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Predicting the Need for Home Oxygen Therapy in Preterm Infants Born Before 28 Weeks' Gestation

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Abstract

Objective—To discover a predictor, that could be used at least 3 to 4 weeks' before discharge, to identify infants who would need home oxygen therapy. We hypothesized that infants requiring a high level of respiratory support at 34 weeks' postmenstrual age (PMA) would require home oxygen.

Study Design—Single center retrospective study of 143 infants less than 28 weeks' gestation. We determined when infants weaned from each level of respiratory support (mechanical ventilation, nasal continuous airway pressure [nCPAP] or biphasic positive pressure, nasal cannula flow ≥ 2 L/min, nasal cannula flow < 2 L/min or no respiratory support). Our primary outcome was need for home oxygen.

Result—Infants who required nCPAP at 34 weeks' PMA had a 100% positive predictive value for home oxygen therapy.

Conclusion—Higher levels of respiratory support at 34 weeks' PMA can predict the need for home oxygen and is useful in preparing patients and families for discharge.

Keywords

home oxygen therapy; bronchopulmonary dysplasia; prematurity

Respiratory morbidity continues to be a significant complication of premature birth. Approximately 42% of infants, born before 28 weeks' gestation, continue to need oxygen at 36 postmenstrual age (PMA).[1] Home oxygen therapy is commonly needed when appropriate developmental milestones have been met and the sole reason for continued hospitalization is the need for supplemental oxygen.

Preparing a family for home oxygen therapy provokes anxiety in the parents and requires a substantial amount of teaching and planning.[2–4] Therefore, it is important to be able to identify infants who are likely to require home oxygen therapy several weeks before discharge. Overall, 2 to 4 weeks are often needed for parents to get used to the idea of taking their infant home with oxygen. In addition, several weeks are needed to organize oxygen

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supplies at home, ensure that proper postdischarge appointments and services are in place, and to teach the parents the skills needed to care for a child with home oxygen therapy.

The goal of our study was to discover a predictor that could identify infants who would need oxygen at the time of hospital discharge. The need for home oxygen therapy is determined by an infant's continuing requirement for respiratory support despite having achieved other necessary developmental milestones needed for discharge (e.g., ability to regulate temperature, feed independently, and be free of apnea). We sought to find a predictor that could be used 3 to 4 weeks before discharge to identify infants who would definitely need home oxygen therapy (so as not to waste resources or create unnecessary parental anxiety). In other words, we were more interested in a predictor with an extremely low false-positive rate than one with a higher degree of sensitivity (but not as good a positive predictive value).

Several studies have identified predictors of "need for home oxygen therapy." Infants born before 28 weeks' gestation have the highest risk for developing bronchopulmonary dysplasia (BPD) and needing home oxygen therapy.[5–7] Other factors that increase the odds of needing home oxygen therapy are as follows: the need for mechanical ventilation or high FIo_2 requirements in the first 3 days of life, the presence of congenital anomalies or a patent ductus arterious (PDA), and the absence of antenatal steroid exposure.[5] Although early clinical predictors are helpful, later clinical predictors may be more useful as the premature infant's hospital course is frequently quite variable.[7]

We hypothesized that the need for higher levels of respiratory support (i.e., mechanical ventilation or nasal continuous airway pressure [nCPAP]) later in the hospitalization may be a useful predictor for the need for home oxygen therapy at discharge.

Methods

This project was approved by the Institutional Review Board at the University of California, San Francisco.

As infants born before 28 weeks' gestation have the greatest risk for needing home oxygen therapy, we performed a retrospective review of infants, delivered before 28 weeks' gestation and admitted within 24 hours of birth to the William H. Tooley Intensive Care Nursery at UCSF Benioff Children's Hospital, San Francisco, California, between June 2006 and August 2013.

During this period of time, a single consensus-driven approach for respiratory management was used in our nursery. Infants were resuscitated according to the Neonatal Resuscitation Program guidelines. Infants were initially managed with nCPAP. Infants were intubated for persistent respiratory acidosis ($Paco_2$ > 60 mm Hg), persistent apnea episodes, or excessive work of breathing. Surfactant was administered if an infant was intubated within the first 48 hours of life. Infants were ventilated with either a Viasys AVEA (Carefusion, San Diego, CA) conventional ventilator or a Sensormedics 3100 A high-frequency ventilator.

Criteria for weaning respiratory support

Respiratory support was adjusted to maintain $Paco_2$ between 45 and 60 mm Hg, pH between 7.25 and 7.35, and transcutaneous oxygen saturation between 88 and 94%. Infants were treated with caffeine and extubated to nCPAP or biphasic continuous nasal positive airway pressure (SiPAP) (via a Infant Flow, Carefusion, San Diego, CA) once their mean airway pressure was less than 10 cm H_2O and FIO2 less than 0.35. Infants were switched from nCPAP to a humidified gas flow nasal cannula system (wall oxygen plus Neptune Heated Humidifier, Teleflex, Morrisville, NC) once their Fio_2 requirement was < 0.30 (at an nCPAP pressure of 6 cm H_2O) and their retractions and work of breathing did not appear to be excessive. The maximum gas flow through the humidified nasal cannula was 3 L/min. Nasal intermittent positive pressure modes of ventilation were not used during this study.

A loading dose of caffeine was started before the extubation in ventilated patients, followed by maintenance dosing every 24 hours. Caffeine was not routinely prescribed to infants who never required intubation for mechanical ventilation unless they were having frequent or severe (requiring stimulation) episodes of apnea and bradycardia. Caffeine was discontinued in convalescing preterm infants before 36 weeks' PMA.

A detailed description of our approach to the management of a PDA has been published elsewhere.[8]

Criteria for home oxygen therapy

Our primary outcome was the need for home oxygen therapy at the time of discharge. Infants are discharged from hospital in room air when they meet all of the following developmental milestones: are able to maintain their temperature in an open crib, gain weight by taking adequate enteral calories ad libitum, are free of any bradycardia or apneic episodes (lasting greater than 20 seconds) for at least 5 days, and consistently maintain their oxygen saturations greater than or equal to 90% while asleep, awake, and during feedings.[9,10] Home oxygen therapy (with 100% oxygen through a nasal cannula at less than or equal to 1.0 L/min) is used only when all of these milestones have been met and the sole reason for continued hospitalization is the need for supplemental oxygen. Home cardiorespiratory or oxygen saturation monitoring is not prescribed for infants discharged with home oxygen therapy.

A single neonatologist(R. I. C.) prospectively evaluated and recorded the perinatal and in-hospital neonatal risk factors. The outcome, supplemental oxygen requirement beyond 38 weeks' PMA, and age that infants were weaned from various "types" of respiratory support was collected retrospectively. Gestational age was determined by the date of last menstrual period and early ultrasounds (before 24 weeks' gestation). If there were discrepancies, the early ultrasound dating was used. Necrotizing enterocolitis (NEC) was defined as Bell classification II or greater (this included NEC that was treated medically or surgically, and "spontaneous perforations" that occur before 7 days). BPD was defined by the physiologic room air challenge test performed between 36 and 37 weeks' PMA.[11]

Our intent was to determine if the age an infant was successfully weaned from various "types" of respiratory support could act as a strong predictor of the need for home oxygen

therapy. We were particularly interested in identifying an accurate predictor that could be used at least 3 to 4 weeks' before discharge. As a result, we focused our attention on the amount of respiratory support an infant needed between 34 and 35 weeks' PMA.

To be successfully weaned from a "type" of respiratory support, the infant had to be maintained on the new, lower "type" of respiratory support for at least 4 days. The "type" of respiratory support was defined as follows: (1) intubation with mechanical ventilation, (2) nCPAP or SiPAP, (3) nasal cannula system delivering 2 to 3 L/min gas flow, (4) nasal cannula system delivering less than 2 L/min gas flow, or (5) no respiratory support.

Infants with congenital malformations, pulmonary hypoplasia, or airway anomalies were excluded. Infants who died in hospital before having successfully weaned to "no respiratory support" and infants who were still requiring respiratory support at the time of transfer to another hospital were also excluded.

Statistics

Qualitative factors were compared with a chi-square test. The student t-test was used to compare the mean values.

Sensitivities, specificities, and positive predictive values were calculated to determine the discriminating power of various neonatal and perinatal risk factors to identify infants who would need home oxygen therapy.

Results

A total of 224 patients were admitted during the study period. Overall, 81 patients were excluded; 43 patients died and 36 were transferred before weaning from respiratory support. Two other patients were also excluded (one who underwent tracheostomy for tracheal stenosis, and one who had pulmonary hypoplasia). Therefore, 143 patients were available for the study. There were no significant differences between included and excluded infants with regards to gestational age or the neonatal and perinatal risk factors listed in ►Table 1. Infants were discharged from the hospital once they achieved the developmental milestones described in section Methods: those who delivered before $26^{0/7}$ weeks' gestation were discharged at 38.9 ± 2.5 postmenstrual weeks; those who delivered between $26^{0/7}$ and $27^{6/7}$ weeks' gestation were discharged at 38.7 ± 3.2 postmenstrual weeks.

Demographic information is presented in ►Table 1. Overall, 48% of the study infants who delivered before $26^{0/7}$ weeks' gestation, and 25% of the infants who delivered between $26^{0/7}$ and $27^{6/7}$ weeks' gestation required supplemental oxygen beyond 38 weeks and were discharged with home oxygen therapy. As has been observed previously, infants who were discharged with home oxygen therapy needed more respiratory support at 24 hours after birth (higher respiratory severity scores), and had higher incidences of PDA ligation and retinopathy of prematurity (►Table 1). Although several of the previously described predictors for home oxygen need had good positive-predictive values, none was better than 90% in predicting (from a positive result) that an infant would eventually need home oxygen

therapy (►Table 2). Of these predictors, the diagnosis of BPD (which can only be made between 36 and 37 weeks' PMA) had the highest positive predictive value at 89%.

We investigated whether the need for higher levels of respiratory support (i.e., mechanical ventilation or CPAP at 34 weeks' PMA) might have a better positive-predictive value for the need for home oxygen therapy at discharge than other predictors. We chose 34 weeks as identification of an infant at this PMA would allow sufficient time (4 weeks) to prepare a family for taking the infant home with supplemental oxygen. As expected, the need for mechanical ventilation or nCPAP decreased with advancing PMA (►Table 3). By 34 weeks' PMA none of the infants still required mechanical ventilation, and only 16% of infants who delivered before $26^{0/7}$ weeks' gestation, and 10% of those who delivered at or after $26^{0/7}$ weeks' gestation, still required nCPAP (►Table 3). The more mature an infant was, and still required mechanical ventilation or nCPAP, the greater the likelihood that supplemental oxygen therapy would be needed at discharge (►Table 4). At 34 weeks' PMA, all of the infants who still required nCPAP, ultimately needed home oxygen therapy at discharge (►Table 4). The positive predictive value for nCPAP at 34 weeks exceeded the positive predictive values of any of the previously identified risk factors listed in ►Table 2 (►Tables 2 and 4).

Discussion

The goal of our study was to identify a risk factor that had a high enough positive-predictive value that it could be used to initiate the preparations for home oxygen therapy several weeks in advance of discharge. Similar to previous studies, we found that the "need for respiratory support," early in an infant's hospitalization, was a sensitive predictor of the need for home oxygen therapy. However, the positive predictive value of the "need for respiratory support," early in the hospital course, was low indicating that there were many infants, who needed respiratory support early in the hospital course, who did not need oxygen therapy at discharge. BPD had a high positive predictive value and high sensitivity for predicting home oxygen need. The problem with using BPD as a predictor is the diagnosis of BPD can only be made between 36 and 37 weeks' PMA. The average age at discharge in our population was 38.8 weeks. Using BPD, as a predictor for home oxygen at discharge does not give the medical team sufficient time to adequately prepare families before discharge. In addition, the risk factor BPD, still, incorrectly identified 11% of the infants who did not require home oxygen therapy (►Tables 2 and 4). Initiating training for home oxygen in these patients would be a waste of valuable resources.

Conversely, the need for higher levels of respiratory support (i.e., nCPAP, at 34 weeks' PMA) was a very useful predictor (with the highest positive predictive value) for identifying infants who will need home oxygen therapy. Knowing at 34 weeks' PMA, which infants will require home oxygen therapy at discharge, allows the medical team sufficient time for discharge teaching and planning.

As the need for home oxygen therapy is because of the persistent need for respiratory support in an infant who has achieved the other developmental milestones needed for discharge, it is not surprising that the need for respiratory support at a specific

developmental age is the more accurate predictor of “home oxygen therapy” than the need for support at a specific postnatal age (see ►Table 4).

There are several caveats to our study. The small size of our population and retrospective nature of the study are important limitations. In addition, although 100% of the infants who were positive for our predictor (nCPAP at 34 weeks’ PMA) ultimately needed home oxygen therapy, this predictor had a low sensitivity and failed to identify approximately 60% of the infants who needed oxygen therapy at home. Of those infants who required home oxygen, infants on nCPAP at 34 weeks and those on lower levels of support (</= 3LNC or no support) did not differ in any of the variables investigated.

Previous studies have demonstrated that institutional variations are one of the strongest determinants of home oxygen therapy and can account for four- to fivefold differences in the frequency of its use.[5,12,13] Because ours is a single center study, performed at sea level, it may not be applicable to centers that use a different approach to initial respiratory support, or a different approach to weaning respiratory support, or who have different parameters for the timing of infant discharge. Our results need to be interpreted in the context of an intensive care nursery’s current overall respiratory management strategy.

Despite these limitations, the important finding in our study is the utility of late respiratory predictors in determining a population of premature infants whose families can begin preparations for home oxygen therapy several weeks before discharge. We believe that nurseries with different approaches to ventilator management, or different approaches to weaning respiratory support, may still benefit from our findings by identifying late respiratory predictors in their own setting that can predict the need for home oxygen therapy earlier in the hospital course. The next steps may include prospective validation of these findings in a larger population of premature infants and identification of combinations of late respiratory predictors and neonatal and perinatal predictors that are associated with the need for home oxygen therapy.

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Table 1

Demographics

	$24^{0/7}$–$25^{6/7}$ wk (gestation at birth)		$26^{0/7}$–$27^{6/7}$ wk (gestation at birth)		Total population		
	No home O_2 therapy	Home O_2 therapy	No home O_2 therapy	Home O_2 therapy	No home O_2 therapy	Home O_2 therapy	*p*-Value[a]
	n = 23	*n* = 21	*n* = 74	*n* = 25	*n* = 97	*n* = 46	
Race—White (%)	43	33	35	48	37	41	–
Gender—Male (%)	52	52	57	64	57	59	–
Antenatal betamethasone (any) (%)	70	81	85	76	81	78	–
Antenatal betamethasone (> 24 h) (%)	57	71	74	76	70	74	–
Preeclampsia (%)	13	19	16	36	15	28	0.070
Gestational diabetes (%)	17	14	12	16	13	15	–
Chorioamnionitis (%)	30	33	24	12	26	22	–
Small for gestational age (%)	9	19	3	24	4	22	< 0.001
RDS (%)	96	100	89	96	91	98	–
Surfactant (%)	96	100	88	100	90	100	0.020
RSS at 24 h (mean ± SD)	1.9 ± 0.6	2.1 ± 0.6	1.5 ± 0.6	2.8 ± 2.3	1.6 ± 0.6	2.5 ± 1.7	< 0.001
Bronchopulmonary dysplasia (%)	4	86	5	92	5	90	< 0.001
NEC/perforation (%)	4	14	15	12	12	13	–
ICH (grades 3, 4, or periventricular leukomalacia) (%)	22	24	9	12	12	17	–
Infection (%)	43	57	30	20	33	37	–
ROP (%)	35	52	12	16	18	33	0.040
PDA ligation (%)	22	24	4	24	8	24	0.010

Abbreviations: ICH, intracranial hemorrhage; NEC, necrotizing enterocolitis; PDA, patent ductus arterious; RDS, respiratory distress syndrome; ROP, retinopathy of prematurity; RSS, respiratory severity score.

[a] *p* values ≥ 0.1 are not shown.

Notes: Values represent mean ± standard deviation or percent (%). Definitions: Betamethasone > 24 hours, antenatal betamethasone exposure more than 24 hours before delivery; Bronchopulmonary dysplasia: the need for supplemental oxygen to maintain oxygen saturation > 90% at 36 weeks' corrected age (physiologic definition); Infection, any culture positive infection (bacteremia, pneumonia, urinary tract infection, and meningitis); ICH≥ Grade III and /or cystic periventricular leukomalacia diagnosed by ultrasound; NEC/perforation Bell classification ≥ II (treated medically or surgically) and

"spontaneous perforations" occurring before 7 days of life; RDS (respiratory support for > 24 hours and radiographic criteria); ROP, stage 2 with plus disease or stage 3 treated with either laser or bevacizumab; RSS (mean airway pressure × fraction of inspired oxygen) at 24 hours after birth; Small for gestational age, birth weight < 10th percentile for gestational age.[14]

Table 2

Sensitivity, specificity, positive predictive value, and negative predictive value of variables previously identified as predictors of the need for home oxygen therapy

Variable	PPV (%)	Specificity (%)	Sensitivity (%)	NPV (%)
No antenatal betamethasone	36	81	22	69
No or < 24 h antenatal betamethasone	29	70	26	67
Small for gestational age	71	96	22	74
RSS > 2 at 24 h	52	78	50	77
Endotracheal intubation at 24 h	41	41	85	85
FIO_2 > 0.30 at 24 h	64	92	30	74
Necrotizing enterocolitis	35	89	13	68
PDA ligation	58	92	24	72
Brochopulmonary dysplasia	89	95	89	95

Abbreviations: PDA, patent ductus arterious; PPV, positive predictive value; NPV, negative predictive value; RSS, respiratory severity score.

Note: Definitions (see ►Table 1).

Table 3

Percentage of infants receiving different types of respiratory support between 30 and 34 weeks' postmenstrual age

	% who require different types of respiratory support							
	24 $^{0/7}$–25 $^{6/7}$ wk (gestation at birth)				26 $^{0/7}$–27 $^{6/7}$ wk (gestation at birth)			
PMA	**Mechanical ventilation**	**nCPAP**	**≥ 2 LNC**	**< 2LNC**	**Mechanical ventilation**	**nCPAP**	**≥ 2LNC**	**< 2LNC**
30 wk	23	48	11	18	12	23	27	37
31 wk	16	30	14	41	5	21	21	53
32 wk	7	25	14	55	5	14	10	71
33 wk	2	20	7	70	2	11	11	76
34 wk	0	16	9	75	0	10	6	84

Abbreviations: PMA, postmenstrual age in weeks; mechanical ventilation, intubated infants who were receiving mechanical ventilation; nCPAP, nasal CPAP or biphasic continuous nasal positive pressure; ≥ 2 LNC, nasal cannula system delivering 2–3 L/min of humidified gas flow; < 2 LNC, nasal cannula system delivering less than 2 L/min gas flow or no respiratory support.

Table 4

Sensitivity, specificity, positive predictive value, and negative predictive value of the variable “mechanical ventilation or nCPAP at 34 weeks’ postmenstrual age” as a predictor of home oxygen therapy at discharge

PMA	Incidence of home oxygen (%)[a]	24 0/7–25 6/7 wk (gestation at birth)				Incidence of home oxygen (%)[a]	26 0/7–27 6/7 wk (gestation at birth)			
		PPV (%)	Specificity (%)	Sensitivity (%)	NPV (%)		PPV (%)	Specificity (%)	Sensitivity (%)	NPV (%)
30 wk	61	39	48	90	85	54	54	78	76	91
31 wk	70	70	74	67	71	69	69	89	72	90
32 wk	86	86	91	57	70	79	79	95	60	88
33 wk	90	90	96	43	65	92	92	99	48	88
34 wk	100	100	100	33	63	100	100	100	40	83

Abbreviations: nCPAP, nasal continuous airway pressure; PMA, postmenstrual age; PPV, positive predictive value; NPV, negative predictive value.

Note: For definitions see ►Table 3.

[a]Incidence of home oxygen therapy at discharge among infants who still need “mechanical ventilation or nCPAP” at a specific postmenstrual age (between 30 and 34 wk PMA).