benefit of avoiding exposure to mechanical ventilation have resulted in reductions in the frequency of initiation and duration of endotracheal ventilation among extremely preterm infants.[1–4] As an increasing number of infants at the border of viability receive full intensive care with the goal of intact survival, estimates of the duration of respiratory support are important for understanding and predicting resource utilisation, and for antenatal counselling for anticipated preterm birth. In addition, clinical assessment of the trajectory of respiratory improvement among preterm infants receiving ventilatory support may be assisted by population-level data describing the duration of endotracheal and non-invasive respiratory support.

Population-level estimates of the duration of respiratory support have been reported, but represent treatment in an earlier era.[5 6] Previous research also often focused on investigating the association of the duration of respiratory support with neurodevelopmental outcomes for preterm infants who survive to discharge from neonatal intensive care.[1 6] Including infants who die in-hospital may render estimates of the duration of respiratory support more complex, as death and prolonged mechanical ventilation may be competing events. Contemporary estimates of the duration of respiratory support

among extremely preterm infants that account for mortality have not, to the best of our knowledge, been previously reported. Thus, the objective of this study was to provide clinically useful estimates of annual trends and duration of respiratory support and risk of mortality among extremely preterm infants.

METHODS

This was a retrospective analysis of data from the Canadian Neonatal Network (CNN), which maintains a reliable, standardised database of all admissions to 31 participating Canadian tertiary neonatal intensive care units (NICUs).[7] Infants born at gestational age (GA) $23^{+0/7}$–$27^{+6/7}$ weeks who received intensive care from 1 January 2010 to 31 December 2017 were included. Infants were excluded if they were recorded as having never received any PPS, or as having been discharged home prior to weaning from PPS or prior to 34 weeks corrected GA (CGA), as these likely represented the provision of comfort care after birth or data entry errors. Infants were also excluded if they were admitted after the third day of age (due to missing data) or if they remained in the NICU for longer than 8 months (outliers with comorbidities unrelated to extreme prematurity).

Detailed daily data regarding respiratory support were collected for each infant from admission until discharge. For an infant who received more than one type of support (eg, endotracheal ventilation and non-invasive PPS) on a calendar day, the highest mode of respiratory support received was assigned for that day. Infants who received intratracheal surfactant but without administration of positive pressure ventilation through an endotracheal tube (eg, minimally invasive surfactant treatment (MIST), less invasive surfactant administration (LISA) or the intubate-surfactant-extubate (INSURE) method) were categorised as having received surfactant but not endotracheal ventilation. Data on the administration of systemic corticosteroids for prevention of bronchopulmonary dysplasia (BPD) were also abstracted.

The main outcomes of interest were (1) time to first successful extubation, which was defined as extubation from endotracheal ventilation and remaining extubated for 7 days without reintubation; (2) time to definitive successful extubation, which occurred when infants did not require subsequent therapeutic intubation; (3) time to wean from all PPS (both endotracheal and non-invasive); and (4) time to wean from all respiratory support (PPS and low-flow oxygen).

Death was considered a competing event; that is, its occurrence precluded the determination of the timing of weaning for an infant still treated with respiratory support. Some infants were transferred from a level III to a level II NICU while on respiratory support and were censored, as level II NICUs do not provide data to the CNN. The methodology for determining the duration of respiratory support and event status for infants who died, had missing data or were transferred prior to weaning from respiratory support is presented in online supplementary table S1.

Statistical analysis

Descriptive statistics summarised the antenatal and perinatal characteristics of included infants. The median and IQR of the duration of endotracheal ventilation, non-invasive PPS and low-flow oxygen were determined for both surviving and non-surviving infants. A flexible, non-parametric competing risks model[8 9] using the Nelson-Aalen estimator was fitted in order to estimate the percentage of infants who achieved the outcomes of interest or experienced a competing event (death). The cumulative incidence function gives the proportion of patients at specific time points who have experienced the outcome of interest while accounting for competing events. It is a function of the cause-specific hazard for the event of interest, but also incorporates the cause-specific hazard for the competing event of death. GA was used as the main predictor in the models given its association with duration of respiratory support.[10] Given that the risks of death and transfer to a level II unit vary during the course in the NICU, the models incorporated time-dependent effects.

Cox proportional hazards models were fitted to evaluate the annual trend in duration of respiratory support over the study period by GA at birth. To evaluate the potential influence of the competing outcome of death, logistic regression models were fitted to evaluate the annual trend in survival to hospital discharge over the study period. To further explore secular changes in respiratory management, linear regression models were fitted to evaluate the annual trend in endotracheal intubation and surfactant administration during the first 2 days after birth and treatment with oral or intravenous corticosteroids for prevention of BPD. Analyses were performed using SAS V.9.4.

RESULTS

During the study period, 9678 infants born at GA $23^{+0/7}$–$27^{+6/7}$ weeks received intensive care in a CNN NICU. Of these, 797 infants were excluded (online supplementary figure S2) and the remaining 8881 infants were included in the analysis, of whom 7788 (88%) were treated with endotracheal ventilation and 1588 (17.9%) died prior to discharge from hospital (online supplementary table S3).

GA-based analysis

The estimated time to first successful extubation (online supplementary figure S4), definitive successful extubation (figure 1), weaning off all PPS (figure 2), and weaning off all PPS and low-flow oxygen (online supplementary figure S5) are presented as stacked plots showing percentages of infants separated by GA at birth. Death occurred more frequently with decreasing GA, although most deaths occurred within the first 2 weeks after birth across all GA subgroups.

Time to weaning from respiratory support for all infants, according to GA at birth, is displayed in table 1. For example, infants born at 23 weeks GA were definitively extubated at a median of 30.4 weeks CGA (IQR 28.4–33.7) and weaned from all PPS at 36.9 weeks CGA (IQR 34.6–39.7). With increasing GA, successful extubation (both initial and definitive), weaning from all PPS and weaning from all respiratory support (positive pressure ventilation and low-flow oxygen) occurred ordinally earlier during the course in the NICU (table 1).

Annual trends in duration of PPS and survival

Among infants born at 23 and 24 weeks GA, initial successful extubation occurred progressively earlier in successive years (crude HR (cHR) 1.06, 95% CI 1.01 to 1.11 and cHR 1.05, 95% CI 1.03 to 1.08, respectively, per year), as did definitive extubation (cHR 1.06, 95% CI 1.01 to 1.11 and cHR 1.05, 95% CI 1.02 to 1.08, respectively, per year) (figure 3 and online supplementary table S6). The timing of initial successful and definitive extubation was similar during the study period for infants born at 25–27 weeks GA.

Year over year, infants born at 23 weeks GA were weaned off all PPS earlier (cHR 1.06, 95% CI 1.01 to 1.11, per year), while infants born at 26 and 27 weeks remained on PPS for

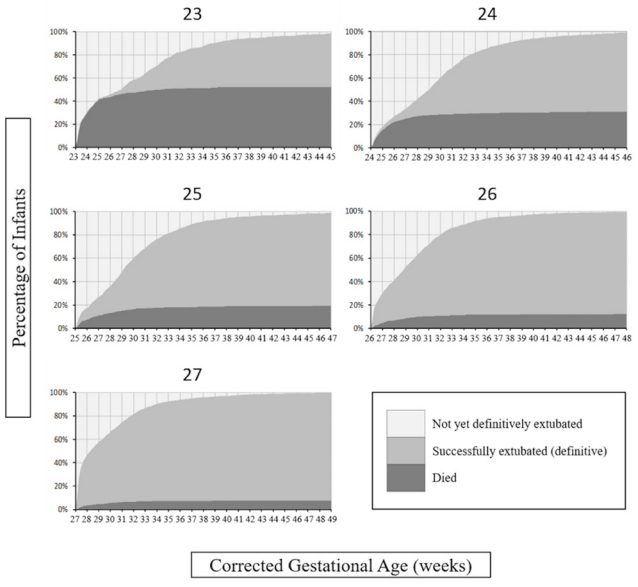

Figure 1 Cumulative incidence plot: time to definitive extubation. Definitive extubation was defined as survival for at least 7 days after an infant's last endotracheal extubation. The plot displays the percentages of infants over time who died before definitive extubation (dark grey), achieved definitive extubation (intermediate grey) or continued to be treated in the neonatal intensive care unit without achieving definitive extubation (light grey). A total of 7788 infants were treated with endotracheal ventilation and were included in the analysis.

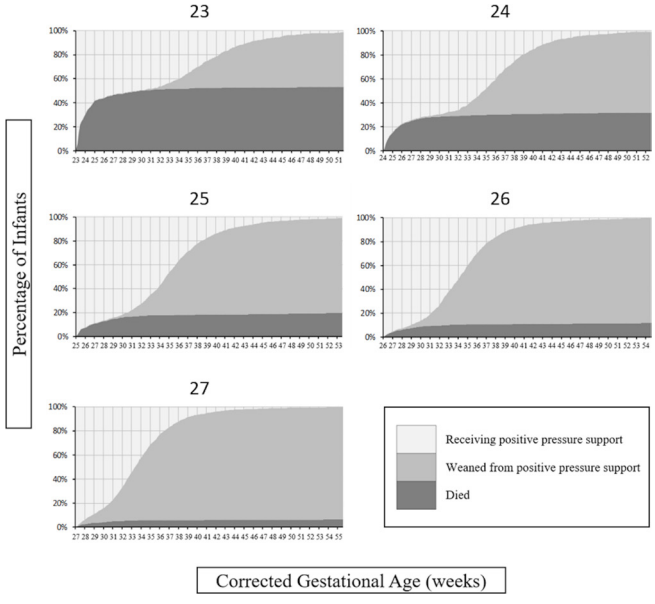

Figure 2 Cumulative incidence plot: time to weaning off all positive pressure support (PPS). Weaning off all PPS (endotracheal or non-invasive) was defined as 7 days without readministration of PPS. The plot displays the percentages of infants over time who died before weaning off all PPS (dark grey), were successfully weaned off all PPS (intermediate grey) or continued to be treated in the neonatal intensive care unit with positive pressure ventilation (light grey). A total of 8881 infants were treated with PPS.

Table 1 Time to weaning off respiratory support according to gestational age at birth

GA (n)	ETTV at any time, n (%)	ETTV within the first 7 days after birth, n (%)	PPS within the first 7 days after birth, n (%)	Died while on ETTV or within 7 days after extubation, n (%)	Died while on PPS or within 7 days after weaning off PPS, n (%)	In-hospital mortality, n (%)	Postnatal age (days) at first successful extubation*	CGA (weeks) at first successful extubation*	Postnatal age (days) at definitive extubation*	CGA (weeks) at definitive extubation*	Postnatal age (days) at weaning off PPS†	CGA (weeks) at weaning off PPS†	Postnatal age (days) at weaning off all respiratory support (PPS or LFO_2)‡	CGA (weeks) at weaning off all respiratory support (PPS or LFO_2)‡
23 (n=638)	636 (100)	635 (100)	638 (100)	332 (52)	336 (53)	338 (53)	42 (31–56.5)	29.4 (27.4–31.1)	52 (38–75)	30.4 (28.4–33.7)	97 (81–117)	36.9 (34.6–39.7)	104 (84–122)	37.9 (35.0–40.4)
24 (n=1432)	1413 (99)	1375 (96)	1428 (100)	442 (31)	452 (32)	452 (32)	36 (20–49)	29.1 (26.9–31.0)	44 (31–62)	30.3 (28.4–32.9)	87 (72–104)	36.4 (34.3–38.9)	97 (80–112)	37.9 (35.4–40.0)
25 (n=1959)	1873 (96)	1775 (91)	1954 (100)	365 (19)	377 (19)	375 (19)	22 (6–37)	28.1 (25.9–30.3)	32 (18–51)	29.6 (27.6–32.3)	72 (58–89)	35.3 (33.3–37.7)	78 (63–98)	36.1 (34.0–39.0)
26 (n=2251)	1940 (86)	1786 (79)	2249 (100)	242 (11)	257 (11)	262 (12)	9 (2–26)	27.3 (26.3–29.7)	21 (5–38)	29.0 (26.7–31.4)	59 (45–74)	34.4 (32.4–36.6)	64 (49–82)	35.1 (33.0–37.7)
27 (n=2601)	1926 (74)	1771 (68)	2597 (100)	153 (6)	161 (6)	161 (6)	4 (2–15)	27.6 (27.3–29.1)	9 (2–29)	28.3 (27.3–31.1)	45 (31–60)	33.4 (31.4–35.6)	48 (34–65)	33.9 (31.9–36.3)

Data presented as median (IQR).
*Estimated using only infants treated with endotracheal ventilation who were successfully extubated.
†Estimated using only infants treated with positive pressure ventilation who successfully weaned off.
‡Estimated using only infants treated with positive pressure ventilation and/or low-flow oxygen who were successfully weaned off.
CGA, corrected gestational age; ETTV, endotracheal ventilation; GA, gestational age; LFO_2, low-flow oxygen; PPS, positive pressure support.

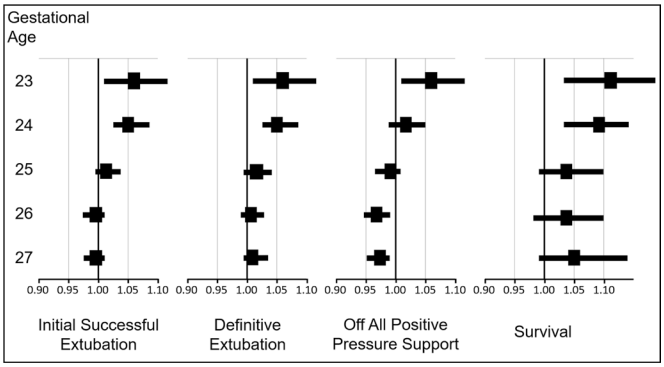

Figure 3 Annual trend in the hazard of remaining on positive pressure support and the odds of survival over the study period (2010–2017). Displayed as HR or OR with 95% CI representing year-over-year change. HR >1 signifies an annual trend of increased earlier weaning from respiratory support (ie, shorter duration) and HR <1 signifies an annual trend of increased later weaning of respiratory support (ie, longer duration). OR >1 signifies an annual trend of increased survival and OR <1 signifies an annual trend of decreased survival.

longer durations (cHR 0.97, 95% CI 0.95 to 0.98 and cHR 0.97, 95% CI 0.95 to 0.99, respectively, per year) (figure 3 and online supplementary table S6). Survival increased by 11% per year among infants born at 23 weeks GA (crude OR (cOR) 1.11, 95% CI 1.03 to 1.18) and by 9% among infants born at 24 weeks (cOR 1.09, 95% CI 1.03 to 1.14), but not among more mature infants.

Online supplementary tables S7 and S8, respectively, present the number of infants who were successfully extubated or weaned off all PPS (invasive and non-invasive) and/or low-flow oxygen, along with the number of those who died or were censored. The annual trend in the hazard of remaining on any form of respiratory support (PPS and/or low-flow oxygen) was not evaluated due to a large proportion of infants (2282 of 8881; 25.7%) being censored for this outcome, predominantly due to transfer of infants to level II NICUs or being discharged home while on low-flow oxygen.

The proportions of infants treated with endotracheal intubation during the first 2 days after birth declined, year over year, among infants born at 25, 26 and 27 weeks GA (figure 4A), while the proportions of infants treated with intratracheal surfactant during the first 2 days after birth also declined, year over year, among infants born at 24, 25, 26 and 27 weeks GA (figure 4B). Postnatal systemic corticosteroid administration for prevention of BPD increased, year over year, only among infants born at 24 weeks GA (+2.1% annually, 95% CI 0.5% to 3.8%; online supplementary figure S9).

DISCUSSION

In this large, multicentre, national cohort of extremely preterm infants, we present, by GA at birth, estimates of postnatal and corrected GA at first and definitive successful endotracheal extubation, weaning from all PPS and weaning from all respiratory support (endotracheal or non-invasive PPS, or low-flow oxygen) while accounting for the competing outcome of death. These estimates may be used by clinicians for antenatal and postnatal counselling and benchmarking and quality improvement initiatives, by administrators for resource planning, and by researchers for identifying ways to improve the efficiency of weaning infants from respiratory support. For example, prospective parents may be counselled that infants born at 24 weeks gestation are treated

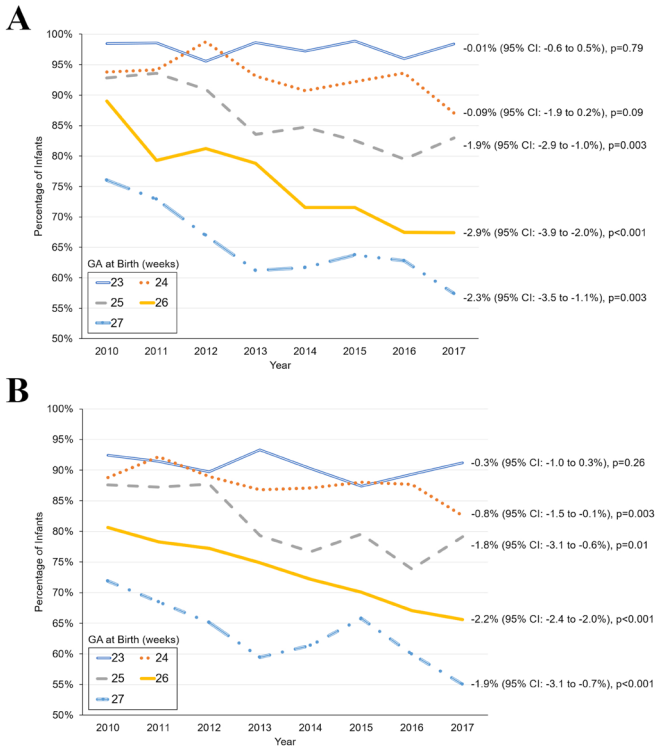

Figure 4 Annual trends in the percentages of infants treated with endotracheal intubation (A) and surfactant (B) during the first 2 days after birth, according to gestational age (GA). Trend presented as year-over-year percentage change with 95% CI. All infants who received intratracheal surfactant were included (B), irrespective of the method of administration (eg, endotracheal tube followed by mechanical ventilation, minimally or less invasive surfactant administration, or the intubate-surfactant-extubate method).

with mechanical ventilation for a median of 6 weeks and definitive extubation occurs at a median of 30 weeks CGA, with half of infants (IQR) extubated in the range of 28–33 weeks CGA.

We identified an annual trend of earlier initial and definitive extubation among infants born at 23 and 24 weeks GA. Coupled with the finding of an annual increase in survival, our results suggest that these high-risk infants have experienced improved survival without concomitant increases in the duration of endotracheal ventilation. Previous studies have identified a trend of lower mortality over the past two decades among infants born at the border of viability,[11 12] and associated a shorter duration of mechanical ventilation with improved neurodevelopmental outcomes in childhood.[13 14] Additional study is required to determine if the reduction in duration of ventilatory support in our cohort is associated with improved neurodevelopmental outcomes.

Interestingly in our study, improved survival and earlier extubation occurred, among infants born at 24 weeks, amidst a reduction in surfactant administration and increase in postnatal treatment with systemic corticosteroids. This occurred with concomitant year-over-year declines in endotracheal intubation and surfactant administration among infants 25–27 weeks GA, possibly reflecting the adoption of practice recommendations favouring prophylactic nasal continuous positive airway pressure (nCPAP) and early selective surfactant over primary intubation, prophylactic surfactant and subsequent endotracheal ventilation.[15–20] More recently, amidst reports of the safety,[21] benefit[22–24]

and increasing integration[25] of MIST/LISA into routine clinical care to avoid early nCPAP failure, the annual trend in declining endotracheal ventilation, but not necessarily surfactant administration, may be expected to continue. Evidence that exposure to endotracheal ventilation contributes to neonatal lung injury,[26] combined with the potential to uncouple surfactant administration from endotracheal ventilation (eg, using MIST/LISA), may limit further declines in surfactant treatment.

We unexpectedly identified an annual trend of progressively longer duration of PPS among infants born at 26 and 27 weeks GA, which was not accompanied by a significant improvement in survival. The absence of a change in the duration of endotracheal ventilation suggests that an increased duration of non-invasive PPS likely accounts for the additional time until infants were weaned from all PPS. Several factors may explain this finding. First, treatment with non-invasive PPS may be overused in contemporary practice.[27] The threshold for commencing and maintaining infants on nCPAP or other non-invasive PPS is low, possibly due to a perception that nCPAP supports pulmonary development and long-term function[28 29] and does not invoke the same deleterious effects of pulmonary inflammation and maldevelopment as does endotracheal ventilation.[30] The adoption of higher oxygen saturation targets for preterm infants during our study period[31] may have also influenced the duration of non-invasive respiratory support as clinicians may have eschewed increased volumes of low-flow supplemental oxygen in favour of non-invasive PPS with a low fraction of inspired oxygen. In addition, reduced administration of surfactant may potentially contribute to increased pulmonary inflammation and a longer duration of positive pressure ventilation. Surfactant administration has been associated with reduced lung cytokine expression in animal models of preterm respiratory distress syndrome,[32 33] and in our study infants born at 26 and 27 weeks GA concomitantly experienced an increased duration of PPS and the largest year-over-year annual decline in surfactant administration. Finally, our study period (2010–2017) is an epoch characterised by the broad adoption of newer methods of non-invasive PPS as alternatives to nCPAP,[3 4 34] such as heated and humidified high-flow nasal cannula (HHHFNC).[35] While high-quality evidence exists to guide clinicians on weaning preterm infants off nCPAP,[36] the current paucity of studies addressing weaning from these alternative modalities of non-invasive PPS[37] may have resulted in delays in discontinuation.[38 39]

Strengths and limitations

Strengths of this study include the use of a large, national, multicentre cohort with reliable data collection. While previous studies have associated a shorter duration of endotracheal ventilation with improved neurodevelopmental outcomes in early childhood,[13 14] we were limited by an absence of follow-up data for this cohort. We did not capture data on the frequency of the INSURE method, which may have influenced the annual trend in endotracheal intubation. In addition, the influence of centre-specific characteristics (eg, altitude) or management practices (eg, criteria for extubation or surfactant administration) was not explored and we did not have data on trends in providers' attitude towards the provision of intensive care for infants born at 23 and 24 weeks GA; infants born at 22 weeks GA were excluded from the study due to small numbers at the beginning of the study period; and a minority of infants were censored in the analysis due to transfer to a level II NICU. Finally, this study did not differentiate among modalities of endotracheal ventilation (eg, high frequency oscillatory or conventional mechanical) or non-invasive PPS (eg, HHHFNC or nCPAP) to provide a more granular characterisation of the course of respiratory support, including reasons for variation and annual trends identified in the duration of PPS.

Future implications

The results of this study may aid clinicians and researchers in identifying mechanisms to optimise respiratory support requirements and duration among preterm infants, with an aim to minimise lung injury and promote lung growth. The most commonly used definition of BPD is based on an association of the intensity of respiratory support at 36 weeks CGA and later respiratory and neurodevelopmental outcomes.[40] The adjudication of the presence or absence of BPD occurs at this 'cut-off' irrespective of GA at birth, a paradigm of evaluation that may be less reliable among contemporary cohorts comprising larger proportions of infants born at 23 and 24 weeks GA.[41] Continuous rather than binary measures of respiratory function, such as duration of respiratory support, may represent a more flexible, targeted (by GA) and patient-centred outcome to facilitate the evaluation of interventions for improving respiratory function.

CONCLUSIONS

In this large cohort of extremely preterm infants, both mortality and duration of all forms of positive pressure ventilation decreased, year over year, for infants born at 23 and 24 weeks GA, while infants born at 26 and 27 weeks GA remained on non-invasive PPS longer. The rates of surfactant administration and endotracheal ventilation also declined, especially among preterm infants born at 25–27 weeks GA. Estimates of the duration of respiratory support and mortality may assist in counselling parents, benchmarking and quality improvement activities, and resource planning.

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Contributors DEW conceptualised and designed the study, interpreted the data, drafted the initial manuscript, and critically reviewed and revised the final manuscript. EY conceptualised and designed the study, analysed and interpreted the data, and critically reviewed and revised the final manuscript. BR and MD, JE, AM and PSS conceptualised and designed the study, interpreted the data, and critically reviewed and revised the final manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. PSS had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of data analysis. EY conducted the data analysis.

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REFERENCES

1 Asztalos EV, Church PT, Riley P, *et al*. Neonatal factors associated with a good neurodevelopmental outcome in very preterm infants. *Am J Perinatol* 2017;34:388–96.
2 Finer NN, Carlo WA, SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network, *et al*. Early CPAP versus surfactant in extremely preterm infants. *N Engl J Med* 2010;362:1970–9.
3 Bottino R, Pontiggia F, Ricci C, *et al*. Nasal high-frequency oscillatory ventilation and CO_2 removal: A randomized controlled crossover trial. *Pediatr Pulmonol* 2018;53:1245–51.
4 Zhu X-W, Shi Y, Shi L-P, *et al*. Non-Invasive high-frequency oscillatory ventilation versus nasal continuous positive airway pressure in preterm infants with respiratory distress syndrome: study protocol for a multi-center prospective randomized controlled trial. *Trials* 2018;19:1–151.
5 Soll RF, Edwards EM, Badger GJ, *et al*. Obstetric and neonatal care practices for infants 501 to 1500 G from 2000 to 2009. *Pediatrics* 2013;132:222–8.
6 Walsh MC, Morris BH, Wrage LA, *et al*. Extremely low birthweight neonates with protracted ventilation: mortality and 18-month neurodevelopmental outcomes. *J Pediatr* 2005;146:798–804.
7 Shah PS, Seidlitz W, Chan P, *et al*. Internal audit of the Canadian neonatal network data collection system. *Am J Perinatol* 2017;34:1241–9.
8 Hinchliffe SR, Lambert PC. Flexible parametric modelling of cause-specific hazards to estimate cumulative incidence functions. *BMC Med Res Methodol* 2013;13:13.
9 Seaton SE, Barker L, Draper ES, *et al*. Estimating neonatal length of stay for babies born very preterm. *Arch Dis Child Fetal Neonatal Ed* 2019;104:F182–6.
10 Phibbs CS, Schmitt SK. Estimates of the cost and length of stay changes that can be attributed to one-week increases in gestational age for premature infants. *Early Hum Dev* 2006;82:85–95.
11 Patel RM, Kandefer S, Walsh MC, *et al*. Causes and timing of death in extremely premature infants from 2000 through 2011. *N Engl J Med* 2015;372:331–40.
12 Younge N, Goldstein RF, Bann CM, *et al*. Survival and neurodevelopmental outcomes among Periviable infants. *N Engl J Med* 2017;376:617–28.
13 Vliegenthart RJS, van Kaam AH, Aarnoudse-Moens CSH, *et al*. Duration of mechanical ventilation and neurodevelopment in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2019;104:F631–5.
14 Vliegenthart RJS, Onland W, van Wassenaer-Leemhuis AG, *et al*. Restricted ventilation associated with reduced neurodevelopmental impairment in preterm infants. *Neonatology* 2017;112:172–9.
15 Subramaniam P, Ho JJ, Davis PG. Prophylactic nasal continuous positive airway pressure for preventing morbidity and mortality in very preterm infants. *Cochrane Database Syst Rev* 2016:Cd001243.
16 Isayama T, Iwami H, McDonald S, *et al*. Association of noninvasive ventilation strategies with mortality and bronchopulmonary dysplasia among preterm infants: a systematic review and meta-analysis. *JAMA* 2016;316:611–24.
17 Bahadue FL, Soll R. Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome. *Cochrane Database Syst Rev* 2012;11:Cd001456.
18 Stevens TP, Harrington EW, Blennow M, *et al*. Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome. *Cochrane Database Syst Rev* 2007:CD003063.
19 Sweet DG, Carnielli V, Greisen G, *et al*. European Consensus Guidelines on the Management of Respiratory Distress Syndrome - 2016 Update. *Neonatology* 2017;111:107–25.
20 , Committee on Fetus and Newborn, American Academy of Pediatrics. Respiratory support in preterm infants at birth. *Pediatrics* 2014;133:171–4.
21 Herting E, Kribs A, Härtel C, *et al*. Two-Year outcome data suggest that less invasive surfactant administration (LISA) is safe. results from the follow-up of the randomized controlled AMV (avoid mechanical ventilation) study. *Eur J Pediatr* 2020;179:1309–13.
22 Kribs A, Roll C, Göpel W, *et al*. Nonintubated surfactant application vs conventional therapy in extremely preterm infants: a randomized clinical trial. *JAMA Pediatr* 2015;169:723–30.
23 Isayama T, Chai-Adisaksopha C, McDonald SD. Noninvasive ventilation with vs without early surfactant to prevent chronic lung disease in preterm infants: a systematic review and meta-analysis. *JAMA Pediatr* 2015;169:731–9.
24 Aldana-Aguirre JC, Pinto M, Featherstone RM, *et al*. Less invasive surfactant administration versus intubation for surfactant delivery in preterm infants with respiratory distress syndrome: a systematic review and meta-analysis. *Arch Dis Child Fetal Neonatal Ed* 2017;102:F17–23.
25 Herting E, Härtel C, Göpel W. Less invasive surfactant administration (LISA): chances and limitations. *Arch Dis Child Fetal Neonatal Ed* 2019;104:F655–9.
26 Fischer HS, Bührer C. Avoiding endotracheal ventilation to prevent bronchopulmonary dysplasia: a meta-analysis. *Pediatrics* 2013;132:e1351–60.
27 Doyle LW, Carse E, Adams A-M, *et al*. Ventilation in extremely preterm infants and respiratory function at 8 years. *N Engl J Med* 2017;377:329–37.
28 Polin RA, Sahni R. Newer experience with CPAP. *Semin Neonatol* 2002;7:379–89.
29 Lam R, Schilling D, Scottoline B, *et al*. The effect of extended continuous positive airway pressure on changes in lung volumes in stable premature infants: a randomized controlled trial. *J Pediatr* 2020;217:66–72.
30 Vliegenthart RJ, Onland W, van Kaam AH. Ventilation in preterm infants and lung function at 8 years. *N Engl J Med* 2017;377:1600–1.
31 Askie LM, Darlow BA, Davis PG, *et al*. Effects of targeting lower versus higher arterial oxygen saturations on death or disability in preterm infants. *Cochrane Database Syst Rev* 2017;4:Cd011190.
32 Hillman NH, Nitsos I, Berry C, *et al*. Positive end-expiratory pressure and surfactant decrease lung injury during initiation of ventilation in fetal sheep. *Am J Physiol Lung Cell Mol Physiol* 2011;301:L712–20.
33 Sato A, Whitsett JA, Scheule RK, *et al*. Surfactant protein-D inhibits lung inflammation caused by ventilation in premature newborn lambs. *Am J Respir Crit Care Med* 2010;181:1098–105.
34 Lemyre B, Davis PG, De Paoli AG, *et al*. Nasal intermittent positive pressure ventilation (NIPPV) versus nasal continuous positive airway pressure (nCPAP) for preterm neonates after extubation. *Cochrane Database Syst Rev* 2017;2:Cd003212.
35 Wilkinson D, Andersen C, O'Donnell CPF, *et al*. High flow nasal cannula for respiratory support in preterm infants. *Cochrane Database Syst Rev* 2016;2:Cd006405.
36 Jardine LA, Inglis GD, Davies MW. Strategies for the withdrawal of nasal continuous positive airway pressure (nCPAP) in preterm infants. *Cochrane Database Syst Rev* 2011:Cd006979.
37 Farley RC, Hough JL, Jardine LA. Strategies for the discontinuation of humidified high flow nasal cannula (HHFNC) in preterm infants. *Cochrane Database Syst Rev* 2015:Cd011079.
38 Abdel-Hady H, Shouman B, Aly H. Early weaning from CPAP to high flow nasal cannula in preterm infants is associated with prolonged oxygen requirement: a randomized controlled trial. *Early Hum Dev* 2011;87:205–8.
39 Yoder BA, Stoddard RA, Li M, *et al*. Heated, humidified high-flow nasal cannula versus nasal CPAP for respiratory support in neonates. *Pediatrics* 2013;131:e1482–90.
40 Ehrenkranz RA, Walsh MC, Vohr BR, *et al*. Validation of the National Institutes of health consensus definition of bronchopulmonary dysplasia. *Pediatrics* 2005;116:1353–60.
41 Isayama T, Lee SK, Yang J, *et al*. Revisiting the definition of bronchopulmonary dysplasia: effect of changing Panoply of respiratory support for preterm neonates. *JAMA Pediatr* 2017;171:271–9.