Respiratory Medications in Infants <29 Weeks during the First Year Postdischarge: The Prematurity and Respiratory Outcomes Program (PROP) Consortium

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Objective To determine patterns of respiratory medications used in neonatal intensive care unit graduates.

Study design The Prematurity Respiratory Outcomes Program enrolled 835 babies <29 weeks of gestation in the first week. Of 751 survivors, 738 (98%) completed at least 1, and 85% completed all 4, postdischarge medication usage in-person/telephone parental questionnaires requested at 3, 6, 9, and 12 months of corrected age. Respiratory drug usage over the first year of life after in neonatal intensive care unit discharge was analyzed.

Results During any given quarter, 66%-75% of the babies received no respiratory medication and 45% of the infants received no respiratory drug over the first year. The most common postdischarge medication was the inhaled bronchodilator albuterol; its use increased significantly from 13% to 31%. Diuretic usage decreased significantly from 11% to 2% over the first year. Systemic steroids (prednisone, most commonly) were used in approximately 5% of subjects in any one quarter. Inhaled steroids significantly increased over the first year from 9% to 14% at 12 months. Drug exposure changed significantly based on gestational age with 72% of babies born at 23-24 weeks receiving at least 1 respiratory medication but only 40% of babies born at 28 weeks. Overall, at some time in the first year, 55% of infants received at least 1 drug including an inhaled bronchodilator (45%), an inhaled steroid (22%), a systemic steroid (15%), or diuretic (12%).

Conclusion Many babies born at <29 weeks have no respiratory medication exposure postdischarge during the first year of life. Inhaled medications, including bronchodilators and steroids, increase over the first year. *(J Pediatr 2019;208:148-55)*.

Despite improvements in survival among infants born extremely premature, a significant number continue to experience the complication of bronchopulmonary dysplasia (BPD). Several large North American series in the last few years report between 41% and 46% of infants born at <29 weeks of gestation receive supplemental oxygen (and/or other respiratory support) at 36 weeks of postmenstrual age (PMA), the most common definition of BPD.[1-4] BPD is associated with significant long-term morbidity and contributes to considerable costs, both in the neonatal intensive care unit (NICU) and beyond.[5-11]

A wide variety of medications, ranging from diuretics to bronchodilators to anti-inflammatory agents, are used to prevent or treat BPD among infants at risk.[12-14] Multicenter and single-center observational studies have reported that caffeine citrate and furosemide are among the 10 most commonly used medications overall in the NICU, with other diuretics and albuterol also appearing on some lists.[15,16] Analysis of data from a collaborative of freestanding children's hospitals showed that, among infants born at <29 weeks of gestation with BPD (defined as oxygen administration at 28 days), 89% received diuretics, 25% received inhaled steroids, and 33% received bronchodilators during hospitalization.[17-19] However, the frequency and patterns of postdischarge medication use have not been well characterized.

As data on medication use following hospital discharge in infants born premature are limited, we pursued the hypothesis that respiratory medication use would be common after discharge in infants born extremely premature

BPD	Bronchopulmonary dysplasia
NHLBI	National Heart, Lung, and Blood Institute
NICU	Neonatal intensive care unit
PMA	Postmenstrual age
PROP	Prematurity and Respiratory Outcomes Program

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and use would correlate with degree of prematurity and a diagnosis of BPD. We report a comprehensive assessment of respiratory medication use from discharge to 12 months of corrected age in a multicenter cohort of infants born premature at <29 weeks of gestation. In-hospital/NICU respiratory medication use is being reported separately.

Methods

The National Heart, Lung, and Blood Institute (NHLBI) Prematurity and Respiratory Outcomes Program (PROP) is an observational prospective cohort study performed by a consortium of 6 clinical centers incorporating 13 tertiary NICUs and a data-coordinating center (NCT01435187). A key scientific aim of PROP is to identify early clinical, physiologic, and biochemical biomarkers during the initial NICU hospitalization that can predict respiratory morbidity through 1 year of age. With funding from the Best Pharmaceuticals for Children Act, another aim of PROP was to evaluate dosing, safety, and efficacy of therapeutics surrounding BPD. Individual centers enrolled between 105 and 184 participants in the cohort for a total of 835 subjects. Detailed descriptions of the PROP study design, and the status of the 765 infants surviving at 36 weeks of PMA, have been published.[4,20,21]

Study Infants

Infants between $23^{0/7}$ and $28^{6/7}$ weeks of gestation were eligible for enrollment within the first 7 days after birth. Infants not considered viable, those with congenital heart disease or structural abnormalities of the upper airway, lungs, or chest wall or other congenital malformations that adversely affect cardiopulmonary development, or those whose families were unlikely to be available for long-term follow-up were excluded. The study was approved by the institutional review board at each participating clinical site and by the data-coordinating center at the University of Pennsylvania, with written informed consent from a parent or guardian for each baby enrolled.

Measurements and Procedures

Trained research personnel collected detailed anthropometric and medication data on a daily basis until discharge home, transfer, or 40 weeks of PMA. Follow-up data were collected from the parents at 3, 6, 9, and 12 months of corrected age (±1 month) through a focused questionnaire adminstered via telephone or at a clinic visit. At the time of each questionnaire, respiratory medication use during the previous 3 months was reported by parents and was immediately recorded on the clinical research form by research staff.

Outcomes

The diagnosis of BPD was assigned by the need for supplemental oxygen at exactly $36^{0/7}$ weeks of PMA. Using this definition, those on respiratory support with fraction of inspired oxygen 21% at 36 weeks of PMA are assigned "no BPD" status, regardless of type or level of respiratory support.[3] This definition was modified by assigning the outcome of "no BPD" to infants who were discharged home off respiratory support before 36 weeks of PMA (modified Shennan definition).[3,4]

Statistical Analyses

We report the demographic characteristics of patients who are included in the follow-up cohort. These summaries are presented for the following populations: patients alive at discharge (n = 751); patients who completed at least 1 follow-up assessment (n = 738); and patients who completed all 4 follow-up assessments (n = 641). Each factor is summarized by frequencies with percentages, means with SDs, or medians with IQRs, as appropriate. Similarly, we summarize and compare medication use at each follow-up time point (eg, months 3, 6, 9, and 12).

Because babies are assessed at multiple time points, a logistic generalized estimating equations (GEE) approach, with an exchangeable correlation structure, was used to determine differences in medication usage over time. In summarizing medication usage by baseline gestational age and overall differences across gestational age groups, *P* values from χ^2 tests or Fisher exact tests are presented, as appropriate. Additionally, *P* values from Cochran–Armitage trend tests are presented. Finally, we examined medication usage as a function of time and BPD status (yes/no) using a logistic-GEE approach as described previously in which models included the main effect time (categorical), BPD, and their interaction. *P* values are presented for the odds of medication usage comparing babies with and without BPD at each time point from the logistic-GEE model. All analyses were performed using SAS 9.4 software (SAS Institute, Cary, North Carolina) by the Data Coordinating Center.

Results

Of 751 infants discharged to home, 738 infants (98.3%) had at least 1 follow-up survey completed after discharge and 641 (85.4%) completed all 4 follow-up visits (**Figure 1**; available at www.jpeds.com). Of the 751 discharged, 696 (92.7%) completed the 12-month follow-up at an average chronological age of 15.36 ± 1.45 months and a corrected gestational age 12.31 ± 1.41 months. The 738 infants with at least 1 visit (**Table I**), were similar to the 765 infants who survived to 36 weeks of PMA, as were the smaller cohorts with more complete data (data not shown). This was a cohort of infants born extremely premature, at a median of 27 weeks of gestation and just >900 g at birth, with approximately one-half male infants and one-fourth products of multiple gestation. The cohort had 90% survival from birth to discharge.

Detailed respiratory medication exposure in each quarter for the most common drugs used is detailed in **Table II**.

Table I. Demographic characteristics of PROP cohort for infants: (1) alive at hospital discharge, (2) who participated in at least 1 visit over 12-month follow-up, and (3) who participated in all 4 follow-up visits

Characteristics	Alive at discharge n = 751	Participated in at least 1 follow-up visit n = 738	Participated in all 4 follow-up visits n = 641
Gestational age, wk, median (IQR)	27.0 (25.7, 27.9)	27.0 (25.7, 27.9)	27.0 (25.7, 27.9)
Birth weight, g, mean (SD)	919.0 (231.1)	918.7 (231.8)	922.9 (234.0)
Race, n (%)			
White	441/752 (58.6%)	433/738 (58.7%)	386/639 (60.4%)
Black	274/752 (36.4%)	269/738 (36.4%)	222/639 (34.7%)
Maternal age, y, mean (SD)	28.1 (6.3)	28.1 (6.3)	28.1 (6.3)
Finished high school, n (%)	568/684 (83.0%)	555/670 (82.8%)	494/589 (83.9%)
Exposed to second-hand smoke - discharge, n (%)*	71/741 (9.6%)	71/729 (9.7%)	63/636 (9.9%)
Exposed to second-hand smoke - discharge, month 6, n (%)†	292/745 (39.2%)	292/733 (39.8%)	264/638 (41.4%)
Exposed to second-hand smoke - month 12, n (%)†	343/745 (46.0%)	343/733 (46.8%)	300/638 (47.0%)
BPD (modified Shennan), n (%)	302/729 (41.4%)	300/718 (41.8%)	257/622 (41.3%)
Days on mechanical ventilation, median (IQR)	7.0 (1.0, 24.5)	7.0 (1.0, 25.0)	7.0 (1.0, 25.0)
Days on oxygen, median (IQR)	51.0 (22.0, 83.0)	51.0 (22.0, 84.0)	51.0 (22.0, 83.0)
Days on respiratory support,‡ median (IQR)	66.0 (43.0, 91.0)	66.5 (43.0, 91.0)	66.0 (44.0, 91.0)
Postdischarge respiratory hospitalizations,§ mean (SD)	0.4 (1.0)	0.4 (1.0)	0.4 (1.1)

*Measured at hospital discharge; is there smoking in the home or in your vehicle?
†Measured at the 6- or 12-month visit; positive response to any of the following: (1) is there smoking in the home or in your vehicle? (2) Is your child exposed to smoke in the home? (3) Does the mother or primary caregiver smoke in the home? Or (4) is there at least 1 smoker in the home?
‡Respiratory support is defined as those infants who reported receiving supplemental oxygen or other respiratory support.
§If 12-month follow-up missing, postdischarge hospitalizations assigned a value of zero for calculating respiratory hospitalization mean and SD.

Beclomethasone, caffeine, furosemide, hydrochlorothiazide, hydrocortisone, ipratropium, and racemic epinephrine were used in <5% of infants, and amiloride, aminophylline, bumetanide, formoterol, methylprednisolone, montelukast, sildenafil, and theophylline in <1% of subjects. Despite the high use of caffeine described in the neonatal period (95% in this cohort), postdischarge use remained low. In any given quarter, 66%-75% of infants received no respiratory

Table II. Quarterly drug use over the first year of life

Drug	Month 3 (n = 712*)	Month 6 (n = 708*)	Month 9 (n = 688*)	Month 12 (n = 696*)	*P* value†
No respiratory drug	533 (74.9%)	481 (67.9%)	466 (67.7%)	462 (66.4%)	.0005
At least one	179 (25.1%)	227 (32.1%)	222 (32.3%)	234 (33.6%)	.0005
Inhaled bronchodilator	93 (13.1%)	184 (26.0%)	198 (28.8%)	218 (31.3%)	<.0001
Albuterol	92 (12.9%)	184 (26.0%)	197 (28.6%)	216 (31.0%)	<.0001
Formoterol	0	1 (0.1%)	0	0	–
Ipratropium	3 (0.4%)	1 (0.1%)	4 (0.6%)	6 (0.9%)	.1294
Racemic epinephrine	7 (1.0%)	3 (0.4%)	2 (0.3%)	3 (0.4%)	.4182
Diuretic	78 (11.0%)	41 (5.8%)	11 (1.6%)	11 (1.6%)	<.0001
Amiloride	1 (0.1%)	0	0	0	–
Bumetanide	1 (0.1%)	1 (0.1%)	0	2 (0.3%)	–
Chlorothiazide	36 (5.1%)	22 (3.1%)	4 (0.6%)	3 (0.4%)	<.0001
Furosemide	30 (4.2%)	13 (1.8%)	6 (0.9%)	5 (0.7%)	.0001
Hydrochlorothiazide	23 (3.2%)	10 (1.4%)	4 (0.6%)	3 (0.4%)	.0002
Spironolactone	42 (5.9%)	22 (3.1%)	4 (0.6%)	3 (0.4%)	<.0001
Methylxanthine	18 (2.5%)	11 (1.6%)	0	0	–
Aminophylline	1 (0.1%)	0	0	0	–
Caffeine	17 (2.4%)	11 (1.6%)	0	0	–
Theophylline	1 (0.1%)	0	0	0	–
Systemic corticosteroid	29 (4.1%)	30 (4.2%)	40 (5.8%)	39 (5.6%)	.2294
Dexamethasone	12 (1.7%)	5 (0.7%)	10 (1.5%)	7 (1.0%)	.2535
Hydrocortisone	10 (1.4%)	4 (0.6%)	2 (0.3%)	2 (0.3%)	.0842
Methylprednisolone	2 (0.3%)	2 (0.3%)	0	2 (0.3%)	–
Prednisone/prednisolone	14 (2.0%)	23 (3.2%)	29 (4.2%)	29 (4.2%)	.0185
Inhaled steroid	61 (8.6%)	70 (9.9%)	86 (12.5%)	99 (14.2%)	.0008
Beclomethasone	2 (0.3%)	5 (0.7%)	7 (1.0%)	10 (1.4%)	.0416
Budesonide	51 (7.2%)	53 (7.5%)	57 (8.3%)	61 (8.8%)	.6050
Fluticasone	8 (1.1%)	15 (2.1%)	22 (3.2%)	30 (4.3%)	.0016
Leukotriene receptor antagonist	0	0	2 (0.3%)	3 (0.4%)	–
Montelukast	0	0	2 (0.3%)	3 (0.4%)	–
Pulmonary vasodilator	2 (0.3%)	7 (1.0%)	6 (0.9%)	6 (0.9%)	.1611
Sildenafil	2 (0.3%)	7 (1.0%)	6 (0.9%)	6 (0.9%)	.1611

*Number of babies completing the specified follow-up visit.
†Reported *P* value for overall "time" effect (df = 3) for logistic generalized estimating equations model for drug use (yes/no), with working exchangeable correlation structure.

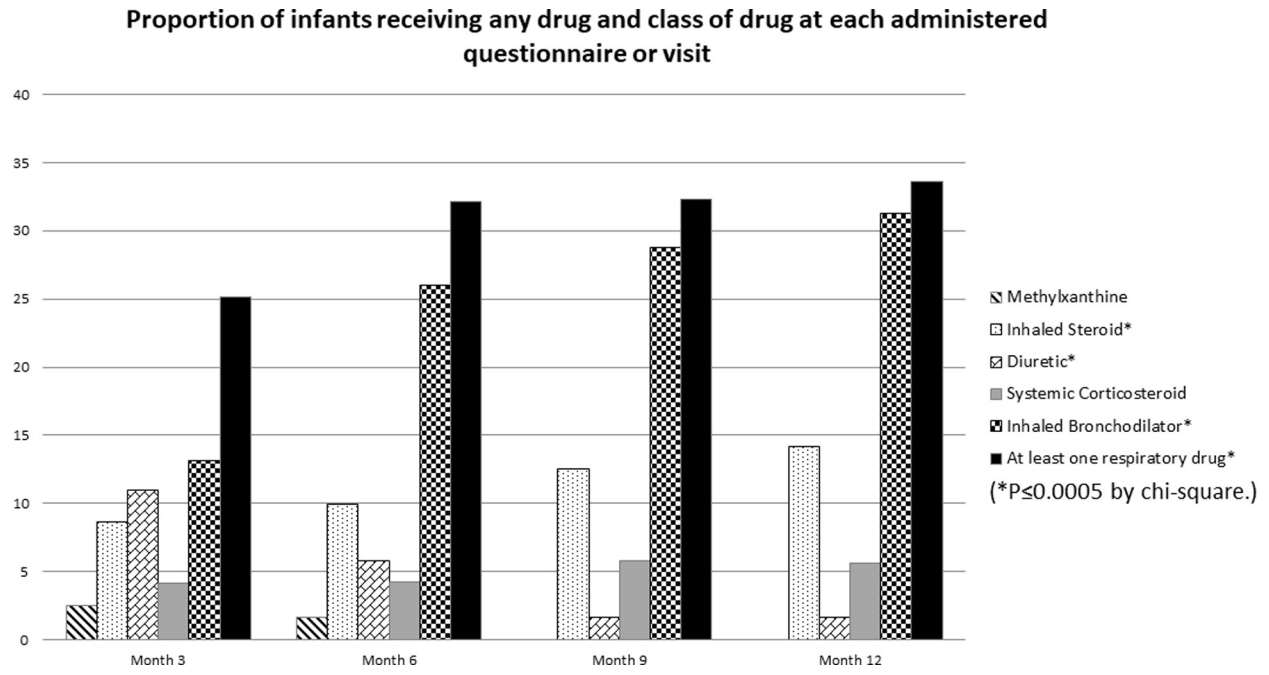

Figure 2. Each *bar* represents the proportion of infants whose caregiver reported use of a medication in that class during the previous 3-month period at the corrected age in months as noted. The proportion of those who were on at least 1 respiratory drug increased significantly over time, as did the use of inhaled steroids and inhaled bronchodilators. Conversely, diuretic use decreased significantly over the first year of life (*$P \leq .0005$ by χ^2). The denominators (n) for each time period are 712 (month 3), 708 (month 6), 688 (month 9), and 696 (month 12).

medications, with the lowest medication use in the first quarter after discharge.

There were significant changes in respiratory medication use over the first year of life (Figure 2). The percentage of patients receiving any of the drugs in a class, and those receiving any drug at all, are reported by quarter (Figure 2). After the 3-month questionnaire, approximately one-third of infants were exposed to any respiratory drug each quarter. Reported exposure to diuretics decreased significantly ($P < .0001$ by GEE model) over the year, whereas systemic corticosteroid use increased slightly, from 4.1% to 5.7%, $P = .23$, inhaled corticosteroid use increased modestly, from 8.6% to 14.2% ($P = .0008$), and inhaled bronchodilator use increased substantially, from 13% to 31.0% ($P < .0001$).

We examined the effect of gestational age at birth on post NICU-discharge drug usage (Table III). The proportion of infants with any exposure significantly decreased with increasing gestational age group (Figure 3; available at www.jpeds.com). Data are shown by 1-week gestational age at birth categories, except for the least-mature infants, in which infants at 23 and 24 weeks of gestation are combined. Respiratory medication use was more likely in less-mature infants. For example, 28.9% of babies born at 23-24 weeks received diuretics after discharge sometime in the first year, in contrast to 3.2% of babies born at 28 weeks. The effect of gestational age was highly significant ($P < .0001$). Overall, 45.5% of babies did not report exposure to any of the medications of interest at any time during the year of follow-up. Only 3.0%, 0.9%, and 0.6% of infants were exposed to methylxanthines, pulmonary vasodilators, and leukotriene receptor antagonists, respectively. Nearly 90% (89.7%) of patients had at least one quarter without respiratory medication exposure.

Infants with a diagnosis of BPD (modified Shennan)[4] were more likely to have any respiratory medication exposure at 3 of the 4 survey time points (Table IV), in unadjusted analyses and after adjustment for race and sex (model a). In the models that adjusted for gestational age, BPD significantly increased the odds of medication use only at month 3. BPD had an OR of 1.65 (1.11-2.45) at 3 months in the fully adjusted model (model d), compared with 2.06 (1.46-2.91) in the unadjusted model. For inhaled medications (inhaled bronchodilators and inhaled corticosteroids), BPD was a significant predictor only in the second half of the year (9- and 12-month surveys) for the unadjusted model and after adjustment for race and sex. When we used a modification of the National Institutes of Health workshop definition of BPD,[4] the pattern of significant differences in medication exposure was similar.

Discussion

This comprehensive assessment of respiratory medication use from discharge to 12 months of corrected age in a multicenter cohort of infants born premature born at <29 weeks of gestation provides important insights into

Table III. Drug use by gestational age for babies completing all 4 visits follow-up visits (n = 641)

Drug	All babies (n = 641*)	23 0/7-24 6/7 (n = 83*)	25 0/7-25 6/7 (n = 98*)	26 0/7-26 6/7 (n = 135*)	27 0/7-27 6/7 (n = 169*)	28 0/7-28 6/7 (n = 156*)	*P* value (Fisher†)	*P* value (trend‡)
No respiratory drug at least 1 visit	579 (90.3%)	70 (84.3%)	86 (87.8%)	120 (88.9%)	157 (92.9%)	146 (93.6%)	.1029	.0071
At least 1 drug	350 (54.6%)	60 (72.3%)	63 (64.3%)	77 (57.0%)	87 (51.5%)	63 (40.4%)	<.0001	<.0001
No exposure to any drug	291 (45.4%)	23 (27.7%)	35 (35.7%)	58 (43.0%)	82 (48.5%)	93 (59.6%)	<.0001	<.0001
Diuretic	79 (12.3%)	24 (28.9%)	21 (21.4%)	14 (10.4%)	15 (8.9%)	5 (3.2%)	<.0001	<.0001
Amiloride	1 (0.2%)	0	1 (1.0%)	0	0	0		
Bumetanide	2 (0.3%)	1 (1.2%)	0	0	1 (0.6%)	0		
Chlorothiazide	37 (5.8%)	14 (16.9%)	9 (9.2%)	8 (5.9%)	5 (3.0%)	1 (0.6%)		
Furosemide	31 (4.8%)	7 (8.4%)	9 (9.2%)	6 (4.4%)	7 (4.1%)	2 (1.3%)		
Hydrochlorothiazide	24 (3.7%)	7 (8.4%)	9 (9.2%)	3 (2.2%)	3 (1.8%)	2 (1.3%)		
Spironolactone	43 (6.7%)	16 (19.3%)	13 (13.3%)	5 (3.7%)	7 (4.1%)	2 (1.3%)		
Inhaled bronchodilator	292 (45.6%)	46 (55.4%)	50 (51.0%)	67 (49.6%)	71 (42.0%)	58 (37.2%)	.0311	.0014
Albuterol	290 (45.2%)	45 (54.2%)	50 (51.0%)	67 (49.6%)	70 (41.4%)	58 (37.2%)		
Formoterol	1 (0.2%)	0	0	1 (0.7%)	0	0		
Ipratropium	11 (1.7%)	1 (1.2%)	3 (3.1%)	4 (3.0%)	2 (1.2%)	1 (0.6%)		
Racemic epinephrine	12 (1.9%)	2 (2.4%)	3 (3.1%)	0	6 (3.6%)	1 (0.6%)		
Inhaled steroid	140 (21.8%)	25 (30.1%)	28 (28.6%)	30 (22.2%)	36 (21.3%)	21 (13.5%)	.0121	.0007
Beclomethasone	15 (2.3%)	3 (3.6%)	2 (2.0%)	4 (3.0%)	5 (3.0%)	1 (0.6%)		
Budesonide	102 (15.9%)	15 (18.1%)	21 (21.4%)	21 (15.6%)	28 (16.6%)	17 (10.9%)		
Fluticasone	40 (6.2%)	10 (12.0%)	11 (11.2%)	7 (5.2%)	7 (4.1%)	5 (3.2%)		
Leukotriene receptor antagonist	3 (0.5%)	1 (1.2%)	1 (1.0%)	1 (0.7%)	0	0	.2352	.0827
Montelukast	3 (0.5%)	1 (1.2%)	1 (1.0%)	1 (0.7%)	0	0		
Methylxanthine	19 (3.0%)	6 (7.2%)	5 (5.1%)	3 (2.2%)	5 (3.0%)	0	.0066	.0013
Aminophylline	1 (0.2%)	0	0	0	1 (0.6%)	0		
Caffeine	18 (2.8%)	5 (6.0%)	5 (5.1%)	3 (2.2%)	5 (3.0%)	0		
Theophylline	1 (0.2%)	1 (1.2%)	0	0	0	0		
Pulmonary vasodilator	5 (0.8%)	2 (2.4%)	0	1 (0.7%)	0	2 (1.3%)	.1710	.5704
Sildenafil	5 (0.8%)	2 (2.4%)	0	1 (0.7%)	0	2 (1.3%)		
Systemic corticosteroid	96 (15.0%)	14 (16.9%)	17 (17.3%)	21 (15.6%)	25 (14.8%)	19 (12.2%)	.7756	.2308
Dexamethasone	29 (4.5%)	4 (4.8%)	7 (7.1%)	5 (3.7%)	9 (5.3%)	4 (2.6%)		
Hydrocortisone	9 (1.4%)	3 (3.6%)	2 (2.0%)	2 (1.5%)	1 (0.6%)	1 (0.6%)		
Methylprednisolone	5 (0.8%)	1 (1.2%)	1 (1.0%)	0	2 (1.2%)	1 (0.6%)		
Prednisone/prednisolone	70 (10.9%)	10 (12.0%)	12 (12.2%)	16 (11.9%)	17 (10.1%)	15 (9.6%)		

*Includes only babies who completed all 4 visits.
†Fisher exact test of association between drug use and gestational age.
‡Cochran–Armitage test of trend between drug use and gestational age.

respiratory morbidity in the first year of life. In any given quarter, 66%-75% of infants received no respiratory medications, with the lowest medication use in the first quarter after discharge. Medications were more likely to be prescribed in the infants born most prematurely and in infants with a diagnosis of BPD, also confounded by gestational age. Reported use of diuretics decreased significantly over the 4 quarters, whereas the use of inhaled bronchodilators and inhaled steroids increased significantly.

Previous studies demonstrate that the frequency and patterns of postdischarge medication use are not well

Table IV. Medication usage in infants with and without BPD (N = 719)*

Drug	Visit	BPD* (n = 301)	No BPD (n = 418)	Unadjusted *P* value	Adjusted *P* value†	Adjusted *P* value‡	Adjusted *P* value§	Adjusted *P* value¶
Any respiratory medication	3 mo	94 (31.2)	80 (19.1)	<.01**	<.01**	<.01**	<.01**	.01**
	6 mo	100 (33.2)	117 (28.0)	.14	.18	.60	.69	.64
	9 mo	108 (35.9)	107 (25.6)	<.01**	<.01**	<.06	.06	.59
	12 mo	110 (36.5)	118 (28.2)	.02**	.03**	.20	.23	.99
Any inhaled respiratory medication††	3 mo	60 (19.9)	65 (15.6)	.06	.08	.23	.25	.47
	6 mo	82 (27.2)	110 (26.3)	.74	.87	.67	.59	.15
	9 mo	101 (33.6)	105 (25.1)	.01**	<.02**	.10	.11	.84
	12 mo	109 (36.2)	116 (27.8)	<.02**	<.03**	.14	.16	.94

*Modified Shennan definition.[4]
†Adjusted for race and sex only.
‡Adjusted for gestational age only.
§Adjusted for gestational age, race, and sex.
¶Adjusted for gestational age, race, sex, mother's education, family asthma, maternal smoking during pregnancy, and second-hand smoke exposure during follow-up (coded as a time-varying binary exposure variable for second-hand smoke exposure between discharge and current visit. See **Table I** footnote for details).
**$P < .05$.
††Inhaled medications include inhaled bronchodilators and inhaled corticosteroids.

characterized.[9,22-26] In 1 cohort of infants ≤32 weeks of gestation at birth followed for a year after NICU discharge, at least 1 medication prescription was filled for 43% of the infants; infants who had at least 1 prescription filled had an average of 5.5 prescriptions filled per year.[24] Of these, 49% were for respiratory medications, including inhaled bronchodilators, 29% were for antibiotics, and 4% were for diuretics. A long-term follow-up study of a cohort of infants born premature in Quebec found that, among subjects 5-25 years of age followed during an 11-year period, more than one-half received inhaled bronchodilators and/or inhaled corticosteroids.[9] Infants diagnosed with BPD had approximately double the medication use of those diagnosed only with respiratory distress syndrome. Stevens et al conducted a secondary analysis of long-term respiratory outcomes in the Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT) cohort.[27] They included a summary of medication use defined by general categories of diuretics, systemic steroids, inhaled steroids, and home oxygen but did not document specific medication use (eg, loop diuretics vs thiazides) or longitudinal data across the first year of life. More detailed reports of patterns of use for individual medications have been restricted to single-center experiences.[26,28-30]

Inhaled bronchodilators were the most frequent class of respiratory medication prescribed postdischarge in the PROP cohort, with 30% of infants receiving inhaled bronchodilators and an increase in inhaled bronchodilator use from 3 months of age (12%) to 12 months of age (30%). Although this analysis did not compare symptomatology to medication use, bronchodilator use may represent increased cough or wheezing after respiratory viral exposure. Inhaled bronchodilator use was more commonly seen among patients born at lower gestational age and those with a diagnosis of BPD at 36 weeks, which may be related to the fact that infants with lower baseline lung function are more likely to have symptomatic lower respiratory tract infection.[31] The β_2-agonist albuterol is the most common inhaled bronchodilator used. Ipratropium and inhaled steroids have been recommended for management of tracheomalacia[32] but are not supported by well-designed studies.[33] Ipratropium was used by only 7 patients in the study population.

Systemic and inhaled steroids and diuretics were used in 12%-20% of the population. Inhaled corticosteroid use increased from 3 to 12 months of age but not to the same degree as inhaled bronchodilator use. The use of the corticosteroid budesonide, delivered by nebulization, remained relatively flat from 3 to 12 months of corrected age and may represent medication started in the NICU in those patients with a more severe BPD phenotype and then continued at home in the year after discharge. The corticosteroids fluticasone and beclomethasone, delivered by a meter dose inhaler and mask, account for the increase in inhaled corticosteroids given over this time period. These medications are included in NHLBI guidelines[34] for the management of persistent asthma, but their effectiveness has not been established in younger children with recurrent wheezing. Although our analysis of the PROP medication database does not provide direct evidence for why these medications were initiated, or by which type of clinician, the frequency of inhaled bronchodilator use likely reflects the initiation of a medication to treat symptoms of cough or wheezing.

Variable diuretic use in the NICU is well-documented through analysis of national administrative data sets[17] and in the PROP cohort.[35] There was no significant preferential use in our postdischarge cohort by diuretic class (loop, thiazide spironolactone). Although there is no clinical consensus regarding how and when to wean diuretics, we found minimal use by 12 months of corrected age, accompanied by increased prevalence of other respiratory medications. Given the absence of studies on efficacy, this shift may reflect provider preference or other unappreciated factors.

Although there is increased recognition of pulmonary hypertension as a co-morbid condition associated with severe BPD,[36] the use of any pulmonary vasodilator medication was <2% in the PROP cohort. A recent analysis of administrative data for infants born extremely premature during the neonatal hospitalization described variable rates of sildenafil use in infants with a diagnosis of BPD, ranging from 0% to 25%; however, rates of sildenafil use after discharge were not available.[37] A number of factors likely contribute to the low use of pulmonary vasodilators postdischarge in our cohort. Although there have been case reports describing the use of sildenafil and other pulmonary vasodilators in this patient population, there has only recently been a consensus statement to guide evaluation and therapy in infants with BPD complicated by pulmonary hypertension.[38] Routine screening echocardiography was not standard of care before hospital discharge during our study period, and some cases of pulmonary hypertension may not have been clinically recognized. Several PROP centers screened all babies with supplemental oxygen at 36 weeks with an echocardiogram to assess right heart function and pulmonary hypertension. However, even with a universal surveillance protocol, only 15% of infants of extremely low gestational age had abnormalities concerning for pulmonary vascular disease by echocardiography at 36 weeks of PMA.[36]

At any given time, ~70% of the postdischarge PROP cohort were on no respiratory medications, and only one-half were prescribed any respiratory medication over the course of the first year of life. Infants born at lower gestational age and those assigned the diagnosis of BPD were more likely to receive a respiratory medication in the first year of life, suggesting that respiratory medication may serve as a proxy for respiratory morbidity. Conversely, infants born extremely premature who do not require respiratory medications during the first year of life may be relatively healthy, reflecting lower risk for future respiratory compromise.

There are a number of limitations in this study. Medication use was based on provider recall at 3-month

intervals rather than from pharmacy or billing data. Medication adherence also was not collected or reported, and reliance on prescribing data conveyed by parents may have overestimated the reported use of medications. Reasons for the use of inhaled bronchodilators and corticosteroids were not explicitly stated and may have varied by provider. Variations in socioeconomic background and ethnicity may limit the generalizability of the PROP cohort to the general population. We also did not collect any information as to the type of prescribing clinician. Prescribing practices may differ among generalists, as well as neonatologists, pediatric pulmonologists, and other subspecialists involved in postdischarge care of infants born preterm.

Our findings on the pattern and timing of respiratory medication usage in former infants born premature may inform the design of future clinical trials to assess drug efficacy and safety. Specifically, there may be phenotypes of infants born premature who are more responsive to bronchodilators or corticosteroids. Although the use of these medications has likely been limited to symptomatic infants, there may be a role for early use of inhaled corticosteroids to alter the degree of respiratory morbidity in certain phenotypes. ■

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50 Years Ago in *The Journal of Pediatrics*

Acrodermatitis Enteropathica: Defective Metabolism of Unsaturated Fatty Acids

Cash R, Berger CK. J Pediatr 1969;74(5):717-29

Acrodermatitis enteropathica, first described in 1902, is characterized by distinctive skin lesions, gastrointestinal symptoms, hair and skin changes, psychic disturbances, and growth failure. Cash et al reported that a 3-month-old Caucasian infant, fed modified cow's formula, developed failure to thrive. A persistent macular rash with pustules and crusts around the body orifices, occiput, fingers, and toes was present since 2 weeks of age. The child had dystrophic nails with paronychia, draining ears, photophobia, and hepatomegaly. Skin biopsies revealed nonspecific eczematoid and exfoliative dermatitis. He did not respond to numerous changes of formulas and antibiotics over weeks. An evaluation of the child's fatty acid metabolism was performed after administration of arachidonic acid, cottonseed oil (intravenous), and pyridoxine hydrochloride, which revealed an increase in the serum levels of 18:2 and 20:4 acids. A similar response was obtained after giving human breastmilk and diodoquin, resulting in symptomatic improvement. Several intermediate fatty acids of the linoleic to arachidonic acid transformation disappeared from the child's serum after fat-induced remission. The authors thus hypothesized defective metabolism of unsaturated fatty acids as the cause of acrodermatitis enteropathica.

Acrodermatitis enteropathica is now recognized as an inherited form of zinc deficiency caused by its defective absorption. Mutations of the zinc transporter gene *SLC39A4* on chromosome 8q24.3, which codes for the zinc-ligand binding protein ZIP4 (zinc or iron regulated transporter-like protein) results in defective zinc absorption.[1,2] A mutation in *SLC30A2* gene on chromosome 1p36.11 may also cause the disease to manifest in exclusively breastfed infants. Aberrant adenosine triphosphate release from keratinocytes and impaired Langerhans cell-dependent hydrolysis of nucleotides may also play a role in the pathogenesis.[3] Oral supplementation with elemental zinc (3 mg/kg/day) leads to improvement. Recognition of zinc as the limiting nutrient in acrodermatitis enteropathica has revolutionized the treatment of this once considered debilitating disorder.

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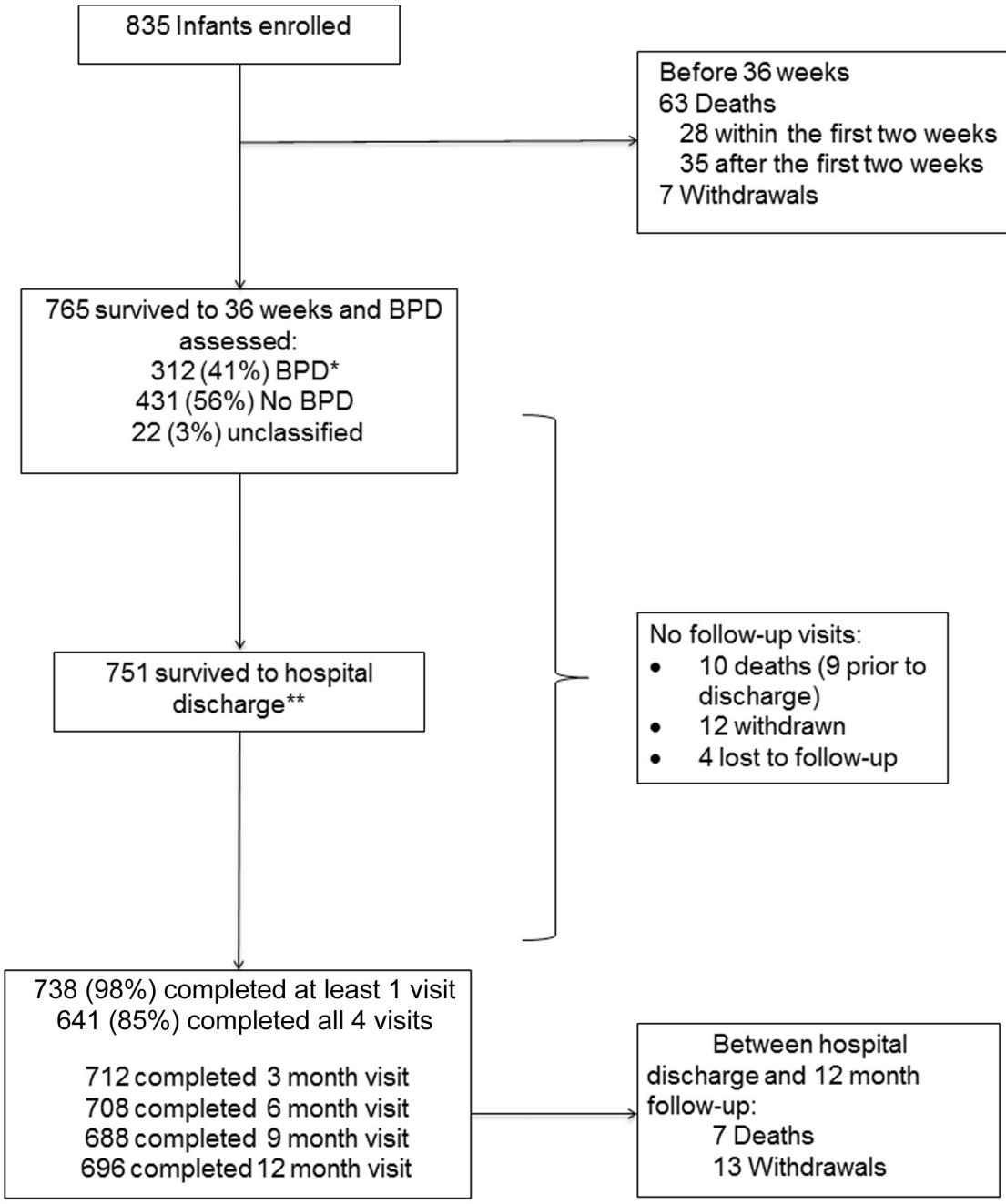

Figure 1. Participant flow diagram.

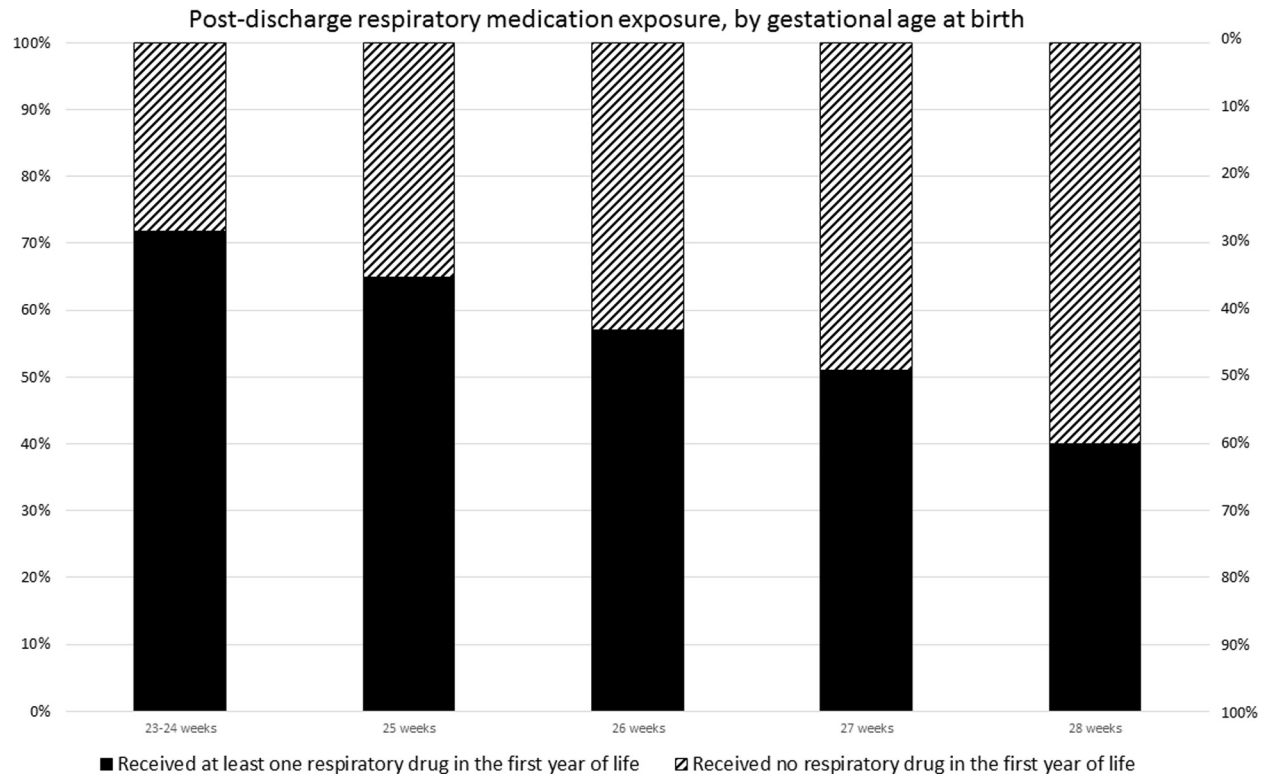

Figure 3. Each *bar* represents the proportion of infants receiving at least 1 respiratory medication post-NICU discharge during the first year of life vs the proportion who received no respiratory medication, grouped by gestational age at birth. This was statistically significant ($P < .0001$ by χ^2). The denominators (n) for each gestational age group are 83 (23-24 weeks), 98 (25 weeks), 135 (26 weeks), 169 (27 weeks), and 156 (28 weeks), for a total of 641 babies who completed all 4 postdischarge visits.