Furosemide Exposure and Prevention of Bronchopulmonary Dysplasia in Premature Infants

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Objective To evaluate the association between furosemide exposure and risk of bronchopulmonary dysplasia (BPD).

Study design This retrospective cohort study included infants (2004-2015) born at 23-29 weeks gestational age and 501-1249 g birth weight. We compared the demographic and clinical characteristics of infants exposed and not exposed to furosemide between postnatal day 7 and 36 weeks postmenstrual age. We examined the association between furosemide exposure and 2 outcomes: BPD and BPD or death. We performed multivariable probit regression models that included demographic and clinical variables in addition to 2 instrumental variables: furosemide exposure by discharge year, and furosemide exposure by site.

Results Of 37 693 included infants, 19 235 (51%) were exposed to furosemide; these infants were more premature and had higher respiratory support. Of 33 760 infants who survived to BPD evaluation, 15 954 (47%) had BPD. An increase in the proportion of furosemide exposure days by 10 percentage points was associated with a decrease in both the incidence of BPD (4.6 percentage points; $P = .001$), and BPD or death (3.7 percentage points; $P = .01$).

Conclusions More days of furosemide exposure between postnatal day 7 and 36 weeks was associated with decreased risk of BPD and a combined outcome of BPD or death. *(J Pediatr 2018;■■:■■-■■).*

See editorial, p ••• and related article, p •••

Bronchopulmonary dysplasia (BPD) is the most common pulmonary morbidity associated with prematurity, and premature infants with BPD are at an increased risk of death and severe developmental disability.[1-4] For infants with BPD who survive, the costs of the disorder are measured in impaired childhood health and quality of life, family stress and economic hardship, and increased healthcare costs.[4-6] Despite the devastating impact of BPD on premature infants, there are currently no therapies labeled by the US Food and Drug Administration to prevent BPD. Off-label therapies shown to decrease the risk of BPD have limitations, including the need for further studies to determine optimization of timing and duration of therapy (caffeine),[7] lack of availability for widespread clinical use (vitamin A),[8] or association with neurodevelopmental impairment (postnatal steroids).[9]

Neonatologists commonly use furosemide off-label in premature infants.[10] Furosemide is a loop diuretic that inhibits the reabsorption of sodium and chloride in the kidney's proximal tubules, distal tubules, and Loop of Henle. Across the US, 34% of infants weighing <1500 g at birth receive furosemide, and the use of furosemide varies widely across centers.[11] This practice variation likely stems from the fear of potential adverse effects of furosemide, combined with a lack of published data surrounding the timing of use, appropriate dose, indication, and level of efficacy for the prevention of BPD. Previous small studies have suggested that furosemide improves lung compliance, airway resistance, and oxygenation in

BPD	Bronchopulmonary dysplasia
PMA	Postmenstrual age

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premature infants,[12] but no randomized, controlled trials of furosemide to prevent BPD have been performed. The objective of this study was to evaluate whether furosemide exposure is associated with a decreased risk of BPD in a large, national cohort of premature infants.

Methods

We identified hospitalized infants discharged from 190 neonatal intensive care units managed by the Pediatrix Medical Group from 2004 to 2015 (**Figure 1**; available at www.jpeds.com). Infants were included if they were gestational age 23-29 weeks and birth weight 501-1249 g. Infants were excluded if they were transferred between hospitals before 36 weeks postmenstrual age (PMA), died before 7 days postnatal age or had an unknown discharge day, were cared for in a unit with <10 infants meeting the inclusion criteria within the study period, or were missing data necessary to estimate the risk of BPD (including race or ethnicity, ventilator status, and fraction of inspired oxygen). Demographic, clinical, and maternal data were extracted from a clinical data warehouse that prospectively captures data from electronic health records, including daily progress notes and other documentation generated by clinicians using a computer-assisted tool.[13] The study was approved by the Duke University Institutional Review Board as exempt research.

Furosemide exposure was defined in 2 distinct ways: (1) as a continuous variable, defined as the percentage of days exposed to furosemide between day of life 7 and 36 weeks PMA or the date of death and (2) as a binary variable, defined as any exposure between postnatal day 7 and 36 weeks PMA. The primary outcome, BPD, was defined by an infant receiving supplemental oxygen or respiratory support (ie, nasal cannula, continuous positive airway pressure, or mechanical ventilation) continuously from a PMA of $36^{0/7}$-$36^{6/7}$ weeks.[14] Secondary outcomes included death, defined as all-cause mortality after postnatal day 7 and before discharge, and a combined outcome of BPD or death. The goal of the analysis was to estimate the association between furosemide exposure and these outcomes while adjusting for measured pretreatment covariates. These other covariates included gestational age, small-for-gestational age status,[15] race or ethnicity, delivery type (vaginal vs cesarean delivery), sex, inborn status, antenatal steroid exposure, 5-minute Apgar score, atrial septal defect or ventricular septal defect, ligation or occlusion of a patent ductus arteriosus, receipt of dexamethasone during the study period, ventilator status on postnatal day 7, fraction of inspired oxygen on postnatal day 7, and estimated risk of BPD or death at postnatal day 7 according to a model developed by the National Institute of Child Health and Human Development Neonatal Research Network.[16,17]

Statistical Analyses

We compared demographic and clinical variables between infants exposed and not exposed to furosemide using the χ^2 test for categorical variables or the Wilcoxon rank-sum test for continuous variables. Among infants who survived to 36 weeks PMA, we calculated the percentage who developed BPD each year. We evaluated furosemide exposure by discharge year and by site using 2 methods: by calculating the percentage of infants ever exposed to furosemide at each discharge year and site, and by calculating the percentage of infant-days occurring between 7 days of life and 36 weeks PMA in which an infant was exposed to furosemide on each discharge year and site.

To examine the association between furosemide exposure and outcomes of BPD in infants surviving to 36 weeks PMA and the combined outcome of BPD or death in all infants, we chose an instrumental variable approach.[18] Although other methods (such as propensity scores, regression, and matching) can adjust for measured confounders, the instrumental variable approach is essential in controlling for unmeasured confounders, such as clinical disease severity. This approach has been used successfully in adult, pediatric, and perinatal settings, and it is sufficiently powerful that it is now being used to reduce bias from noncompliance in randomized, controlled trials.[19-22] The validity of this approach requires that the instruments used correlate with treatment and, except for their influence on treatment, not otherwise be associated with the outcomes of interest.

We performed 2 sets of instrumental variable analyses for each outcome. In our first set of analyses, we constructed a multivariable probit regression model to predict the percentage of days each infant was exposed to furosemide using the measured pretreatment covariates as listed, and 2 instrumental variables, namely the percentage of infant-days occurring between 7 days of life and 36 weeks PMA in which there was exposure to furosemide in that discharge year, and the percentage of infant-days occurring between 7 days of life and 36 weeks PMA in which there was exposure at that site. Infants with uncertain duration of furosemide were excluded from these models. For a second instrumental variable analysis, we constructed a similar multivariable probit regression model, but used the following 2 instrumental variables to predict categorical (0, 1) furosemide exposure for the model percentage of infants exposed during that discharge year, and percentage of infants exposed at that site. Infants with an uncertain duration of furosemide were included in these models. In each of the analyses, the values of the instrumental variables were calculated for each infant individually using the exposure patterns among all other infants at that site or in that year. To evaluate the validity of our instrumental variables, we examined the proportion of infants falling into categories of each covariate among quartiles of each instrumental variable. We also examined the validity of our instrumental variables using F-tests and Wald tests. As a sensitivity analysis, we repeated these instrumental variable analyses using only the instrumental variable involving furosemide exposure by site and eliminating the instrumental variable involving furosemide exposure by discharge year. Finally, because our hypothesis was that furosemide has a physiological effect on the prevention of BPD, but that it should not otherwise be associated with death, we repeated our instrumental variable analyses using death as the dependent variable. Because death is an outcome that should be unrelated to the exposure but is associated with the

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potential confounders in the study, the lack of an association between furosemide exposure and death would indicate that confounding was adequately controlled by our instrumental variable analysis. All analyses were performed using Stata (version 14.1, StataCorp, College Station, Texas). *P* values of <.05 were considered significant.

Results

A total of 37 693 infants from 191 neonatal intensive care units were included in this study, with a median (25th-75th percentiles) gestational age and birth weight of 27 weeks (25-28) and 860 g (710-1028). Among all infants, 19 235 of 37 693 (51%) were exposed to furosemide between postnatal day 7 and 36 weeks PMA and the median percentage of days exposed to furosemide was 1.3% (0%-6.7%). Among infants exposed to furosemide, the median duration of exposure was 4 days (2-10), 22% of exposed infants had a duration of 1 day, 23% of infants had a duration of ≥14 days, and the longest duration was 84 days. Infants exposed to furosemide were more likely to have a lower gestational age, lower birth weight, male sex, exposure to prenatal steroids, lower Apgar scores, exposure to dexamethasone, atrial septal defect or ventricular septal defect, and patent ductus arteriosus surgery ($P < .001$; **Table I**). Infants exposed to furosemide were also more likely to have higher respiratory support and BPD or death risk scores on postnatal day 7 ($P < .001$; **Table I**). Infant demographics, maternal factors, and infant clinical factors were noted to be overall well-distributed among quartiles of the instrumental variables (**Table II** and **Table III**; available at www.jpeds.com). Both prevalence and duration of furosemide exposure varied substantially by site (prevalence: 0%-93%; duration: 0%-45% of days; **Figure 2**) and by discharge year (prevalence: 41%-60%; duration: 4%-13% of days; **Figure 3**), with a decreasing trend of use over time. Wald tests implied that the instrumental variables approach was appropriate ($P < .001$), and F-tests suggested that the instruments we chose provide sufficient explanatory power ($P < .001$).

Of the total 37 693 infants, 19 895 (53%) had BPD or died; 33 760 of the 37 693 infants (90%) survived to 36 weeks PMA and were evaluated for BPD. Of these, 15 954 of the 33 760 (47%) had BPD. The incidence of BPD was relatively stable over the study period (starting at 50% in 2004, hitting a low of 45% in 2013, and ending at 47% in 2015). Among infants with BPD, 7816 of 15 954 (49%) were on low-flow nasal cannula at 36 weeks; 6424 of 15 954 (40%) were on continuous positive airway pressure, noninvasive positive pressure ventilation, or high-flow nasal cannula; and 1567 of 15 954 (10%) were on a ventilator, with the remaining 147 of the 15 954 (0.9%) receiving hood oxygen. On adjusted analysis with furosemide exposure measured as a binary variable, exposure was not significantly associated with either BPD ($P = .62$) or the combined outcome of BPD or death ($P = .82$; **Table IV**). Nevertheless, when furosemide exposure was evaluated in terms of percentage days exposed, a 10-percentage point increase in the proportion of days exposed to furosemide (eg, from 10% to 20%) was associated with a 4.6-percentage point decrease in BPD ($P = .001$) and a 3.7-percentage point decrease in BPD or death ($P = .01$; **Table IV**). Furosemide exposure by either binary or continuous measure was not associated with death (**Table IV**). Our sensitivity analysis including only 1 instrumental variable showed similar results (no significant association between any furosemide exposure and BPD or the combined outcome of BPD or death, but a 4.5-percentage point decrease in BPD [$P = .004$] and 3.8-percentage point decrease in BPD or death [$P = .02$] in response to a 10-percentage point increase in exposure).

Table I. Demographics and clinical characteristics for infants treated with furosemide and not treated with furosemide

	Exposed (n = 19 235)	Not exposed (n = 18 458)	*P* value
Gestational age, weeks			<.001
23-25	41	22	
26-27	38	36	
28-29	21	43	
Birth weight, g			<.001
500-749	38	23	
750-999	40	40	
1000-1249	21	38	
Small for gestational age	14	14	.08
Cesarean delivery	73	74	.02
Prenatal steroids	78	81	<.001
Inborn	85	87	<.001
5-Minute Apgar score			<.001
0-3	7	6	
4-6	26	22	
7-10	67	73	
Male	55	49	<.001
Race/ethnicity			<.001
White	48	48	
Black	31	29	
Hispanic	21	23	
Percentage risk of BPD/death on postnatal day 7, median (25th-75th percentile)	63 (38-79)	35 (17-64)	<.001
Ventilator status on postnatal day 7			<.001
High-frequency	20	11	
Conventional	40	23	
CPAP	24	35	
Nasal cannula/hood	14	24	
None	2	7	
Fractional inspired oxygen on postnatal day 7			<.001
21%	39	63	
22%-50%	57	34	
51%-99%	4	2	
100%	1	1	
Received dexamethasone	28	8	<.001
Atrial septal defect or ventricular septal defect	9	6	<.001
Patent ductus arteriosus ligation	21	6	<.001

CPAP, continuous positive airway pressure ventilation.
Data are expressed as column percentages unless otherwise indicated.

Discussion

In our sample of >36 000 premature infants, increased duration of furosemide exposure was associated with a lower likelihood of developing BPD and BPD or death. Our results

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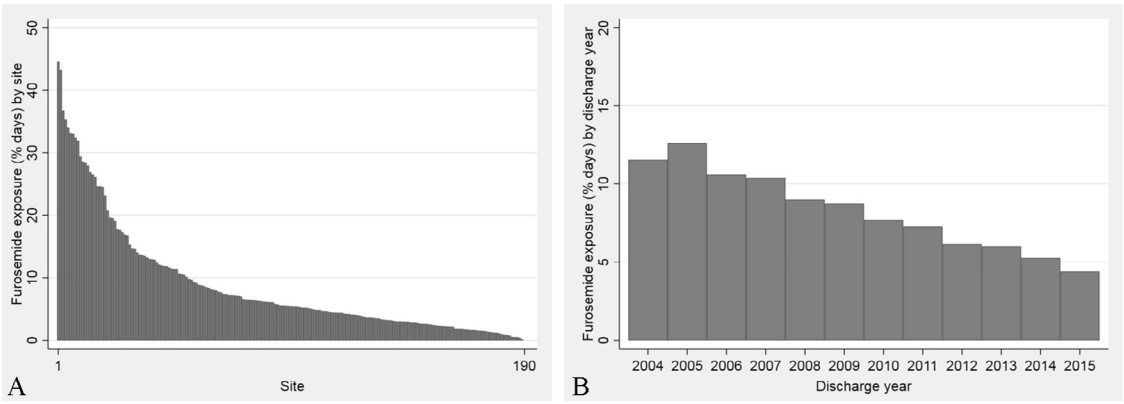

Figure 2. Furosemide exposure (percentage infant-days exposed) by **A,** site; and **B,** discharge year.

indicate that duration of exposure, rather than any exposure, was critical for the prevention of these outcomes. Simple exposure to furosemide, without accounting for duration, was not associated with BPD or the combined outcome of BPD or death.

Furosemide is not indicated by the US Food and Drug Administration for the prevention of BPD in premature infants. Despite this lack of guidance, 50% of infants in our cohort were exposed to furosemide between 7 days of life and 36 weeks PMA. There was substantial variation in the prevalence and duration of furosemide exposure by site. This practice variation in drug prescription has been observed for other drug classes within the Pediatrix Medical Group[23,24] and for diuretics in US hospitals in a study using the Pediatric Health Information System.[10] The degree of variation in prescription results in part from a lack of US Food and Drug Administration labelling for many drugs in infants, which stems from a paucity of data regarding safety and efficacy. Therefore, neonatologists are forced to prescribe drugs with promising physiological mechanisms despite limited data.

In the case of furosemide, administration is believed to promote diuresis and reduce intravascular fluid volume, thereby decreasing fluid flow to the lungs. Furosemide is also hypothesized to act by promoting peripheral or pulmonary vasodilation through prostaglandin synthesis, which decreases pulmonary congestion.[25,26] Decreased pulmonary fluid has been associated with improved respiratory outcomes in critically ill adults and in premature infants.[27,28] Although the proposed physiological mechanism of furosemide is plausible, efficacy data are limited to small randomized controlled trials with short-term outcomes.[29,30] A meta-analysis of the existing data demonstrated that loop diuretics (including furosemide) improve lung compliance, airway resistance, and oxygenation, but no trials have explored the effect of furosemide on the development of BPD. A recent observational study of 835 extremely premature infants concluded that diuretics were not associated with short-term improvements in respiratory support.[31] Although this study attempted to adjust for the multiple demographic factors that were significantly different between the exposed and unexposed groups, it is likely that infants exposed to diuretics had more severe disease. In addition, the study did not account for duration of diuretic exposure. A randomized clinical trial of furosemide safety in premature infants receiving 28 days of furosemide is currently underway,[32] but the trial will not be adequately powered to address efficacy. The findings of our study support the design

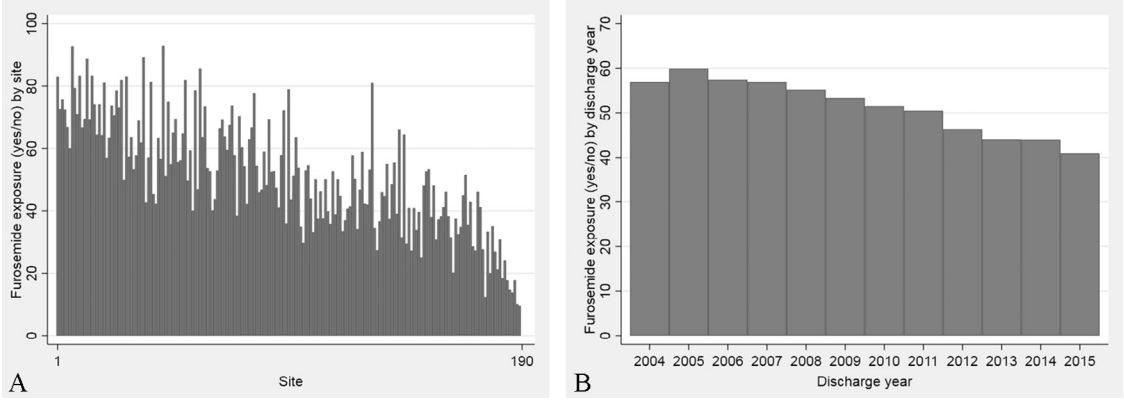

Figure 3. Any furosemide exposure (yes/no) by **A,** site and **B,** discharge year.

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Table IV. Adjusted coefficients to predict outcomes

	Change in the percentage of patients experiencing an outcome in response to a 10 percentage point increase in days exposed to furosemide (95% CI)	*P* value
BPD	−4.6 percentage points (−7.3 to −1.8)	.001
BPD or death	−3.7 percentage points (−6.6 to −0.1)	.01
Death	0.04 percentage points (−0.24 to 0.31)	.78
	Change in the percentage of patients experiencing an outcome associated with any exposure to furosemide (95% CI)	***P* value**
BPD	−2.4 percentage points (−12.2 to 7.3)	.62
BPD or death	−1.2 percentage points (−11.1 to 8.8)	.82
Death	2.2 percentage points (−1.3 to 5.6)	.22

of a future randomized controlled trial to examine the efficacy of furosemide for the prevention of BPD in premature infants. In particular, our data suggest that a longer duration of furosemide exposure may have better effectiveness for the prevention of BPD.

Although the results of our study are promising, clinicians must also consider whether the degree of benefit associated with a 10-percentage point increase in furosemide exposure days (4.6-percentage point decrease in BPD and a 3.7-percentage point decrease in BPD or death) is clinically significant. With any drug, potential benefits must be weighed against potential risks. Although currently available evidence surrounding the risks of furosemide in premature infants is scarce and limited mostly to small cohort and case control studies, an ongoing trial will examine more closely the risk of adverse events such as nephrocalcinosis/nephrolithiasis and ototoxicity.[32]

Our cohort of infants was at high risk for pulmonary morbidity, with 47% developing BPD. The prevalence of BPD in prior cohorts has varied according to the definition used, and the most appropriate definition remains subject to debate.[33,34] Like many of the most commonly used definitions of BPD, including the 2018 National Institutes of Health consensus definition,[35] our definition depends on therapies administered (oxygen and respiratory support) to treat the condition, and it has been applied consistently across studies using data from the Pediatrix Medical Group.[12,36-38] The database does not include radiologic data to support the confirmation of parenchymal lung disease, which is a component of the National Institutes of Health definition. Compared with some definitions that require respiratory or oxygen support for a specified period (eg, ≥28 days) for the diagnosis of BPD, our definition may have led to an overestimate of the prevalence of BPD. Nonetheless, the prevalence of BPD in our cohort was similar to that in a cohort of 34 636 infants cared for at National Institute of Child Health and Human Development Neonatal Research Network centers between 1993 and 2012.[39] In this study of infants 22-28 weeks gestation and 401-1500 g, the diagnosis of BPD became more prevalent over time and was >40% at the end of the study period. Consequently, our cohort seems to be representative of other large multicenter populations of infants at high risk for morbidity.

The potential effect of furosemide on the development of BPD is difficult to address correctly with observational data such as ours, owing to the presence of an important confounding variable: clinical disease severity. Sicker infants are more likely to develop signs and symptoms of lung disease, which makes providers more likely to prescribe furosemide. To address this problem, we chose to use an instrumental variable approach. We identified factors (exposure to furosemide at each discharge year and at each site) that we assumed to be related to furosemide exposure, not so highly correlated with potential confounders, and associated with the outcome (BPD) only through its relationship with treatment.[40] We observed that furosemide exposure varied by both discharge year and site, results that were consistent with the first assumption. Most patient characteristics were fairly evenly distributed across instrumental variable quartiles. Notably, some indicators of disease severity (including the risk of BPD/death and the proportion of infants requiring oxygen, requiring mechanical ventilation, receiving dexamethasone, and undergoing patent ductus arteriosus surgery) seemed to be somewhat lower in the first quartile of the site instrumental variable compared with the other quartiles, suggesting that sites with lower use of furosemide may have treated a population of infants at lower risk. Similarly, disease severity seemed to be modestly greater in higher quartiles of the discharge year instrumental variable. This finding may reflect improved survival and increased lung morbidity over time, as demonstrated in the National Institute of Child Health and Human Development Neonatal Research Network cohort.[39] We attempted to address these potential weaknesses by repeating our analyses using death as a falsification end point.[41] We hypothesized that furosemide exposure should have no direct effect on death. If furosemide were observed to be associated with death, then this would suggest that its association with BPD might be spurious. In fact, there is no association between furosemide exposure and death (**Table IV**), suggesting that our instrumental variables validly account for unmeasured confounders.

The strengths of our study include its focus on a clinical question critical to the field of neonatology for which previous data have been limited or nonexistent. The large sample size over a long study period at 190 centers allowed us to use an instrumental variable approach. Our analysis also benefited from the use of a BPD risk calculator to adjust for patient disease severity. We remained limited by the retrospective study design, and it is possible that our results were due to unmeasured confounders. Although we attempted to address this issue using a falsification end point, it is possible that potential confounders of the association between furosemide exposure and death may differ from those of the association between furosemide exposure and BPD. As noted, we also found a possible association between our instrumental variables and some important disease characteristics. We attempted to mitigate this association through secondary analyses and adjustment for these characteristics in our models. Finally, we did not examine the effects of other therapies on the incidence of BPD, including diuretics less commonly used in the neonatal intensive care unit (eg, chlorothiazide, bumetanide), caffeine, and the use of

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noninvasive ventilation. Genetic variation may also influence the efficacy of furosemide[42,43]; we were unable to explore such effects in our study.

In conclusion, we found that a higher percentage of days exposed to furosemide between postnatal day 7 and 36 weeks PMA in extremely premature infants was associated with a decreased risk of BPD and a combined outcome of BPD or death. These results provide important preliminary data to support the development of prospective studies to evaluate the safety and efficacy of furosemide for the prevention of BPD. ■

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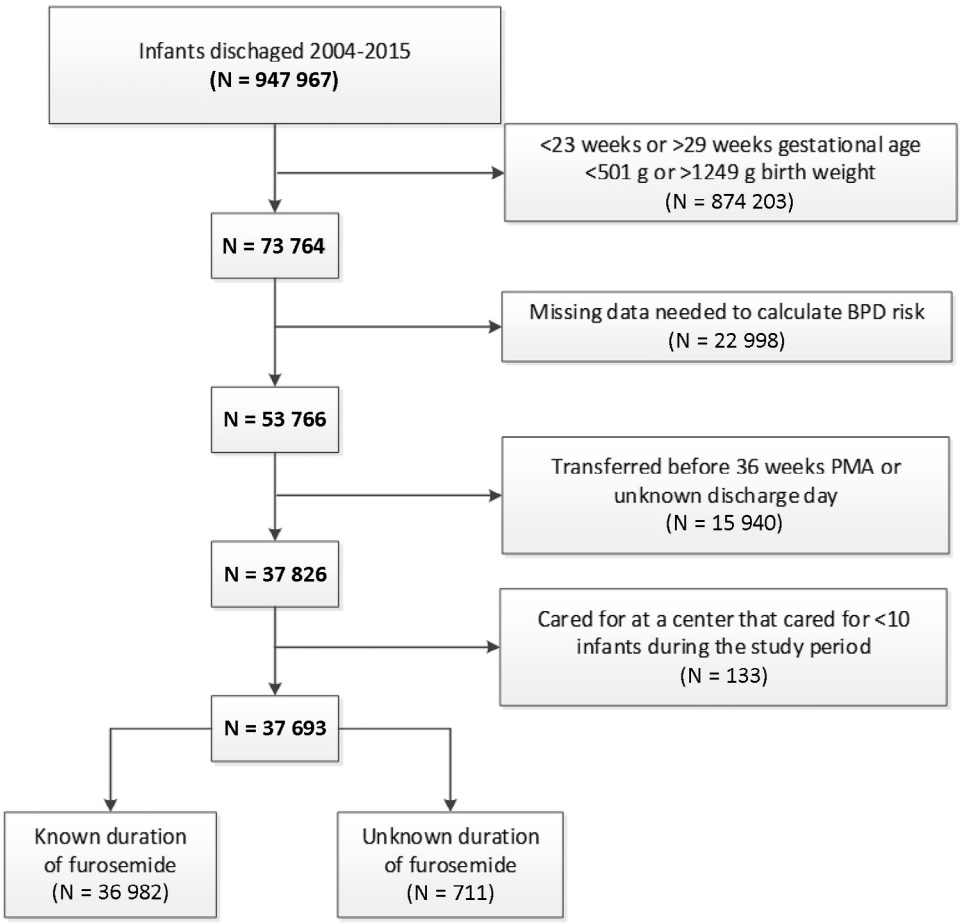

Figure 1. Study flow diagram of the study population, from initial cohort through exclusions.

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Table II. Distribution of infant demographics and clinical characteristics among quartiles of site instrumental variable

	Quartile of site instrumental variable			
	1 (n = 9253)	2 (n = 9293)	3 (n = 9191)	4 (n = 9245)
Median percentage of infants exposed to furosemide	2	5	7	14
Gestational age, weeks				
23-25	29	33	34	29
26-27	36	37	36	38
28-29	35	30	30	33
Birth weight, g				
501-749	28	31	33	29
750-999	40	40	40	41
1000-1249	32	29	27	30
Small for gestational age	14	14	15	14
Cesarean delivery	75	75	72	73
Prenatal steroids	83	81	79	77
Inborn	89	85	84	86
5-minute Apgar score				
0-3	6	6	7	6
4-6	24	23	25	23
7-10	70	71	68	71
Male	52	53	52	52
Race/ethnicity				
White	50	51	46	44
Black	30	26	32	33
Hispanic	20	23	21	23
Percentage risk of BPD/death on postnatal day 7*, median	43	53	52	52
Ventilator status on postnatal day 7				
High-frequency	13	17	17	16
Conventional	26	34	32	36
CPAP	35	30	26	27
Nasal cannula/ hood	22	16	20	17
None	5	4	4	4
Fractional inspired oxygen on postnatal day 7				
21%	55	50	50	49
22%-50%	42	46	47	47
51%-99%	2	3	3	3
100%	0.9	1.1	0.8	1.4
Received dexamethasone	17	20	18	19
Atrial septal defect or ventricular septal defect	6	9	6	9
Patent ductus arteriosus surgery	9	17	14	13
Median number of infants at site	67	157	226	124

CPAP, continuous positive airway pressure ventilation.
*Refers to estimated risk of BPD or death at postnatal day 7 according to a model developed by the National Institute of Child Health and Human Development Neonatal Research Network.[16,17]
Data are expressed as column percentages unless otherwise noted.

Table III. Distribution of infant demographics and clinical characteristics among quartiles of year instrumental variable

	Quartile of year instrumental variable			
	1 (n = 9478)	2 (n = 9157)	3 (n = 9144)	4 (n = 9203)
Median percentage of infants exposed to furosemide	5	7	9	12
Gestational age, weeks				
23-25	29	31	33	31
26-27	38	34	37	38
28-29	33	34	30	31
Birth weight, g				
500-749	29	30	32	32
750-999	40	39	41	41
1000-1249	31	31	28	28
Small for gestational age	14	14	14	15
Cesarean delivery	74	74	74	72
Prenatal steroids	84	82	77	76
Inborn	87	86	86	86
5-minute Apgar score				
0-3	8	7	6	5
4-6	24	24	24	22
7-10	68	69	69	73
Male	51	53	52	53
Race/ethnicity				
White	46	49	47	49
Black	31	31	31	28
Hispanic	22	20	22	23
Percentage risk of BPD/death on postnatal day 7*, median	44	47	53	55
Ventilator status on postnatal day 7				
High-frequency	15	16	17	14
Conventional	24	28	34	41
CPAP	44	31	23	19
Nasal cannula/ hood	14	20	22	20
None	3	4	5	6
Fractional inspired oxygen on postnatal day 7				
21%	57	56	49	42
22%-50%	41	42	47	53
51%-99%	2	2	3	4
100%	0.7	0.9	1.0	1.6
Received dexamethasone	16	17	19	21
Atrial septal defect or ventricular septal defect	10	8	7	6
Patent ductus arteriosus surgery	8	12	16	18

*Refers to estimated risk of BPD or death at postnatal day 7 according to a model developed by the National Institute of Child Health and Human Development Neonatal Research Network.[16,17]
Data are expressed as column percentages unless otherwise noted.

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