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15-Year trends in respiratory care of extremely preterm infants: Contributing factors and consequences on health and growth during hospitalization

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Abstract

Objectives: To review 15-year trends in respiratory care of extremely preterm infants managed in a tertiary perinatal center; to identify the factors contributing to their evolution; and to determine whether these changes had an impact on infant mortality, severe morbidity, and growth.

Methods: Retrospective cohort study of infants born at 23 to 26 weeks' gestation between 2003 and 2017. Changes in respiratory care were assessed in three 5-year periods. Logistic regression was used to examine the factors associated with prolonged duration (ie, greater than the median) of invasive mechanical ventilation (IMV), noninvasive ventilation (NIV), and overall respiratory support (ORS), and those associated with adequate weight and head circumference growth.

Results: Of the 396 actively treated neonates, 268 (68%) survived to discharge. Between the first and third periods, IMV duration decreased from 22 (6-37) to 4 (1-14.0) days ($P < .001$), that of NIV increased from 24 (14-34) to 56 (44-66) days ($P < .001$), and that of ORS from 50 (34-68) to 63 (52-77) days ($P < .001$). Study period (2003-2007 vs 2013-2017) was the main factor associated with prolonged IMV ($P < .001$). Use of high-flow nasal cannula was the main factor associated with prolonged NIV ($P = .02$) and ORS ($P = .02$). NIV duration was associated with adequate postnatal weight ($P = .003$) and head circumference ($P = .03$) growth. Severe morbidities in survivors, including bronchopulmonary dysplasia, and survival at hospital discharge were comparable across the study periods.

Conclusions: Respiratory management was characterized by a marked reduction in IMV. NIV withdrawal protocols are necessary to limit ORS duration while respecting postnatal growth requirements.

KEYWORDS

bronchopulmonary dysplasia, critical care, mechanical ventilation, neonatal pulmonary medicine, noninvasive ventilation

1 | INTRODUCTION

Prolonged invasive mechanical ventilation (IMV) has been associated with increased risks of death, severe respiratory morbidity, and adverse neurodevelopmental outcomes in preterm infants.¹ The strategy of respiratory care for these patients over the last few decades has focused on reducing exposure to IMV as much as possible to reduce these risks. Noninvasive ventilation (NIV) has become more extensively used, particularly continuous positive airway pressure (CPAP), which was found to be an effective primary respiratory support in premature infants.^{2,3} Heated, humidified, high-flow nasal cannula (HFNC) therapy has also been proposed to reduce the nasal damage and discomfort associated with prolonged CPAP, yet without demonstrating comparable efficacy.⁴ Similarly, alternate routes of surfactant delivery have been designed to obviate the need for or reduce the duration of endotracheal tube ventilation, including the procedure of intubation and surfactant administration followed by immediate extubation (INSURE) and techniques to administer exogenous surfactant through a less invasive (LISA) route.⁵

Most of the trials on neonatal respiratory distress management included a limited number of extremely preterm infants, although these infants constitute a large portion of perinatal death and morbidity.⁶ A major challenge for implementing less invasive devices and policies for these infants born at the border of viability is the profound immaturity of several of their systems, notably respiratory. Therefore, it is particularly important to evaluate whether guidelines can be concretely translated into clinical practice. Between-hospital variations in care and outcomes have been described, mainly influenced by the initiation of active treatment.⁷ A longitudinal observational study within a single department would document those factors related to medical determinism, that is, the application of recommendations or protocols, and patient characteristics.

The first objective of this study was therefore to identify the factors contributing to the evolution in the respiratory care of extremely preterm infants managed in our institution over the last 15 years. Our second objective was to determine whether this evolution had an impact on mortality, severe morbidity, or growth during hospitalization.

2 | METHODS

2.1 | Study location

The department of neonatal medicine of Montpellier University Hospital, France, has a capacity of 47 beds. The medical team is made up of about 10 pediatricians, including fellows. The number of pediatric nurses per neonate is framed by the French perinatal decrees of 1998; that is, one nurse for two neonates for type 3 beds ($n = 14$), corresponding to the neonatal intensive care unit (NICU), one nurse for three neonates for type 2b beds ($n = 18$), and one nurse for six neonates for type 2a beds ($n = 15$).

2.2 | Study design

2.2.1 | Population

This observational study was conducted over a 15-year period, from January 2003 to December 2017. All premature infants born at less than 27 weeks' gestational age (GA) who were actively treated were included in this study. Infants who received palliative care and those born in another hospital (out-born) were excluded.

2.2.2 | Data collection

Perinatal data for each premature infant were collected prospectively by two clinicians in a database created in 2003 for neonates born before 33 weeks' GA and/or with a birthweight less than 1500 g. The database uses a predetermined form, with detailed definitions of each item. More than 150 variables were assessed for each infant concerning antenatal history and the neonatal period.

2.2.3 | Definitions

Anthropometric data, including weight, height, and head circumference, were recorded at birth and hospital discharge and expressed as Z scores, according to Olsen et al.⁸ Growth during hospitalization was expressed by the difference in anthropometric parameter Z scores between discharge and admission.

The duration of IMV was defined as the cumulative duration of conventional mechanical ventilation (CMV) and high-frequency oscillatory ventilation (HFOV), the duration of NIV as the cumulative duration of CPAP and HFNC, and the duration of overall respiratory support (ORS) as the cumulative duration of IMV and NIV.

Severe morbidity was defined by at least one of the following conditions⁹: (a) severe bronchopulmonary dysplasia (BPD), defined as administration of oxygen for at least 28 days plus need for 30% or more oxygen and/or IMV or CPAP at 36 weeks' postmenstrual age; (b) grade 3 to 4 intraventricular hemorrhage (IVH) or cystic periventricular leukomalacia (PVL); (c) grade 2 to 3 necrotizing enterocolitis (NEC); and (d) severe retinopathy of prematurity (ROP), defined as grade 3 or more and/or laser treatment. Figure 1

2.3 | Main evolutions in respiratory and nutritional practices over the study period (Figure 1)

The surfactant administration policy for less than 30 weeks' GA neonates was early selective treatment with 200 mg/kg of poractant alfa (Curosurf, Chiesi). This treatment targeted patients with a Silverman-Anderson retraction score greater than 3 and FiO_2 greater than 30% despite respiratory support with +5 to 6 cmH_2O CPAP, applied from the first minutes of life. From 2010, premedication before intubation was generally performed using nasal midazolam or ketamine.¹⁰ At the same time,

	2003-2007	2008-2012	2013-2017
Respiratory practices			
-Surfactant	Early selective treatment	Premedication, INSURE	LISA
-IMV	Pressure-limited CMV	Pressure-limited CMV	Volume-targeted CMV
-NIV	nCPAP	nCPAP and HFNC	nCPAP and HFNC
-Systemic glucocorticoids	Betamethasone	Hydrocortisone	Hydrocortisone
-SpO ₂ target	85%-92%	85%-92%	90%-95%
Nutritional practices			
-Enteral nutrition	Started after stability Daily increase ≤ 10 ml/kg	Started since day 1 Daily increase ≥ 20 ml/kg	Started since day 1 Daily increase ≥ 20 ml/kg
-Parenteral nutrition	Since day 1 AA: 1-2 g/kg/day L: 0.5 g/kg/day	Since day 1 AA: 1-2 g/kg/day L: 0.5 g/kg/day	Since day 1 AA: 2-3 g/kg/day L: 1 g/kg/day

FIGURE 1 Chronology of standardized changes in respiratory and nutritional practices during the study periods. AA, amino acids; CMV, conventional mechanical ventilation; HFNC, high-flow nasal cannula; IMV, invasive mechanical ventilation; INSURE, intubation and surfactant administration followed by immediate extubation; L, lipids; LISA, less invasive surfactant administration; nCPAP, nasal continuous positive airway pressure; NIV, noninvasive ventilation; SpO₂, pulse oximetry [Color figure can be viewed at wileyonlinelibrary.com]

the INSURE procedure was implemented, with the aim of reducing IMV duration. LISA was the subject of a written protocol from October 2017.

CMV was provided with a synchronized ventilation mode. From 2014, volume-targeted ventilation was used preferentially to pressure-limited ventilation.¹¹ Elective HFOV was indicated for neonates with peak inspiratory pressure greater than 22 cm H₂O and FiO₂ greater than 50% with CMV. Whatever the ventilation mode, the target value for transcutaneous PCO₂ was 40 to 60 mm Hg.

Depending on the birth conditions, hemodynamic and respiratory status and wakefulness, extubation was performed as soon as possible. After weaning off IMV, neonates were systematically placed on nasal CPAP. The use of HFNC as an alternative means of providing noninvasive respiratory support to very preterm infants was noted as a written protocol in 2009.¹² This protocol called for HFNC use at a flow rate of 1 to 2 L/kg/min, 1 to 2 hours every 8 to 12 hours, in neonates whose respiratory status was stable with CPAP, with a progressive increase until complete weaning off CPAP. This relatively moderate flow rate was not revised thereafter.

Oxygen therapy was adapted to the objectives of SpO₂. Until 2013, the SpO₂ target was 85% to 92%. This was increased to 90% to 95% after the publication of the Neonatal Oxygenation Prospective Meta-analysis (NeOProM) collaborative study in 2014.¹³ Inhaled nitric oxide was used when the oxygenation index was greater than 15. Postnatal glucocorticoids were indicated in cases of failed IMV weaning or “aggressive IMV” in neonates older than 7 days. The treatment was based on betamethasone until 2006 and then on hydrocortisone hemisuccinate from 2007.¹⁴

Soon after admission to the NICU, a central venous catheter was inserted. Parenteral and enteral nutrition was prescribed daily, by

means of an in-house computerized physician order entry system¹⁵ that integrates the guidelines of the European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN). Before 2010, the protocol of the department indicated to wait for a “state of stability” before enteral administration of human milk. After publication of the 2010 ESPGHAN guidelines,¹⁶ enteral feeding was started a few hours after birth, and daily increases in enteral nutrition were twice higher. In 2013, specificities were added to the parenteral nutrition protocol for neonates less than 1500 g. Parenteral nutrition was started as soon as possible after birth. Intake then increased rapidly over the first postnatal week, up to 90 to 120 kcal/kg/day with about 3.5 g/kg/day of amino acids and 3 g/kg/day of lipids.¹⁷ Neonates with repetitive blood glucose levels greater than 10 mmol/L were treated with insulin therapy when reasonable adaptation of the glucose infusion rate was insufficient.

2.4 | Statistical analysis

The data collected in the database were divided into three equivalent periods of 5 years (2003-2007, 2008-2012, 2013-2017). Survival and survival without severe morbidity were the only two analyses performed for all actively treated patients. All other analyses were performed for infants surviving to discharge. Between-period comparisons were made using Kruskal-Wallis and χ^2 tests. Post-hoc multiple comparison corrections included the DSCF test for continuous variables and the Bonferroni correction for categorical variables. The duration of ventilation (IMV, NIV, and ORS) and postnatal growth of head circumference were studied dichotomously from the median values. For weight growth, the

difference in Z scores was centered on -1 .¹⁸ Univariate and multivariate logistic regression analyses were performed to study the influence of each covariate on the judgment criteria. The model was constructed by a step-by-step procedure based on the likelihood ratio test (input and output thresholds =0.20). The adjusted odds ratios and their 95% confidence intervals were calculated. The quality of the model was estimated by the Hosmer-Lemeshow adequacy test. Statistical analysis was performed with SAS Version 9 software (SAS Institute, Cary, NC). Values are expressed as numbers (%) or medians (Q25; Q75). *P* less than .05 were considered statistically significant.

2.5 | Ethical considerations

Approval of this study was obtained from the institutional review board of Montpellier University Hospital (IRB-MTP-2020-01-202000332).

3 | RESULTS

The department of neonatal medicine managed 434 neonates with less than 27 weeks' GA at birth during the study period. Among them,

396 (91%) were actively treated: 128/139 (92%) in the 2003-2007 period, 126/139 (91%) in the 2008-2012 period, and 142/156 (91%) in the 2013-2017 period (*P* = .26).

3.1 | Evolution in perinatal characteristics and respiratory management

Of the 268 survivors, 3 (1%) were born at 23 weeks, 29 (11%) at 24 weeks, 98 (37%) at 25 weeks, and 138 (51%) at 26 weeks. The median GA, birthweight, and head circumference of the cohort were, respectively, 26.0 (25.3; 26.4) weeks, 800 (700; 900) g, and 23 (22.5; 24) cm. Perinatal characteristics (notably rates of multiple pregnancy, exposure to antenatal glucocorticoids, cesarean section, and sex ratio) and anthropometric data were comparable across the three study periods (Supporting Information Table S1).

Cardiorespiratory care over the 15 years was characterized by increasingly systematic use of surfactant with less frequent administration of multiple doses, less resort to postnatal glucocorticoids, stable use of nitric oxide and cyclooxygenase inhibitors for ductal closure, and a comparable duration of supplemental oxygen (Table 1).

TABLE 1 Cardiorespiratory care and ventilatory strategy

	2003-2017 (n = 268)	2003-2007 (n = 86)	2008-2012 (n = 77)	2013-2017 (n = 105)	<i>P</i>
Cardiorespiratory care					
Surfactant, n% (268)	244 (91.0)	69 (80.2)	74 (96.1)	101 (96.2)	<.001 ^{a,b}
Multiple surfactant doses, n% (264)	56 (21.2)	34 (41.5)	8 (10.4)	14 (13.3)	<.001 ^{a,b}
HSPDA treated with COI, n% (263)	178 (67.7)	54 (65.9)	50 (65.8)	74 (70.5)	.63
Postnatal glucocorticoids, n% (268)	80 (29.9)	29 (33.7)	31 (40.3)	20 (19.0)	<.001 ^{b,c}
Nitric oxide, n% (263)	64 (24.3)	25 (30.5)	19 (25.0)	20 (19.0)	.22
Supplemental oxygen, days (256)	47.0 (26.0; 70.5)	44.5 (24.0; 81.0)	40.5 (18.0; 70.0)	49.0 (29.5; 68.5)	.19
Ventilatory strategy					
Invasive mechanical ventilation, n% (268)	244 (91.0)	77 (89.5)	75 (97.4)	92 (87.6)	.05
HFOV, n% (268)	133 (49.6)	41 (47.7)	48 (62.3)	44 (41.9)	.02 ^c
Invasive mechanical ventilation, days (268)	10.0 (2; 28)	21.5 (5.50; 36.5)	20.0 (3.0; 30.0)	4.0 (0.8; 14.0)	<.001 ^{b,c}
CMV, days (268)	6.0 (1.0; 15.0)	15.0 (3.0; 23.0)	7.0 (2.0; 13.7)	2.0 (0.6; 6.9)	<.001 ^{b,c}
HFOV, days (133)	11.0 (3.5; 23.0)	14.0 (5.0; 23.0)	13.0 (4.0; 25.0)	6.5 (2.0; 12.5)	.03 ^b
Noninvasive ventilation, n% (268)	261 (97.4)	81 (94.2)	75 (97.4)	105 (100)	.04 ^b
CPAP, n% (268)	258 (96.3)	81 (94.2)	75 (97.4)	102 (97.1)	.55
HFNC, n% (268)	103 (38.4)	-	10 (13.0)	93 (88.6)	<.001 ^c
Noninvasive ventilation, days (268)	40.0 (24.0; 56.0)	24.0 (13.0; 34.0)	38.0 (27.0; 48.0)	56.0 (44.0; 66.0)	<.001 ^{a,b,c}
CPAP, days (268)	32.5 (21.0; 43.0)	24.0 (13.0; 34.0)	38.0 (25.0; 46.0)	35.0 (26.0; 45.5)	<.001 ^{a,b}
HFNC, days (103)	17.0 (10.0; 27.0)	-	19.5 (8.0; 31.0)	17.0 (10.0; 27.0)	.69
Overall respiratory support, days (268)	59.1 (43.2; 70.0)	49.5 (33.7; 67.5)	56.6 (45.0; 68.0)	63.0 (52.0; 77.0)	<.001 ^b
Invasive/overall (268)	0.22 (0.04; 0.51)	0.47 (0.19; 0.70)	0.30 (0.10; 0.53)	0.06 (0.02; 0.22)	<.001 ^{a,b,c}

Values are numbers (%) or medians (Q25; Q75). Values in parentheses following each variable in the left column correspond to the number of documented variables.

Abbreviations: CMV, conventional mechanical ventilation; COI, cyclooxygenase inhibitor; CPAP, continuous positive airway pressure; HFNC, high-flow nasal cannula; HFOV, high-frequency oscillatory ventilation; HSPDA, hemodynamically significant persistent ductus arteriosus.

^aLess than .05 between 2003-2007 and 2008-2012.

^bLess than .05 between 2003-2007 and 2013-2017.

^cLess than .05 between 2008-2012 and 2013-2017.

TABLE 2 Outcome in survivors and in actively treated infants

	2003-2017 (n = 268)	2003-2007 (n = 86)	2008-2012 (n = 77)	2013-2017 (n = 105)	P
Outcome in survivors (268)					
BPD severe form, n% (268)	68 (25.4)	21 (24.4)	19 (24.7)	28 (26.7)	.94
Grade 3-4 IVH, n% (267)	35 (13.6)	13 (15.3)	14 (18.2)	9 (8.6)	.14
Cystic PVL, n% (264)	5 (1.9)	3 (3.6)	1 (1.3)	1 (1.0)	.52
Grade 2-3 NEC, n% (261)	16 (6.1)	3 (3.8)	7 (9.1)	6 (5.7)	.37
Spontaneous intestinal perforation, n% (263)	15 (5.7)	3 (3.7)	4 (5.2)	8 (7.6)	.53
Grade 3-5 ROP, n% (268)	25 (9.3)	7 (8.1)	7 (9.1)	11 (10.5)	.87
Absence of severe morbidity, n% (268)	150 (56.0)	51 (59.3)	42 (54.5)	57 (54.3)	.77
Outcome in actively treated infants (396)					
Survival (396)	268 (67.7)	86 (67.2)	77 (61.1)	105 (73.9)	.08
23 wk (10)	3 (30)	2 (50)	0 (0)	1 (25)	.43
24 wk (66)	29 (43.9)	6 (42.9)	7 (31.8)	16 (53.3)	.33
25 wk (146)	98 (67.1)	27 (64.3)	31 (64.6)	40 (71.4)	.70
26 wk (174)	138 (79.3)	51 (78.5)	39 (70.9)	48 (88.9)	.06
Survival without severe morbidity, n% (396)	150 (37.9)	51 (39.8)	42 (33.3)	57 (40.1)	.44

Values are numbers (%) or medians (Q25; Q75). Values in parentheses following each variable in the left column correspond to the number of documented variables.

Abbreviations: BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity.

In terms of ventilatory strategy, we observed a marked reduction in the duration of IMV, for CMV as for HFOV. On the other hand, the duration of NIV increased, particularly that of CPAP in the second period. Use of HFNC also increased steadily over the last 5 years. These two opposing trends resulted in an increase in the duration of ORS. The ratio of IMV/ORS decreased from 0.47 (0.19; 0.70) in the first period to 0.06 (0.02; 0.22) in the third (Supporting Information Figure S1).

Severe morbidities in survivors and survival at hospital discharge without severe morbidity in actively treated infants were comparable across the study periods (Table 2).

3.2 | Factors associated with prolonged duration of IMV, NIV, and ORS

3.2.1 | IMV

The median duration of IMV was 10 (2; 28) days. In univariate analysis, the variables significantly associated with a value greater than or equal to the median were the study period, male sex, GA, and occurrence of grade 3 to 4 IVH or grade 2 to 3 NEC. These variables were included in a multivariate model, which confirmed a predominant role of the study period in the occurrence of prolonged IMV.

3.2.2 | NIV

The median duration was 40 (24; 56) days. In univariate analysis, the variables significantly associated with a value greater than or equal to the median were the study period, shorter durations of IMV and

HFOV, use and longer duration of HFNC, time from birthdate to initiation of enteral feeding, postnatal growth (ie, every 0.5 point increase in the Z-score difference between weight at discharge and birthweight), duration of parenteral nutrition, and occurrence of grade 3 to 4 IVH. These variables were included in a multivariate model. The need to administer greater than 1 dose of surfactant was also included, as we considered this a marker of respiratory severity. The analysis found that IMV duration and use of HFNC had opposite influences on the occurrence of prolonged NIV.

3.2.3 | ORS

The median duration was 59 (43; 70) days. In univariate analysis, the variables significantly associated with a value greater than or equal to this median were GA, vaginal delivery, longer durations of IMV, HFOV, and NIV, use and longer duration of HFNC, postnatal growth (as expressed above), duration of parenteral nutrition, insulin treatment, hemodynamically significant persistent ductus arteriosus (HSPDA) and grade 2 to 3 NEC. These variables, and the study period, were included in a multivariate model. The analysis indicated that HFNC use was the sole independent factor associated with the occurrence of prolonged ORS (Table 3).

3.3 | Growth during hospitalization

3.3.1 | Nutritional strategy and anthropometric data

Over the course of the study period, we observed an increasingly earlier introduction of enteral feeding and shorter

TABLE 3 Logistic regression models for prolonged durations (ie, \geq median values) of invasive mechanical ventilation (IMV), noninvasive ventilation (NIV), and overall respiratory support (ORS)

Covariate	Odds ratio (95% CI)	P
<i>IMV ≥ 10 d</i>		
NEC/SIP	15.03 (2.35-95.95)	.004
Grade 3-4 IVH	7.6 (1.60-36.43)	.011
Low gestational age (week)	2.52 (1.25-5.05)	.009
Male sex	2.20 (0.89-5.44)	.087
2003-2007 vs 2013-2017	35.20 (8.53-145.31)	<.001
2008-2012 vs 2013-2017	4.98 (1.60-15.56)	.006
Concordance 94.1% Hosmer and Lemeshow test 0.77		
<i>NIV ≥ 40 d</i>		
HFNC	20 (1.8-223.6)	.02
Multiple surfactant doses	15.2 (2.6-88.1)	.002
2013-2017 vs 2003-2007	10 (0.5-100)	.14
Delayed enteral feeding (per day)	1.1 (0.97-1.3)	.13
Invasive ventilation (per day)	0.9 (0.86-0.99)	.02
HFOV (per day)	0.9 (0.82-1)	.09
Grade 3-4 IVH	0.45 (0.14-1.42)	.08
Concordance 93.7% Hosmer and Lemeshow test 0.81		
<i>ORS ≥ 60 d</i>		
Grade 2-3 NEC	4.7 (0.7-32.7)	.12
HFNC	3.6 (1.2-10.7)	.02
Vaginal delivery	2.3 (0.8-6.3)	.13
Low gestational age (week)	1.7 (0.8-3.3)	.14
Concordance 85.4% Hosmer and Lemeshow test 0.74		

Abbreviations: HFNC, high-flow nasal cannula; HFOV, high-frequency oscillatory ventilation; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; SIP, spontaneous intestinal perforation.

duration of parenteral nutrition. Immediate postnatal weight loss was less pronounced. Weight and length growth, expressed as the Z-score differences between hospital discharge and birth, improved over time. Head circumference growth was comparable across the three study periods (Table 4).

3.3.2 | Factors involved in postnatal weight growth

The median value of the Z-score difference for weight between hospital discharge and birth was -1.22 (-1.87 ; -0.7). We considered that growth was adequate—that is, following the curve—if the difference was lower than or equal to -1 .¹⁸

In univariate analysis, the factors associated with this growth were birthweight Z-score, duration of NIV, duration of oxygen therapy, and initial weight loss. The multivariate model included these variables, as well as others with potential influence on weight growth. The multivariate analysis confirmed that NIV duration was associated with adequate postnatal weight gain (Table 5).

3.3.3 | Factors involved in postnatal head circumference growth

The median value of the Z-score difference for head circumference between hospital discharge and birth was -0.60 (-1.23 ; 0.10). In univariate analysis, the variables significantly associated with a difference lower than this median value were birthweight Z-score, duration of NIV, duration of ORS, and postnatal weight growth. The multivariate model included these variables and others with potential influence on head circumference growth. The model confirmed that NIV duration was associated with adequate postnatal head circumference growth (Table 5).

4 | DISCUSSION

This study, which was conducted in a population of extremely premature neonates managed in the same department of neonatology, demonstrated a considerable change in the respiratory care of these patients over the last 15 years. Despite a significant reduction in the duration of IMV, we observed a marked increase in the duration of ORS, related to a great increase in the duration of NIV. Among survivors, this change in ventilatory strategy was not associated with lower severe morbidity at discharge but with improved weight and length gain during hospitalization.

Unsurprisingly, very low GA at birth and complications of prematurity like NEC and IVH were associated with prolonged IMV. However, the independent influence of the 5-year periods suggested a change in the respiratory support strategy over time in our department, regardless of the infants' health status. The decreased IMV duration in the last 5-year period can be attributed to a wider application of the INSURE procedure in this population. In addition, the 2009 implementation of a neonatal pain management module in the computerized physician order entry system meant more systematic assessment of signs of awakening and reactivity in the newborns, potentially leading to earlier extubation decisions.¹⁵

Prospective and retrospective cohort studies have suggested that the cumulative duration of IMV is a risk factor for BPD in very low birthweight infants.^{19,20} Yet, despite the marked reduction in IMV duration, our rate of severe morbidity remained unchanged, particularly BPD. Even when the duration is short, IMV increases the risk of BPD in this population,¹⁹ and we therefore assume that its duration in the third period was most likely not sufficiently reduced to affect this outcome.²¹ A meta-analysis indicated that avoiding IMV had a slight but significant beneficial impact on preventing BPD.²² More than 90% of our patients were exposed to IMV, in the delivery room or later in the NICU. Such wide exposure might be linked to the delayed adoption of LISA, which occurred only at the end of the third period. LISA can be applied to extremely premature infants, avoiding recourse to IMV in about a quarter of the patients.^{23,24} However, the meta-analysis on this procedure is difficult to interpret with respect to the optimal respiratory care for

TABLE 4 Nutritional management and postnatal growth

	2003-2017 (n = 268)	2003-2007 (n = 86)	2008-2012 (n = 77)	2013-2017 (n = 105)	P
Nutritional management					
Parenteral nutrition, days (264)	30.0 (19.0; 43.0)	37.0 (29.0; 52.0)	32.0 (24.0; 43.0)	19.0 (14.0; 31.0)	<.001 ^{a,b}
Enteral feeding introduction, days (259)	2.0 (1.0; 3.0)	3.0 (2.0; 6.0)	2.0 (2.0; 3.0)	1.0 (1.0; 1.0)	<.001 ^{a,b,c}
Insulin treatment, n% (259)	158 (61.0)	46 (56.1)	49 (65.3)	63 (61.8)	.48
Postnatal growth					
First-days weight loss, % (257)	9.2 (5.2; 13.5)	12.85 (9.0; 17.0)	9.0 (5.0; 14.0)	6.95 (3.4; 10.6)	<.001 ^{a,b,c}
Discharge weight, g (262)	2500 (2080; 2900)	2345 (1965; 2625)	2586 (2145; 3055)	2600 (2145; 2950)	.005 ^{b,c}
Discharge weight Z-score (262)	-1.22 (-1.66; -0.80)	-1.42 (-1.80; -0.90)	-1.41 (-1.80; -0.90)	-1.05 (-1.40; -0.60)	<.001 ^{a,b}
Discharge Z-score—birth Z-score (262)	-1.22 (-1.87; -0.70)	-1.38 (-2.00; -0.80)	-1.25 (-2.00; -0.80)	-1.14 (-1.60; -0.60)	.01 ^b
Discharge length, cm (258)	45.0 (42.0; 47.0)	44.0 (42.0; 45.5)	45.0 (43.0; 47.0)	45.0 (43.0; 47.0)	.004 ^{b,c}
Discharge length Z-score (258)	-1.78 (-2.33; -1.30)	-1.93 (-2.50; -1.43)	-1.94 (-2.48; -1.26)	-1.63 (-2.12; -1.15)	.004 ^{a,b}
Discharge Z-score—birth Z-score (255)	-1.91 (-2.54; -1.20)	-2.29 (-2.70; -1.40)	-1.96 (-2.60; -1.50)	-1.65 (-2.32; -1.05)	.009 ^b
Discharge HC, cm (258)	33.0 (31.2; 34.0)	32.5 (31.0; 34.0)	33.5 (32.0; 34.5)	33.0 (31.5; 34.0)	.08
Discharge HC Z-score (258)	-0.69 (-1.38; 0.00)	-0.76 (-1.53; 0.06)	-0.52 (-1.29; 0.12)	-0.69 (-1.35; -0.12)	.31
Discharge Z-score—birth Z-score (255)	-0.60 (-1.23; 0.10)	-0.54 (-1.50; 0.10)	-0.61 (-1.10; -0.10)	-0.61 (-1.20; -0.20)	.74
Corrected GA at discharge, weeks (268)	38.0 (36.0; 40.0)	37.0 (35.0; 39.5)	38.0 (37.0; 40.0)	38.0 (36.0; 40.0)	.13

Values are numbers (%) or medians (Q25; Q75). Values in parentheses following each variable in the left column correspond to the number of documented variables.

Abbreviations: GA, gestational age; HC, head circumference.

^aLess than .05 between 2008-2012 and 2013-2017.

^bLess than .05 between 2003-2007 and 2013-2017.

^cLess than .05 between 2003-2007 and 2008-2012.

this subgroup of infants,²⁵ as it included only one trial of less than 27 weeks' GA neonates and this trial did not find improved survival without BPD.²⁴ Avoiding IMV and limiting the duration of IMV exposure may be one component of a strategy to reduce BPD in this population.²⁶ Notably, early low-dose hydrocortisone has favorable

effects on BDP in infants born at 24 and 25 weeks of gestation.²⁷ Our protocols called for late use of systemic glucocorticoids. From the second period, we replaced betamethasone with hydrocortisone, whose anti-inflammatory effect is 25 to 30 times lower. In addition, the use of hydrocortisone was halved between the second and third periods. It has been suggested that such a change in the policy for postnatal glucocorticoid use may blunt the possibly favorable effect of NIV strategies on BPD.²⁸

Our infants exposed to prolonged NIV likely had more severe initial respiratory illness, as suggested by their requirement of multiple surfactant doses. Another explanatory factor was the introduction of HFNC, whose use became markedly more frequent in the third period. This device has steadily won the trust of the department's neonatologists since the 2013 publication demonstrating its efficacy, comparable to that of CPAP, as a respiratory support after extubation.²⁹ For extremely preterm infants, our practices were extubation to CPAP, and only then followed by a switch to HFNC; this was because data about the safety and efficacy of HFNC in this subgroup of patients are sparse.³⁰ According to our results, use of HFNC to wean these infants off CPAP led to a marginal reduction in CPAP duration and to longer NIV duration. Other studies have reported prolonged respiratory support with the use of this device.^{4,31-33} As there is no evidence available to suggest the best method to wean or withdraw neonates off HFNC,³⁴ we adopted an ad hoc method for gradual HFNC weaning. A recent study performed in a pediatric intensive care unit suggested that rapid reduction in HFNC flow based on regular and systematic assessment of respiratory distress may be more effective to successfully wean patients.³⁵

TABLE 5 Logistic regression models for adequate postnatal weight gain and postnatal head circumference growth

Covariate	Odds ratio (95% CI)	P
<i>Adequate postnatal weight gain^a</i>		
Birthweight Z-score, per 0.5	4.0 (2.5-6.7)	<.001
Noninvasive ventilation, per day	1.03 (1.01-1.05)	.003
First-days weight loss, per %	0.92 (0.86-0.98)	.01
Concordance 81.0% Hosmer and Lemeshow test 0.75		
<i>Adequate postnatal head circumference growth^b</i>		
Postnatal weight growth, ^c per 0.5 Z-score	3.0 (1.9-4.9)	<.001
Noninvasive ventilation, per day	1.03 (1.01-1.05)	.03
Insulin treatment resistance	0.47 (0.23-0.95)	.04
HSPDA, despite treatment with COI	0.43 (0.20-0.91)	.03
Concordance 76.0% Hosmer and Lemeshow test 0.83		

Abbreviations: COI, cyclooxygenase inhibitor; HSPDA, hemodynamically significant persistent ductus arteriosus.

^aDefined as a maximal Z-score difference between discharge and birth for weight lower than or equal to -1.

^bDefined as a maximal Z-score difference between discharge and birth for head circumference lower than or equal to -0.6.

^cAssessed by Z-score difference between discharge and birth for weight.

Another longitudinal study in extremely premature infants noted prolonged ORS duration despite shorter IMV.³⁶ Our findings emphasize the role of introducing the HFNC device in this increase, but it is important to understand the meaning of this relationship. Our hypothesis is that clinicians maintain NIV, notably HFNC, for respiratory as well as nutritional purposes; in other words, to facilitate the growth of these patients. Most likely, adoption of the 2010 ESPGHAN guidelines for enteral nutrient supply and the changes in our parenteral nutrition protocol in 2013 limited the initial weight loss and favored adequate postnatal growth in our patients. Our study also found a positive influence of NIV on weight and head circumference growth, with each additional day of NIV increasing slightly but significantly the odds of satisfactory growth. Physiological studies have generally supported the concept that the work of breathing can be reduced by noninvasive respiratory support, including CPAP and HFNC, thus reducing energy expenditure.³⁷ Few data are available on the influence of NIV weaning modalities on weight gain. In less than 30 weeks' GA preterm babies, one study suggested that ceasing CPAP at standard criteria did not adversely affect the time to reach full feeds compared to cycling off CPAP gradually.³⁸ The transition to active bottle-feeding or breast-feeding is particularly challenging for these patients, who often experience physiological instability. NIV may be perceived at this stage as providing assistance during these supplementary efforts, as well as reducing the occurrence of apnea/bradycardia events during active feeding.

Our study has several limitations. This monocentric observation only considered inborn patients of a tertiary perinatal center hospitalized in a single NICU, which limits the generalizability of our experience. Yet these restrictions seemed unavoidable given our objective of analyzing the strategies we had implemented over a decade and a half. Furthermore, we wanted only factual data on patient outcomes, with no imputed or projected data. We made the choice to present most of the data collected in the patients surviving hospitalization because we wanted to assess the real burden of all types of respiratory support, which is reduced if patients who survive only a few days or weeks are not excluded. This study in patients born at the limits of viability included very few survivors born less than 24 weeks. The general policy in our country is to propose palliative care but not intensive care in this situation.⁹ We acknowledge that the suggested relationships between protocols, daily clinical practice, and patient outcomes are hypothetical. Observational studies have many biases and this requires that the results be interpreted with great caution. Last, our results only apply to the immediate neonatal period. Further studies are needed to evaluate the long-term benefits and risks associated with evolving practices for respiratory support in extremely premature neonates.

5 | CONCLUSION

This study clearly shows the priority given to NIV for the respiratory management of extremely premature infants in a NICU over the last

15 years. It emphasizes the propensity to prolong a ventilation that is considered "noninvasive" and the difficulty of effectively weaning infants off it. There is currently no evidence that this change in practice has short- or long-term benefits for neurodevelopment or lung function.^{36,39,40} Nevertheless, our study suggests that NIV may contribute to improving postnatal growth during hospitalization. This point should not be neglected in studies examining NIV and weaning strategies in these patients.

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CONFLICT OF INTERESTS

The authors do not have any relevant financial interests or conflict of interests to disclose.

REFERENCES

1. 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(6):798-804.
2. Morley CJ, Davis PG, Doyle LW, Brion LP, Hascoet JM, Carlin JB, COIN Trial Investigators. Nasal CPAP or intubation at birth for very preterm infants. *N Engl J Med*. 2008;358(7):700-708. <https://doi.org/10.1056/NEJMoa072788>. Erratum in: *N Engl J Med*. 2008; 358(14):1529.
3. SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network, Finer NN, Carlo WA, Walsh MC, et al. Early CPAP versus surfactant in extremely preterm infants. *N Engl J Med*. 2010;362(21):1970-1979. <https://doi.org/10.1056/NEJMoa0911783>
4. Roberts CT, Owen LS, Manley BJ, et al. Nasal high-flow therapy for primary respiratory support in preterm infants. *N Engl J Med*. 2016; 375(12):1142-1151. <https://doi.org/10.1056/NEJMoa1603694>
5. Dumpa V, Bhandari V. Surfactant, steroids and non-invasive ventilation in the prevention of BPD. *Semin Perinatol*. 2018;42(7):444-452. <https://doi.org/10.1053/j.semperi.2018.09.006>
6. Stoll BJ, Hansen NI, Bell EF, et al. Trends in care practices, morbidity, and mortality of extremely preterm neonates, 1993-2012. *JAMA*. 2015;314(10):1039-1051. <https://doi.org/10.1001/jama.2015.10244>
7. Rysavy MA, Li L, Bell EF, et al. Between-hospital variation in treatment and outcomes in extremely preterm infants. *N Engl J Med*. 2015; 372(19):1801-1811. <https://doi.org/10.1056/NEJMoa1410689>
8. Olsen IE, Groveman SA, Lawson ML, Clark RH, Zemel BS. New intrauterine growth curves based on United States data. *Pediatrics*. 2010;125(2):e214-e224. <https://doi.org/10.1542/peds.2009-0913>
9. Ancel PY, Goffinet F, EPIPAGE-2 Writing Group, et al. Survival and morbidity of preterm children born at 22 through 34 weeks' gestation in France in 2011: results of the EPIPAGE-2 cohort study. *JAMA Pediatr*. 2015;169(3):230-238. <https://doi.org/10.1001/jamapediatrics.2014.3351>
10. Milési C, Baleine J, Mura T, et al. Nasal midazolam vs ketamine for neonatal intubation in the delivery room: a randomised trial. *Arch Dis Child Fetal Neonatal Ed*. 2018;103(3):F221-F226. <https://doi.org/10.1136/archdischild-2017-312808>
11. Peng W, Zhu H, Shi H, Liu E. Volume-targeted ventilation is more suitable than pressure-limited ventilation for preterm infants: a systematic review and meta-analysis. *Arch Dis Child Fetal Neonatal*

- Ed. 2014;99(2):F158-F165. <https://doi.org/10.1136/archdischild-2013-304613>
2. Kubicka ZJ, Limauro J, Darnall RA. Heated, humidified high-flow nasal cannula therapy: yet another way to deliver continuous positive airway pressure? *Pediatrics*. 2008;121(1):82-88. <https://doi.org/10.1542/peds.2007-0957>
 13. Saugstad OD, Aune D. Optimal oxygenation of extremely low birth weight infants: a meta-analysis and systematic review of the oxygen saturation target studies. *Neonatology*. 2014;105(1):55-63. <https://doi.org/10.1159/000356561>
 14. Cambonie G, Mesnage R, Milési C, Rideau A, Veyrac C, Picaud JC. Hydrocortisone treatment for severe evolving bronchopulmonary dysplasia and cerebral haemodynamics. *Arch Dis Child Fetal Neonatal Ed*. 2009;94(2):F154-F155.
 15. Mazars N, Milési C, Carbajal R, et al. Implementation of a neonatal pain management module in the computerized physician order entry system. *Ann Intensive Care*. 2012;2(1):38. <https://doi.org/10.1186/2110-5820-2-38>
 16. Agostoni C, Buonocore G, Carnielli VP, et al. Enteral nutrient supply for preterm infants: commentary from the European Society of Paediatric Gastroenterology, Hepatology and Nutrition Committee on Nutrition. *J Pediatr Gastroenterol Nutr*. 2010;50(1):85-91. <https://doi.org/10.1097/MPG.0b013e3181adaee0>
 17. Senterre T, Rigo J. Parenteral nutrition in premature infants: practical aspects to optimize postnatal growth and development. *Arch Pediatr*. 2013;20(9):986-993. <https://doi.org/10.1016/j.arcped.2013.05.021>
 18. Guellec I, Lapillonne A, Marret S, et al. Effect of intra- and extrauterine growth on long-term neurologic outcomes of very preterm infants. *J Pediatr*. 2016;175:93-99e1. <https://doi.org/10.1016/j.jpeds.2016.05.027>
 19. Jensen EA, DeMauro SB, Kornhauser M, Aghai ZH, Greenspan JS, Dysart KC. Effects of multiple ventilation courses and duration of mechanical ventilation on respiratory outcomes in extremely low-birth-weight infants. *JAMA Pediatr*. 2015;169(11):1011-1017. <https://doi.org/10.1001/jamapediatrics.2015.2401>
 20. Choi YB, Lee J, Park J, Jun YH. Impact of prolonged mechanical ventilation in very low birth weight infants: results from a national cohort study. *J Pediatr*. 2018;194:34-39e3. <https://doi.org/10.1016/j.jpeds.2017.10.042>
 21. Vliegenthart RJ, Onland W, van Kaam AH. Ventilation in preterm infants and lung function at 8 years. *N Engl J Med*. 2017;377:1600-1601. <https://doi.org/10.1056/NEJMc1711170>
 22. Fischer HS, Bühner C. Avoiding endotracheal ventilation to prevent bronchopulmonary dysplasia: a meta-analysis. *Pediatrics*. 2013;132(5):e1351-e1360. <https://doi.org/10.1542/peds.2013-1880>
 23. Klebermass-Schrehof K, Wald M, Schwindt J, et al. Less invasive surfactant administration in extremely preterm infants: impact on mortality and morbidity. *Neonatology*. 2013;103(4):252-258. <https://doi.org/10.1159/000346521>
 24. 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(8):723-730. <https://doi.org/10.1001/jamapediatrics.2015.0504>
 25. Aldana-Aguirre JC, Pinto M, Featherstone RM, Kumar M. 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(1):F17-F23. <https://doi.org/10.1136/archdischild-2015-310299>
 26. Kugelman A, Durand M. A comprehensive approach to the prevention of bronchopulmonary dysplasia. *Pediatr Pulmonol*. 2011;46(12):1153-1165. <https://doi.org/10.1002/ppul.21508>
 27. Baud O, Maury L, Lebail F, et al. Effect of early low-dose hydrocortisone on survival without bronchopulmonary dysplasia in extremely preterm infants (PREMILOC): a double-blind, placebo-controlled, multicentre, randomised trial. *Lancet*. 2016;387(10030):1827-1836. [https://doi.org/10.1016/S0140-6736\(16\)00202-6](https://doi.org/10.1016/S0140-6736(16)00202-6)
 28. Kugelman A. Ventilation in preterm infants and lung function at 8 years. *N Engl J Med*. 2017;377:1599. <https://doi.org/10.1056/NEJMc1711170>
 29. Manley BJ, Owen LS, Doyle LW, et al. High-flow nasal cannulae in very preterm infants after extubation. *N Engl J Med*. 2013;369(15):1425-1433. <https://doi.org/10.1056/NEJMoa1300071>
 30. Wilkinson D, Andersen C, O'Donnell CP, De Paoli AG, Manley BJ. High flow nasal cannula for respiratory support in preterm infants. *Cochrane Database Syst Rev*. 2016;2:CD006405. <https://doi.org/10.1002/14651858.CD006405.pub3>
 31. Yoder BA, Stoddard RA, Li M, King J, Dirnberger DR, Abbasi S. Heated, humidified high-flow nasal cannula versus nasal CPAP for respiratory support in neonates. *Pediatrics*. 2013;131(5):e1482-e1490. <https://doi.org/10.1542/peds.2012-2742>
 32. Kugelman A, Riskin A, Said W, Shoris I, Mor F, Bader D. A randomized pilot study comparing heated humidified high-flow nasal cannulae with NIPPV for RDS. *Pediatr Pulmonol*. 2015;50(6):576-583. <https://doi.org/10.1002/ppul.23022>
 33. Taha DK, Kornhauser M, Greenspan JS, Dysart KC, Aghai ZH. High flow nasal cannula use is associated with increased morbidity and length of hospitalization in extremely low birth weight infants. *J Pediatr*. 2016;173:50-55e1. <https://doi.org/10.1016/j.jpeds.2016.02.051>
 34. 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;(6):CD011079. <https://doi.org/10.1002/14651858.CD011079.pub2>
 35. Betters KA, Hebbar KB, McCracken C, Heitz D, Sparacino S, Petrillo T. A novel weaning protocol for high-flow nasal cannula in the PICU. *Pediatr Crit Care Med*. 2017;18(7):e274-e280. <https://doi.org/10.1097/PCC.0000000000001181>
 36. Doyle LW, Ranganathan S, Cheong JLY. Ventilation in preterm infants and lung function at 8 years. *N Engl J Med*. 2017;377(16):1601-1602. <https://doi.org/10.1056/NEJMc1711170>
 37. Roberts CT, Hodgson KA. Nasal high flow treatment in preterm infants. *Matern Health Neonatol Perinatol*. 2017;3:15. <https://doi.org/10.1186/s40748-017-0056-y>
 38. Broom M, Ying L, Wright A, et al. Ceasing Cpap At standarD criteria (CICADA): impact on weight gain, time to full feeds and caffeine use. *Arch Dis Child Fetal Neonatal Ed*. 2014;99(5):F423-F425. <https://doi.org/10.1136/archdischild-2013-304581>
 39. Lo J, Zivanovic S, Lunt A, et al. Longitudinal assessment of lung function in extremely prematurely born children. *Pediatr Pulmonol*. 2018;53(3):324-331. <https://doi.org/10.1002/ppul.23933>
 40. Zhang H, Dysart K, Kendrick DE, et al. Prolonged respiratory support of any type impacts outcomes of extremely low birth weight infants. *Pediatr Pulmonol*. 2018;53(10):1447-1455. <https://doi.org/10.1002/ppul.24124>