Home Oxygen and 2-Year Outcomes of Preterm Infants With Bronchopulmonary Dysplasia

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abstract

OBJECTIVES: To compare medical and developmental outcomes over the first 2 years of life in extremely preterm infants with bronchopulmonary dysplasia (BPD) who were discharged on supplemental oxygen via nasal cannula with outcomes of infants with a similar severity of respiratory illness who were discharged breathing in room air.

METHODS: We performed a propensity score–matched cohort study. Eligible infants were born at <27 weeks' gestation, were receiving supplemental oxygen or respiratory support at 36 weeks' postmenstrual age, and were assessed at 18 to 26 months' corrected age. Study outcomes included growth, resource use, and neurodevelopment between discharge and follow-up. Outcomes were compared by using multivariable models adjusted for center and age at follow-up.

RESULTS: A total of 1039 infants discharged on supplemental oxygen were propensity score matched 1:1 to infants discharged breathing in room air. Infants on oxygen had a marginal improvement in weight *z* score (adjusted mean difference 0.11; 95% confidence interval [CI] 0.00 to 0.22), with a significantly improved weight-for-length *z* score (adjusted mean difference 0.13; 95% CI 0.06 to 0.20) at 22 to 26 months' corrected age. Infants on oxygen were more likely to be rehospitalized for respiratory illness (adjusted relative risk 1.33; 95% CI 1.16 to 1.53) and more likely to use respiratory medications and equipment. Rates of neurodevelopmental impairment were similar between the groups.

CONCLUSIONS: In this matched cohort of infants with BPD, postdischarge oxygen was associated with marginally improved growth and increased resource use but no difference in neurodevelopmental outcomes. Ongoing and future trials are critical to assess the efficacy and safety of postdischarge supplemental oxygen for infants with BPD.

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Dr DeMauro conceptualized and designed the study, drafted the initial manuscript, performed and reviewed analyses, and reviewed and revised the manuscript for submission; Drs Jensen and Lorch conceptualized and designed the study, provided interpretation of data, and critically reviewed and revised the manuscript for important intellectual content; Dr Bann participated in the design of the study, conducted all analyses and provided interpretation of data, and reviewed the final manuscript as submitted; Drs Bell, Hibbs, and Hintz participated in the design of the study and interpretation of the data and revised the article for important intellectual content; and all authors approved the final manuscript as submitted.

This trial has been register at www.clinicaltrials.gov (identifier NCT00063063).

WHAT'S KNOWN ON THIS SUBJECT: The incidence of bronchopulmonary dysplasia (BPD) in extremely preterm infants is increasing; approximately one-quarter of extremely preterm infants are discharged with supplemental oxygen. Continued use of supplemental oxygen after discharge in infants with BPD has potential risks and potential benefits.

WHAT THIS STUDY ADDS: In this propensity score–matched cohort study of extremely preterm infants with BPD, discharge with supplemental oxygen was associated with improved growth and increased postdischarge health care use and was not associated with neurodevelopmental benefits.

To cite: DeMauro SB, Jensen EA, Bann CM, et al. Home Oxygen and 2-Year Outcomes of Preterm Infants With Bronchopulmonary Dysplasia. *Pediatrics.* 2019;143(5): e20182956

Bronchopulmonary dysplasia (BPD) affects nearly half of extremely preterm infants who survive to 36 weeks' postmenstrual age (PMA).[1] Unlike other neonatal morbidities, the incidence of BPD is increasing over time.[1] Supplemental oxygen is an essential therapy for premature infants and a common treatment of BPD. The American Thoracic Society considers oxygen a "a safe and relatively convenient means for maximizing growth and development" in infants with BPD,[2] and approximately one-quarter of extremely preterm infants are discharged with home oxygen therapy.[3,4] However, there is significant variation in the initiation and titration of home oxygen in infants with BPD, in part, because the risks and benefits of supplemental oxygen use beyond the newborn period are not well established.[5–7]

No study has revealed improvement in developmental outcomes among infants who received supplemental oxygen after discharge.[8,9] Authors of 1 study reported lower health care use costs among young children born in centers that frequently discharged infants with home oxygen therapy,[10] and authors of 2 small studies reported growth failure in former preterm infants after weaning from home supplemental oxygen.[11,12] On the other hand, supplemental oxygen carries potential risks. Early oxygen exposure is implicated in the development of retinopathy of prematurity, and prolonged use may result in pulmonary oxygen toxicity.[13,14] Moreover, home oxygen therapy may impose an emotional, physical, and financial burden on families.[15,16]

In the current study, we compared medical and developmental outcomes over the first 2 years of life between extremely preterm infants with BPD who were discharged from the hospital on supplemental oxygen via nasal cannula and propensity score–matched infants discharged breathing in room air. We hypothesized that home oxygen use would be associated with improved growth and decreased medical resource use between discharge and 18 to 26 months' corrected age (CA).

METHODS

Population and Data Source

We performed a retrospective matched cohort study using prospectively collected data from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN) generic database and follow-up registry. Eligible infants were born at <27 + 0/7 weeks' gestation between January 1, 2006, and December 31, 2014, received supplemental oxygen or respiratory support at 36 weeks' PMA, and had outcomes assessed at 18 to 26 months' CA. Infants who died before discharge, were transferred out of an NRN center, underwent tracheostomy during the initial neonatal hospitalization, or had severe congenital malformations or genetic syndromes were excluded. Institutional review boards at all participating NRN centers approved collection of generic database and follow-up registry data; parental informed consent was obtained per local guidelines.

Study Exposure and Outcome Definitions

The primary exposure of interest was discharge from the initial newborn hospitalization with supplemental oxygen. The primary outcomes were rehospitalization for a respiratory illness between discharge and follow-up and weight *z* score at follow-up. Secondary outcomes were (1) additional growth parameters (length, head circumference, and weight-for-length *z* scores at 18 to 26 months' CA), (2) measures of medical resource use (tracheostomy placement between discharge and follow-up; treatment with medications for asthma or BPD in the past 3 months; current use of oxygen, pulse oximeter, or a feeding tube at follow-up; and current or past home nursing care, physical or occupational therapy, or treatment by a pulmonologist), (3) neurodevelopmental outcomes (cerebral palsy; Gross Motor Function Classification System[17] level ≥2; performance on the cognitive, language, and motor domains of the *Bayley Scales of Infant and Toddler Development, Third Edition* [Bayley-3][18]; and behavior problems as assessed by the Brief Infant-Toddler Social and Emotional Assessment [BITSEA] or Child Behavior Checklist [CBCL]), and (4) death between 36 weeks' PMA and anticipated follow-up. The motor domain of the Bayley-3 was administered during follow-up visits beginning in January 2010, and the CBCL replaced the BITSEA for visits beginning in August 2014. The *z* scores for height, length, weight for length, and head circumference at birth were calculated with the Fenton growth curves, and *z* scores at follow-up were computed by using the World Health Organization growth reference standards.[19–21] The Fenton and World Health Organization growth curves overlap at 50 weeks' PMA.

Statistical Analysis

Our goal for the current study was to assess the association between home supplemental oxygen and later outcomes. To reduce bias from treatment selection (ie, infants discharged on supplemental oxygen who were sicker) and improve causal inference, we used propensity score methods to identify infants with similar severity of respiratory illness who were treated and untreated. A propensity score for the likelihood each infant would be discharged from the hospital on oxygen was developed by using the following

variables independently associated with supplemental oxygen use at discharge: sex, race and/or ethnicity, private insurance, completed maternal education less than high school, antenatal steroids, delivery room intubation, small for gestational age, birth weight, gestational age, surfactant, surgery for necrotizing enterocolitis, postnatal corticosteroids, discharge on diuretics, discharge on bronchodilators, and a study-defined variable for prolonged positive airway pressure. This latter variable was defined as a total duration of invasive and noninvasive positive pressure greater than the median duration for the full study cohort.

Next, SAS PSMATCH (SAS Institute, Inc, Cary, NC) was used to identify matched pairs of infants discharged with and without supplemental oxygen who had similar propensities to be discharged from the hospital on oxygen. The groups were first stratified on the basis of the level of BPD (moderate versus severe by using the 2001 National Institutes of Health [NIH] consensus definition[22]) to ensure an equal distribution of BPD severity in each group and then matched 1:1 by using the above clinical and demographic variables. The greedy nearest neighbor approach was used to select each matched pair.[23] With this method, an infant discharged on room air is selected and then the infant in the supplemental oxygen group with the closest propensity score is selected as the match. When 2 potential matches have the same propensity score, 1 is selected at random. The distance between the infants in the 2 groups is based on the logit of the propensity score. The maximum distance between 2 matched infants (ie, the caliper) for this study was set to 0.25. Standardized differences (the difference in means divided by SD) were used to compare baseline characteristics of the matched infants. Standardized differences are expressed as absolute values; values <0.1 indicate negligible differences between the groups.

Multivariable regression models were used to compare outcomes between the matched groups. Log binomial models were used to determine adjusted relative risks (RRs) for dichotomous outcomes (eg, rehospitalization), and Poisson models were used for count outcomes (eg, number of hospitalizations). Linear regression was used to compute adjusted mean differences for continuous outcomes (eg, growth *z* scores). All models were adjusted a priori for CA at follow-up and included the center as a random effect. Analyses were performed with SAS version 9.4 (SAS Institute, Inc).

RESULTS

Of the 2914 infants who were eligible for inclusion in this analysis and were receiving supplemental oxygen or respiratory support at 36 weeks' PMA, 1688 (57.9%) were discharged on home oxygen, and 1226 (42.1%) were discharged breathing in room air. There were significant differences between these groups before implementing the matching algorithm, especially the severity of BPD and the use of postnatal steroids and prolonged ventilation in the home oxygen group (Table 1). After propensity score matching, 1039 infants discharged on supplemental oxygen and 1039 infants discharged on room air were included in the final cohort (71% of eligible infants). Baseline characteristics and measures of respiratory illness severity were well matched between these 2 groups (Table 1). Eighteen percent of infants in each group were diagnosed with a grade 3 or grade 4 intraventricular hemorrhage (standardized difference 0.01). The total number of days receiving positive airway pressure (62.8 ± 25.3 vs 60.8 ± 23.0; standardized difference 0.08) and the length of hospital stay (120 ± 40 vs 124 ± 34 days; standardized difference 0.11) were similar for infants discharged on supplemental oxygen and those discharged on room air.

Rates of mortality between discharge and follow-up were similar between the matched groups ($n = 18$ children on supplemental oxygen versus $n = 20$ on room air; adjusted RR 0.89; 95% confidence interval [CI] 0.43 to 1.87). At 18 to 26 months' CA, children who were discharged on supplemental oxygen had significantly higher medical resource use, particularly for respiratory care (Table 2). They were more likely to have been rehospitalized for a respiratory illness (38% vs 28%; adjusted RR 1.33; 95% CI 1.16 to 1.53; $P < .001$) and had a higher median number of total hospitalizations. They more frequently received medications for asthma or BPD and were more likely to use a pulse oximeter or home oxygen at 18 to 26 months' CA (Table 2). They were more likely to have received or to still be receiving home nursing and care from a pulmonologist. Finally, infants discharged on supplemental oxygen were more likely to have undergone tracheostomy between discharge and follow-up.

Overall, the study cohort exhibited poor growth during early childhood, with most *z* scores <0 at 2 years' CA (Table 2). However, use of supplemental oxygen at discharge was only associated with a significant difference in the weight-for-length *z* score at 18 to 26 months' CA (adjusted mean difference 0.13; 95% CI 0.06 to 0.20; $P < .001$). In post hoc analyses, we evaluated change in weight, length, and head circumference *z* scores between birth and follow-up. The adjusted mean difference in the weight *z* score was 0.10 (95% CI -0.10 to 0.20), the adjusted mean difference in the length *z* score was 0.12 (95% CI -0.10 to 0.25), and the adjusted

TABLE 1 Comparison of Original and Matched Samples

Characteristic	Original Sample			Matched Sample		
	Discharged on Supplemental Oxygen (*N* = 1688)	Discharged Breathing in Room Air (*N* = 1226)	Standardized Difference	Discharged on Supplemental Oxygen (*N* = 1039)	Discharged Breathing in Room Air (*N* = 1039)	Standardized Difference
Gestational age, mean ± SD	24.7 ± 1.1	24.9 ± 1.0	0.17	24.8 ± 1.0	24.8 ± 1.0	0.00
Birth wt, mean ± SD	712.0 ± 149.0	738.9 ± 144.1	0.18	734.3 ± 147.0	731.5 ± 145.2	0.02
Small for gestational age, *n*/*N* (%)	152/1687 (9)	60/1226 (5)	0.16	53/1039 (5)	57/1039 (5)	0.02
Male sex, *n*/*N* (%)	911/1687 (54)	629/1226 (51)	0.05	554/1039 (53)	532/1039 (51)	0.04
Private insurance, *n*/*N* (%)	715/1679 (43)	466/1214 (38)	0.09	418/1033 (40)	396/1029 (38)	0.04
Mother with less than high school education, *n*/*N* (%)	275/1323 (21)	225/928 (24)	0.05	187/804 (23)	190/789 (24)	0.02
White race, *n*/*N* (%)	933/1660 (56)	631/1197 (53)	0.08	576/1015 (57)	539/1014 (53)	0.07
Antenatal steroids, *n*/*N* (%)	1516/1686 (90)	1051/1220 (86)	0.12	912/1037 (88)	895/1033 (87)	0.04
Intubation, *n*/*N* (%)	1482/1688 (88)	1018/1226 (83)	0.14	889/1039 (86)	881/1039 (85)	0.02
Surfactant, *n*/*N* (%)	1630/1688 (97)	1138/1226 (93)	0.17	991/1039 (95)	977/1039 (94)	0.06
Surgery for necrotizing enterocolitis, *n*/*N* (%)	54/1688 (3)	81/1226 (7)	0.16	41/1039 (4)	50/1039 (5)	0.04
Severity of BPD, *n*/*N* (%)			0.39			0.00
Moderate BPD	489/1688 (29)	580/1226 (47)		436/1039 (42)	436/1039 (42)	
Severe BPD	1199/1688 (71)	646/1226 (53)		603/1039 (58)	603/1039 (58)	
Postnatal steroids, *n*/*N* (%)	604/1549 (39)	245/1160 (21)	0.39	241/954 (25)	226/987 (23)	0.06
Prolonged positive pressure respiratory support, *n*/*N* (%)	769/1686 (46)	388/1225 (32)	0.29	341/1039 (33)	341/1039 (33)	0.00
Discharged on diuretics, *n*/*N* (%)	655/1687 (39)	219/1221 (18)	0.47	239/1039 (23)	211/1035 (20)	0.06
Discharged on bronchodilators, *n*/*N* (%)	340/1686 (20)	51/1221 (4)	0.48	60/1039 (6)	50/1035 (5)	0.04

All characteristics listed in the table were included in the propensity scores.

mean difference in the head circumference *z* score was 0.14 (95% CI 0.01 to 0.28), favoring a small improvement in growth among infants discharged with supplemental oxygen.

Neurodevelopmental and behavioral outcomes at follow-up were similar between the matched groups (Table 3). A post hoc analysis comparing rates of developmental delay (defined as scores of <85 or <70 on each of the 3 domains of the Bayley-3, respectively) revealed no differences between the infants discharged on supplemental oxygen and those discharged on room air.

DISCUSSION

Surviving extremely preterm infants with BPD experience poor health outcomes when compared with both term infants and extremely preterm peers without BPD. Preterm infants with BPD are twice as likely to be readmitted to the hospital in the first year of life, have higher rates of growth failure and microcephaly,[24–28,–] and have more than doubled odds of late death or neurodevelopmental disability when compared with preterm infants without BPD.[29,30] It is unknown whether these long-term adverse outcomes depend solely on events and exposures occurring before 36 weeks' PMA, when BPD is diagnosed, or whether ongoing injury occurring after this time point alters the medical and developmental trajectories of children with BPD. Infants with BPD are prone to hypoxemia throughout the first year of life, which may contribute to the neurodevelopmental sequelae observed in later childhood.[24,31,32] Although prolonged supplemental oxygen therapy in infants with BPD may improve oxygen saturation stability, it may also carry risk of oxygen toxicity. Unfortunately, there is little empirical evidence to help clinicians balance these potential risk and benefits, particularly regarding the use of postdischarge supplemental oxygen in infants with BPD. In the current study, we compared early childhood outcomes among extremely preterm infants, for whom some clinicians would prescribe home oxygen therapy at hospital discharge and others might not. In this cohort of >2000 propensity score–matched infants with BPD, use of supplemental oxygen at discharge, compared with room-air breathing, was associated with a marginal improvement in growth but no difference in neurodevelopmental outcomes at 18 to 26 months' CA. Medical resource use during the first 2 years of life was significantly greater among infants discharged on home oxygen therapy.

TABLE 2 Growth and Resource Use in the Matched Cohort at 18–26 Months' CA

Characteristic	Discharged on Supplemental Oxygen (N = 1039)	Discharged Breathing in Room Air (N = 1039)	Adjusted RR or Mean Difference (95% CI)	P
Growth				
Wt z score, mean ± SD	−0.31 ± 1.13	−0.43 ± 1.15	0.11 (0.00 to 0.22)	.05
Length z score, mean ± SD	−0.78 ± 1.45	−0.80 ± 1.32	0.00 (−0.14 to 0.14)	.98
HC z score, mean ± SD	−0.26 ± 1.48	−0.41 ± 1.44	0.14 (−0.01 to 0.29)	.07
Wt-for-length z score, mean ± SD	0.07 ± 1.15	−0.06 ± 1.16	0.13 (0.06 to 0.20)	<.001
Resource use				
Rehospitalized for respiratory issue, n/N (%)	380/1013 (38)	278/1011 (28)	1.33 (1.16 to 1.53)	<.001
No. respiratory-related hospitalizations, median (IQR)	0 (0–1)	0 (0–1)	1.41 (1.17 to 1.69)	<.001
Asthma and/or BPD medications in past 3 mo, n/N (%)	463/1018 (45)	369/1017 (36)	1.30 (1.17 to 1.45)	<.001
Medical technology use at follow-up, n/N (%)				
Apnea monitor	18/1018 (2)	9/1016 (1)	1.96 (0.67 to 5.73)	.22
Supplemental oxygen	79/1018 (8)	24/1016 (2)	3.73 (2.26 to 4.76)	<.001
Ventilator and/or CPAP	17/1018 (2)	4/1016 (<1)	3.73 (1.47 to 9.47)	.006
Tracheostomy	29/1018 (3)	10/1016 (1)	3.11 (1.50 to 6.45)	.002
Pulse oximeter	75/1018 (7)	27/1017 (3)	2.94 (1.78 to 4.86)	<.001
Feeding tube	88/1016 (9)	87/1015 (9)	0.98 (0.68 to 1.43)	.93
Current or past receipt of services, n/N (%)				
Home nurse	115/1017 (11)	75/1018 (7)	1.52 (1.16 to 1.99)	.002
PT and/or OT	670/1018 (66)	641/1018 (63)	1.07 (0.99 to 1.15)	.10
Speech therapist	430/1018 (42)	445/1018 (44)	1.02 (0.92 to 1.14)	.69
Pulmonary specialist	554/1018 (54)	318/1018 (31)	1.79 (1.51 to 2.12)	<.001

All results are among infants who survived to assessment at 18–26 months'. CPAP, continuous positive airway pressure; HC, head circumference; OT, occupational therapy; PT, physical therapy.

The modest improvement in growth and increased health care use associated with home oxygen use suggest that this therapy may be associated with a trade-off of risks and benefits. Growth failure is common among infants with BPD, and growth velocity in extremely preterm infants correlates with both developmental outcomes and lung recovery.[8,33,34] Thus, strategies to optimize growth in this population are critical. Data on the role of supplemental oxygen for promoting growth are conflicted. Two previous trials (Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity [STOP-ROP] and Benefits of Oxygen Saturation Targeting [BOOST]) revealed no difference in growth at 3 and 12 months' CA among infants randomly assigned to higher versus standard oxygen saturation targets at 32 to 35 weeks' PMA and maintained on these targets for several weeks.[13,14] In contrast to these trials, in which differential use of oxygen postdischarge was not specifically studied, authors of 2 small observational studies conducted >20 years ago reported growth failure among infants with BPD after weaning off home oxygen.[11,12] The current study revealed evidence of a growth advantage associated with supplemental oxygen use after discharge, but this benefit was small and possibly of little clinical significance. The marginal improvements in growth observed in this study may not justify continuing supplemental oxygen in preterm infants who are able to be weaned to room air. Until the role of supplemental oxygen in supporting infant growth is better understood, growth of all infants and young children with BPD should be closely monitored.

Similar to growth, reports of health care use among infants receiving home oxygen therapy are conflicting. In a study conducted in the United Kingdom, Greenough et al[12] compared health care use among preterm infants with BPD cared for at centers that commonly prescribed home oxygen with health care use among infants cared for at centers that infrequently used home oxygen therapy. Sixty-four percent of infants in the high-use centers and 10% of infants in the low-use centers were discharged with oxygen. Total cost of care over the first 2 years of life was significantly lower for infants born at the high-use centers. Infants from high-use centers were discharged earlier and had fewer outpatient visits to a physician and fewer contacts with home nurses and other community health care supports but similar rehospitalization rates. In contrast, in our cohort of infants with equal likelihood of receiving home oxygen, this therapy was not associated with significantly earlier discharge from the NICU. In addition, in our study, infants discharged on

TABLE 3 Developmental and Behavioral Outcomes in the Matched Cohort at 18–26 Months' CA

Characteristic	Matched Sample			
	Discharged on Supplemental Oxygen (*N* = 1039)	Discharged Breathing in Room Air (*N* = 1039)	Adjusted RR or Mean Difference (95% CI)	*P*
Cerebral palsy (any severity), *n*/*N* (%)	152/1011 (15)	143/1009 (14)	1.08 (0.85 to 1.37)	.55
Cerebral palsy (moderate or severe), *n*/*N* (%)	76/1011 (8)	67/1009 (7)	1.14 (0.80 to 1.64)	.48
GMFCS level ≥2, *n*/*N* (%)	105/1011 (10)	91/1010 (9)	1.14 (0.78 to 1.67)	.49
Bayley-3 cognitive, mean ± SD	87.4 ± 15.3	86.5 ± 15.1	0.27 (−1.69 to 2.23)	.79
Bayley-3 language, mean ± SD	82.4 ± 17.3	81.7 ± 16.4	−0.27 (−2.25 to 1.71)	.79
Bayley-3 motor, mean ± SD	85.1 ± 15.8	85.0 ± 16.8	−0.51 (−3.38 to 2.36)	.73
Bayley-3 cognitive, *n*/*N* (%)				
<70	112/992 (11)	122/973 (13)	0.96 (0.73 to 1.28)	.80
<85	320/992 (32)	350/973 (36)	0.96 (0.79 to 1.15)	.64
Bayley-3 language, *n*/*N* (%)				
<70	210/973 (22)	212/960 (22)	1.09 (0.86 to 1.39)	.48
<85	529/974 (54)	529/961 (55)	1.04 (0.94 to 1.15)	.49
Bayley-3 motor, *n*/*N* (%)[a]				
<70	107/764 (14)	120/734 (16)	0.90 (0.59 to 1.36)	.61
<85	302/764 (40)	276/734 (38)	1.11 (0.91 to 1.36)	.29
Behavior problem, *n*/*N* (%)[b]	325/983 (33)	345/993 (35)	0.94 (0.82 to 1.08)	.40

[a] The motor domain of the Bayley-3 was administered during follow-up visits beginning in January 2010.
[b] The CBCL replaced the BITSEA for visits beginning in August 2014.

oxygen were more likely to be rehospitalized and experienced a higher number of rehospitalizations. They also used more health care resources, including respiratory medications, equipment, home nursing, and care from pulmonologists.

There are several possible explanations for the increased use of health resources that we observed. Greater supplemental oxygen use may adversely affect pulmonary health. In the STOP-ROP trial, infants were randomly assigned at ∼35 weeks' PMA to pulse oxygen saturation (Spo_2) targets of 89% to 94% vs 96% to 99%.[13] Pneumonia and BPD exacerbations were more common in infants randomly assigned to the higher Spo_2 target group, particularly among the subset of infants with more severe underlying lung disease. Infants in the higher saturation group were also more likely to remain in the hospital or on diuretics at 3 months' CA. In the Benefits of Oxygen Saturation Targeting trial, preterm infants receiving supplemental oxygen at 32 weeks' PMA were randomly assigned to maintain an Spo_2 within a target range of 91% to 94% vs 95% to 98% until oxygen was discontinued. In this trial, two-thirds of the deaths in the high Spo_2 arm were attributed to pulmonary causes compared with only 20% in the low Spo_2 arm.[14] Despite this potential survival disadvantage, higher versus standard oxygen saturation targets did not impact length of hospital stay after randomization, use of diuretics, or rehospitalization rates. Although neither of these studies were focused solely on infants with BPD, the subgroup analysis of the STOP-ROP trial suggested that infants with BPD may have been more likely to experience adverse effects of higher oxygen exposure than infants without BPD.[13] This result is consistent with our finding of higher medication use, rehospitalizations, and technology dependence among the infants discharged with supplemental oxygen. Alternately, health care providers may have a tendency to be more aggressive when caring for infants who were discharged on oxygen, perhaps assuming that they are sicker and therefore require more interventions.

Authors of 2 previous studies reported neurodevelopmental outcomes among children with BPD who were discharged on oxygen.[11,12] Authors of 1 retrospective single-center study reported no difference in 18-month developmental outcomes between infants with BPD discharged on oxygen and those discharged on room air between 2004 and 2010.[9] However, these data may not be generalizable to other settings because 74% of study infants were discharged on oxygen, a higher rate than in most neonatal centers. A multicenter Canadian cohort study demonstrated similar 3-year outcomes, including cognitive function, cerebral palsy, and neurosensory impairment, between infants with BPD discharged on supplemental oxygen and infants with BPD discharged on room air.[8] Our findings, consistent with the results of these 2 previous reports, contradict the common conception that continued use of supplemental oxygen after discharge will promote neurodevelopment in high-risk children with BPD.[2]

By design, our analysis excludes some infants who were discharged on oxygen. We selected this approach, rather than one that included all infants receiving home oxygen therapy, to investigate the early childhood outcomes among infants

who may have been weaned to room air by some clinicians and not by others. This is the subset of infants for whom the critical clinical question of whether to use home oxygen is applicable. The infants with the greatest severity of respiratory disease, those for whom most clinicians would prescribe home oxygen therapy, could not be matched and were excluded. Thus, the results of our study may only be applied to infants with BPD who might be reasonably weaned off supplemental oxygen before discharge and for whom the risk/benefit ratio of continued oxygen use is in question. The generic database and follow-up registry do not include data about what factors influenced individual decisions to discharge infants on supplemental oxygen or the duration of oxygen use. Therefore, we could not test hypotheses related to the duration of postdischarge oxygen exposure. Furthermore, unmeasured differences in illness severity that are not fully balanced by propensity score matching may contribute to the observed differences in outcomes between the groups.

CONCLUSIONS

With this study, we provide important and novel information that may aid the decision of whether to discharge an infant with supplemental oxygen, particularly for those infants who might be weaned off by some clinicians and not by others. This study helps to clarify, both for clinicians and parents, the potential benefits and harms that might be expected from home oxygen therapy among the subset of infants for whom the best course of action is unclear. Definitive evaluation of the risk/benefit ratio of this therapy will require prospective controlled trials. Such research will facilitate a more evidence-based approach to clinical decisions about postdischarge care of infants with BPD.

ABBREVIATIONS

Bayley-3: *Bayley Scales of Infant and Toddler Development, Third Edition*
BITSEA: Brief Infant-Toddler Social and Emotional Assessment
BPD: bronchopulmonary dysplasia
CA: corrected age
CBCL: Child Behavior Checklist
CI: confidence interval
NICHD: *Eunice Kennedy Shriver* National Institute of Child Health and Human Development
NIH: National Institutes of Health
NRN: Neonatal Research Network
PMA: postmenstrual age
RR: relative risk
Spo_2: pulse oxygen saturation
STOP-ROP: Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity

DOI: https://doi.org/10.1542/peds.2018-2956

Accepted for publication Jan 29, 2019

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Funded by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network (see Supplemental Information for grant numbers). Funded by the National Institutes of Health (NIH).

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

COMPANION PAPER: A companion to this article can be found online at www.pediatrics.org/cgi/doi/10.1542/peds.2019-0372.

REFERENCES

1. Stoll BJ, Hansen NI, Bell EF, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Trends in care practices, morbidity, and mortality of extremely preterm neonates, 1993-2012. *JAMA*. 2015;314(10):1039–1051
2. Allen J, Zwerdling R, Ehrenkranz R, et al; American Thoracic Society. Statement on the care of the child with chronic lung disease of infancy and childhood. *Am J Respir Crit Care Med*. 2003;168(3):356–396
3. Lagatta JM, Clark RH, Brousseau DC, Hoffmann RG, Spitzer AR. Varying patterns of home oxygen use in infants at 23-43 weeks' gestation discharged from United States neonatal intensive care units. *J Pediatr*. 2013;163(4):976–982.e2
4. Stevens TP, Finer NN, Carlo WA, et al; SUPPORT Study Group of the Eunice Kennedy Shriver National Institute of

Child Health and Human Development Neonatal Research Network. Respiratory outcomes of the surfactant positive pressure and oximetry randomized trial (SUPPORT). *J Pediatr*. 2014;165(2):240–249.e4

5. Ellsbury DL, Acarregui MJ, McGuinness GA, Eastman DL, Klein JM. Controversy surrounding the use of home oxygen for premature infants with bronchopulmonary dysplasia. *J Perinatol*. 2004;24(1):36–40
6. Solis A, Harrison G, Shaw BN. Assessing oxygen requirement after discharge in chronic lung disease: a survey of current practice. *Eur J Pediatr*. 2002;161(8):428–430
7. Palm K, Simoneau T, Sawicki G, Rhein L. Assessment of current strategies for weaning premature infants from supplemental oxygen in the outpatient setting. *Adv Neonatal Care*. 2011;11(5):349–356
8. Lodha A, Sauvé R, Bhandari V, et al. Need for supplemental oxygen at discharge in infants with bronchopulmonary dysplasia is not associated with worse neurodevelopmental outcomes at 3 years corrected age. *PLoS One*. 2014;9(3):e90843
9. Trittmann JK, Nelin LD, Klebanoff MA. Bronchopulmonary dysplasia and neurodevelopmental outcome in extremely preterm neonates. *Eur J Pediatr*. 2013;172(9):1173–1180
10. Moyer-Mileur LJ, Nielson DW, Pfeffer KD, Witte MK, Chapman DL. Eliminating sleep-associated hypoxemia improves growth in infants with bronchopulmonary dysplasia. *Pediatrics*. 1996;98(4, pt 1):779–783
11. Groothuis JR, Rosenberg AA. Home oxygen promotes weight gain in infants with bronchopulmonary dysplasia. *Am J Dis Child*. 1987;141(9):992–995
12. Greenough A, Alexander J, Burgess S, et al. High versus restricted use of home oxygen therapy, health care utilisation and the cost of care in chronic lung disease infants. *Eur J Pediatr*. 2004;163(6):292–296
13. Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP), a randomized, controlled trial. I: primary outcomes. *Pediatrics*. 2000;105(2):295–310
14. Askie LM, Henderson-Smart DJ, Irwig L, Simpson JM. Oxygen-saturation targets and outcomes in extremely preterm infants. *N Engl J Med*. 2003;349(10):959–967
15. McLean A, Townsend A, Clark J, et al. Quality of life of mothers and families caring for preterm infants requiring home oxygen therapy: a brief report. *J Paediatr Child Health*. 2000;36(5):440–444
16. McAleese KA, Knapp MA, Rhodes TT. Financial and emotional cost of bronchopulmonary dysplasia. *Clin Pediatr (Phila)*. 1993;32(7):393–400
17. Palisano R, Rosenbaum PL, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Dev Med Child Neurol*. 1997;39(4):214–223
18. Bayley N. *Bayley Scales of Infant and Toddler Development*. 3rd ed. San Antonio, TX: Harcort Assessment, Inc; 2006
19. Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. *BMC Pediatr*. 2013;13:59
20. World Health Organization Multicentre Growth Reference Study Group. *WHO Child Growth Standards: Head Circumference-for-Age, Arm Circumference-for-Age, Triceps Skinfold-for-Age and Subscapular Skinfold-for-Age: Methods and Development*. Geneva, Switzerland: World Health Organization; 2007
21. World Health Organization Multicentre Growth Reference Study Group. *WHO Child Growth Standards: Length/Height-for-Age, Weight-for-Age, Weight-for-Length, Weight-for-Height and Body Mass Index-for-Age: Methods and Development*. Geneva, Switzerland: World Health Organization; 2006
22. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *Am J Respir Crit Care Med*. 2001;163(7):1723–1729
23. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res*. 2011;46(3):399–424
24. Majnemer A, Riley P, Shevell M, Birnbaum R, Greenstone H, Coates AL. Severe bronchopulmonary dysplasia increases risk for later neurological and motor sequelae in preterm survivors. *Dev Med Child Neurol*. 2000;42(1):53–60
25. Lifschitz MH, Seilheimer DK, Wilson GS, Williamson WD, Thurber SA, Desmond MM. Neurodevelopmental status of low birth weight infants with bronchopulmonary dysplasia requiring prolonged oxygen supplementation. *J Perinatol*. 1987;7(2):127–132
26. Chye JK, Gray PH. Rehospitalization and growth of infants with bronchopulmonary dysplasia: a matched control study. *J Paediatr Child Health*. 1995;31(2):105–111
27. Greenough A, Alexander J, Boorman J, et al. Respiratory morbidity, healthcare utilisation and cost of care at school age related to home oxygen status. *Eur J Pediatr*. 2011;170(8):969–975
28. Smith VC, Zupancic JA, McCormick MC, et al. Rehospitalization in the first year of life among infants with bronchopulmonary dysplasia. *J Pediatr*. 2004;144(6):799–803
29. Schmidt B, Asztalos EV, Roberts RS, Robertson CM, Sauve RS, Whitfield MF; Trial of Indomethacin Prophylaxis in Preterms (TIPP) Investigators. Impact of bronchopulmonary dysplasia, brain injury, and severe retinopathy on the outcome of extremely low-birth-weight infants at 18 months: results from the trial of indomethacin prophylaxis in preterms. *JAMA*. 2003;289(9):1124–1129
30. Schmidt B, Roberts RS, Davis PG, et al; Caffeine for Apnea of Prematurity (CAP) Trial Investigators. Prediction of late death or disability at age 5 years using a count of 3 neonatal morbidities in very low birth weight infants. *J Pediatr*. 2015;167(5):982–986.e2

31. Garg M, Kurzner SI, Bautista DB, Keens TG. Clinically unsuspected hypoxia during sleep and feeding in infants with bronchopulmonary dysplasia. *Pediatrics*. 1988;81(5): 635–642

32. Sekar KC, Duke JC. Sleep apnea and hypoxemia in recently weaned premature infants with and without bronchopulmonary dysplasia. *Pediatr Pulmonol*. 1991;10(2):112–116

33. Ehrenkranz RA, Dusick AM, Vohr BR, Wright LL, Wrage LA, Poole WK. Growth in the neonatal intensive care unit influences neurodevelopmental and growth outcomes of extremely low birth weight infants. *Pediatrics*. 2006; 117(4):1253–1261

34. Lawlor DA, Ebrahim S, Davey Smith G. Association of birth weight with adult lung function: findings from the British Women's Heart and Health Study and a meta-analysis. *Thorax*. 2005;60(10): 851–858

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Pediatrics 2019;143;
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