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Diuretic exposure in premature infants from 1997–2011

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Abstract

Objective—Diuretics are often prescribed off-label to premature infants, particularly to prevent or treat bronchopulmonary dysplasia (BPD). We examined their use and safety in this group.

Study Design—Retrospective cohort study of infants <32 weeks gestation and <1500 g birth weight exposed to diuretics in 333 neonatal intensive care units from 1997–2011. We examined use of acetazolamide, amiloride, bumetanide, chlorothiazide, diazoxide, ethacrynic acid, furosemide, hydrochlorothiazide, mannitol, metolazone, or spironolactone combination. Respiratory support and F_iO_2 on the first day of each course of diuretic use were identified.

Results—Thirty-seven percent (39,357/107,542) of infants were exposed to at least 1 diuretic; furosemide was the most commonly used (93% with ≥1 recorded dose), followed by spironolactone, chlorothiazide, hydrochlorothiazide, bumetanide, and acetazolamide. Seventy-four percent were exposed to 1 diuretic at a time, 19% to 2 diuretics simultaneously, and 6% to 3 diuretics simultaneously. The most common combination was furosemide/spironolactone, followed by furosemide/chlorothiazide and chlorothiazide/spironolactone. Many infants were not receiving mechanical ventilation on the first day of each new course of furosemide (47%), spironolactone (69%), chlorothiazide (61%), and hydrochlorothiazide (68%). Any adverse event occurred on 42 per 1000 infant-days for any diuretic and 35 per 1000 infant-days for furosemide. Any serious adverse event occurred in 3.8 for any diuretic and 3.2 per 1000 infant-days for furosemide. The most common laboratory abnormality associated with diuretic exposure was thrombocytopenia.

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Conclusion—Despite no FDA indication and little safety data, over one third of premature infants in our population were exposed to a diuretic, many with minimal respiratory support.

Keywords

bronchopulmonary dysplasia; diuretic; safety; drug

Premature infants in the neonatal intensive care unit (NICU) are frequently exposed to diuretics presumably to treat or prevent bronchopulmonary dysplasia (BPD).[1,2] BPD is the most common pulmonary morbidity of prematurity; it is caused by prolonged mechanical ventilation and exposure to oxygen, and the strongest risk factor is prematurity.[3,4] Because BPD is associated with serious long-term consequences, including neurodevelopmental impairment,[5] neonatologists use drugs such as diuretics in an attempt to reduce the incidence of BPD or improve BPD symptoms.

The rationale for diuretic use is based on the physiology of premature infants in the first postnatal weeks. Failure to lose weight, usually due an excessive administration of fluid and/or sodium, during that time is associated with an increased risk of BPD.[6,7] Because premature infants are born with an abundance of extracellular fluid (including both free water and sodium), neonatologists use diuretics to potentiate the naturally occurring weight loss. This rationale extends beyond the first postnatal weeks to chronic administration (>1 month) of diuretics to decrease pulmonary edema and improve lung compliance and oxygenation.[1,2] This approach may reduce exposure to mechanical ventilation and the incidence of BPD. However, no diuretic is FDA-approved to prevent or treat BPD in premature infants. Cochrane reviews on loop and distal renal tubule diuretics demonstrate short-term (usually <1 week) improvement of pulmonary mechanics and oxygenation.[1,2] Unfortunately, none of the available studies demonstrated improvements in BPD, duration of mechanical ventilation, or hospital stay.[1,2]

Given the known risks and potential benefits of diuretics, we sought to describe the current use of diuretics in this population. Identifying and describing the most commonly used diuretics may be helpful to determine potential trial targets. We examined premature infant exposure to common diuretics, the respiratory support that premature infants received at the time of diuretic use, and the safety of diuretics in premature infants.

Methods

Study design and setting

We performed a retrospective cohort study of infants <32 weeks gestational age (GA) and <1500 g birth weight discharged from one of 333 NICUs managed by the Pediatrix Medical Group between 1997 and 2011 who were exposed to at least 1 diuretic of interest (acetazolamide, amiloride, bumetanide, chlorothiazide, diazoxide, ethacrynic acid, furosemide, hydrochlorothiazide, mannitol, metolazone, spironolactone). The dose of medications is not consistently recorded in the database. We collected demographic data, discharge data, laboratory values, and respiratory support information. The study was approved by the Duke University Institutional Review Board.

Definitions

We used counts and proportions to describe diuretic use by 3 different methods. We defined exposure as any exposure to a unique diuretic for each infant. We defined diuretic course as the number of times an infant was exposed to a unique diuretic. To be counted as a new course, each diuretic exposure had to be separated from the prior exposure to the same diuretic in the same infant by >1 day. We defined days of exposure as the number of days each unique diuretic was administered to each infant. We defined a simultaneous diuretic combination as 2 diuretics reported on the same day at least once for each infant and total number of days of simultaneous diuretic exposure.

We identified the level of respiratory support provided on the start day of each new diuretic course. Respiratory support was classified as the highest level of support required by an infant on a given day: room air only, nasal cannula, high-flow nasal cannula/nasal continuous positive airway pressure, conventional mechanical ventilation, and high-frequency mechanical ventilation. We also report the highest daily fraction of inspired oxygen (F_iO_2) received on the start day of each new diuretic course.

Available laboratory information was collected while infants were exposed to diuretics. A laboratory value was included in this report if it occurred between the start of exposure through the end of exposure to a diuretic. Laboratory abnormalities were classified as an adverse event (AE) or serious adverse event (SAE) based on pre-specified cut-off values.[8]We defined renal stones as an AE if a diagnosis of nephrocalcinosis or nephrolithiasis was made after the first exposure to any diuretic, even if the diuretic was discontinued. We examined outcomes for all diuretics and for those infants exposed to furosemide, because it was by far the most common diuretic used. Because hearing tests were not consistently recorded in the database, we did not examine the association between diuretic exposure and hearing loss.

Statistical analysis

Standard summary statistics were used to describe demographic characteristics; continuous variables are presented as median (25^{th} and 75^{th} percentiles), and categorical variables are presented as counts (proportions). Laboratory AEs and SAEs were described at the infant day level (number of days with abnormal laboratory values/1000 infant days exposed to diuretics). The proportion of infants exposed to diuretics over time was calculated by dividing the number of infants exposed to diuretics by the total number of infants discharged from the Pediatrix Medical Group in the same year. The proportion of infants exposed to diuretics by GA is calculated by dividing the number of infants exposed to diuretics by the total number of infants of the same GA. The proportion of infants exposed to diuretics by NICU is calculated by dividing the number of infants exposed to diuretics by the total number of infants discharged from each NICU during the study period. Note that only NICUs with an average of >10 very low birth weight infant discharges per year were included in the analysis of diuretic usage by site. All statistical analyses were performed in STATA 12.0 (College Station, TX).

Results

We identified 107,542 infants meeting birth weight and GA criteria between 1997 and 2011. Of these, 39,357 (37%) infants were exposed to at least 1 diuretic (Table 1). Exposed infants had a lower median GA (27 weeks [25th, 75th% -tile; 25, 28] vs. 29 weeks [27, 30], p<0.001) and lower median birth weight (870 g [700, 1085] vs. 1115 g [865, 1310], p<0.001) compared with infants not exposed. Of the infants exposed to diuretics, 25,975 (66%) were extremely low birth weight (<1000 g birth weight). The median length of diuretic exposure was 6 days (2, 24 days). The median postnatal day that the first course of diuretics was started was 18 (9, 33). Among those infants exposed to a diuretic, the majority were exposed for <28 days (30,528; 78%). The use of diuretics increased from 29% of infants in 1997 to 39% in 2005 (Fig. 1) and remained relatively stable after that time (36% in 2011). The median diuretic exposure by site was 33%, ranging from 0–75% (Fig. 2).

Of the 39,357 infants exposed to at least 1 diuretic during their stay, furosemide was the most commonly used, with 36,759 (93%) of infants with at least 1 recorded dose (Table 2). Furosemide also represented the most frequent number of courses (784 per 1000 infants) and days of use (66 per 1000 infant days). The next most commonly used diuretics were spironolactone, chlorothiazide, hydrochlorothiazide, bumetanide, and acetazolamide (Table 2). Of the infants exposed to a diuretic, 29,144 (74%) were exposed to 1 diuretic at a time; 7576 (19%) were exposed to 2 different diuretics simultaneously; 2554 (6%) were exposed to 3 diuretics simultaneously; and 83 (0.2%) were exposed to 4 or more diuretics simultaneously. The most common combination of diuretics was furosemide + spironolactone (40 per 1000 infants, Table 3), followed by furosemide + chlorothiazide (36 per 1000 infants), then chlorothiazide + spironolactone (36 per 1000 infants).

Overall, the majority of infants were receiving some form of respiratory support on the first day of diuretic therapy. Many infants were not receiving mechanical ventilation on the first day of each new diuretic course for the most commonly used diuretics (Table 4). However, only 8% of infants exposed to bumetanide were not receiving mechanical ventilation. The median F_iO_2 on the first day of a new course of diuretics was similar across most drugs, but was highest for bumetanide at 0.45 (0.30, 0.75).

AEs occurred on 42 per 1000 infant days for any diuretic and 35 per 1000 infant days for furosemide. SAEs occurred on 3.8 per 1000 infant days for any diuretic and 3.2 per 1000 infant days for furosemide (Table 5). The most common laboratory abnormality associated with diuretic exposure was thrombocytopenia. The most common electrolyte abnormality noted was hyperkalemia: the AE level was 12.7 per 1000 infant days for any diuretic and 8.3 per 1000 infant days for furosemide; the SAE level was 1.6 and 1.2 per 1000 infant days, respectively. We found that elevated blood urea nitrogen occurred on 3.7 and 3.1 per 1000 infant days for any diuretic and for furosemide, respectively; an elevated creatinine was observed on 5.4 and 4.3 per 1000 infant days for any diuretic and for furosemide, respectively. Markers of liver damage (aspartate aminotransferase/alanine aminotransferase [AST/ALT]) were rarely increased, while elevated direct bilirubin (9.9 per 1000 infant days for any diuretic and 6.6 per 1000 infant days for furosemide) was more frequently noted. Renal stones were reported in 1.0% of infants exposed to any diuretic and most commonly

in infants exposed to acetazolamide (39/1131; 3.5%), followed by hydrochlorothiazide (74/2326; 3.2%).

Discussion

Neonatologists frequently expose premature infants to diuretics without evidence of long-term benefits. We found that over one third of premature infants <32 weeks gestation at birth and <1500 g birth weight received diuretic therapy during their hospital stay, often for more than a month. Furosemide was by far the most commonly used diuretic in this population, followed by spironolactone and chlorothiazide. These findings are consistent with previous research.[9] The majority of infants receive only 1 type of diuretic during their admission; however, nearly a third received combination therapy with 2 or more diuretics. The majority of diuretic use was likely designed to reduce the risk of BPD or treat BPD symptoms.

BPD is associated with early pulmonary edema localized to the alveoli and interstitium.[10,11] Diuretics improve this edema by removing excess fluid, allowing for improved gas exchange and decreased respiratory support requirements.[12] Because mechanical ventilation is a strong risk factor for BPD, improving pulmonary mechanics theoretically would result in decreased incidence of BPD. Despite the sound physiologic rationale behind the use of diuretics in preventing BPD and evidence to demonstrate short-term improvement, evidence for long-term benefits, such as prevention of BPD, is lacking.[1,2,12] In addition, it is uncertain which subgroup of premature infants (e.g., what GA or level of respiratory support) might benefit from exposure to diuretics.

The search for therapeutics to treat or prevent BPD has been extensive but with limited success. There are no FDA-indicated therapies that prevent BPD or are available to treat BPD symptoms. To date, only vitamin A and caffeine prevent BPD without known significant long-term AEs.[13,14] Postnatal steroids reduce BPD but may increase the risk of cerebral palsy.[15] Although inhaled nitric oxide is beneficial in term infants with hypoxic respiratory failure, the majority of studies demonstrate that it does not prevent BPD in premature infants, although there was a great deal of heterogeneity in the patient populations, dose, and duration of inhaled nitric oxide.[16] Currently, a study in premature infants that emulates the largest successful trial of inhaled nitric oxide[17] has completed recruitment; data analysis is ongoing (clinicaltrials.gov NCT00931632). One problem with the vast majority of trials of drugs to prevent BPD is that they did not establish the pharmacokinetics, pharmacodynamics, or dose prior to implementation of phase III, randomized, controlled trials.[18]

Diuretics are used in the NICU “off-label,” meaning that there is no FDA indication for use in infants. The use of off-label medications is associated with increased risk of AEs, particularly in sick hospitalized infants.[19–22] Neonatal medicine’s history is plagued with examples of SAEs with inadequate study and approval before widespread implementation of therapies.[23–26] While more evidence is required for safe use of diuretics in neonates, trials in this population are difficult. Vulnerable populations (e.g., premature neonates) have an especially low parental consent rate.[27] Randomized controlled trials, while the gold standard

for new drugs, are expensive and time consuming, making it challenging to find support for therapeutics, such as diuretics, that are off-patent generic drugs. Many pediatricians are very familiar with using medications off-label due to limited data and rely heavily on their personal clinical experience.[28,29] Clinical experience bias may further limit the willingness of physicians to withhold or limit diuretics for premature infants at risk for BPD, as in the placebo group in a prospective trial.

We found that exposure of premature infants to diuretics varied widely across sites, which is consistent with previous research demonstrating that a range of 4–86% of infants with BPD receiving a >5 day course of diuretics, depending on the center.[9] In some centers, we found that the exposure was very high, suggesting that diuretics are used prophylactically, presumably to prevent BPD. Conversely, in other centers, exposure was rare. These observations suggest that there is no universally accepted standard of care for when to expose infants to diuretics and that no exposure is an option exercised in some centers.

The strengths of this study include the large sample size. This cohort includes data on infants from 333 NICUs across North America, including both academic and community sites, allowing these results to be generalizable to many institutions as well as a wide range of NICU populations. However, the study was limited by the lack of indication for the diuretic exposure. Thus, clinicians may have, and likely did, use diuretics for a variety of indications, including attempting to reduce F_iO_2 for infants on a low amount of oxygen (e.g., an infant receiving 0.1 L/min of 100% F_iO_2 a week or two prior to anticipated discharge), post-operative fluid changes, following blood product administration, or renal insufficiency. In addition, laboratory values were not obtained uniformly, thus sicker infants—who presumably may have more laboratory draws—may have contributed more data to these values. Finally, AEs and SAEs reported were not necessarily caused by diuretic use. These premature infants have multiple other physiologic derangements that may have led to these observations.

While there are many challenges—including common use, low consent rates, and other aspects of study design—further studies must be conducted to ensure that diuretics are safe and effective in premature infants.

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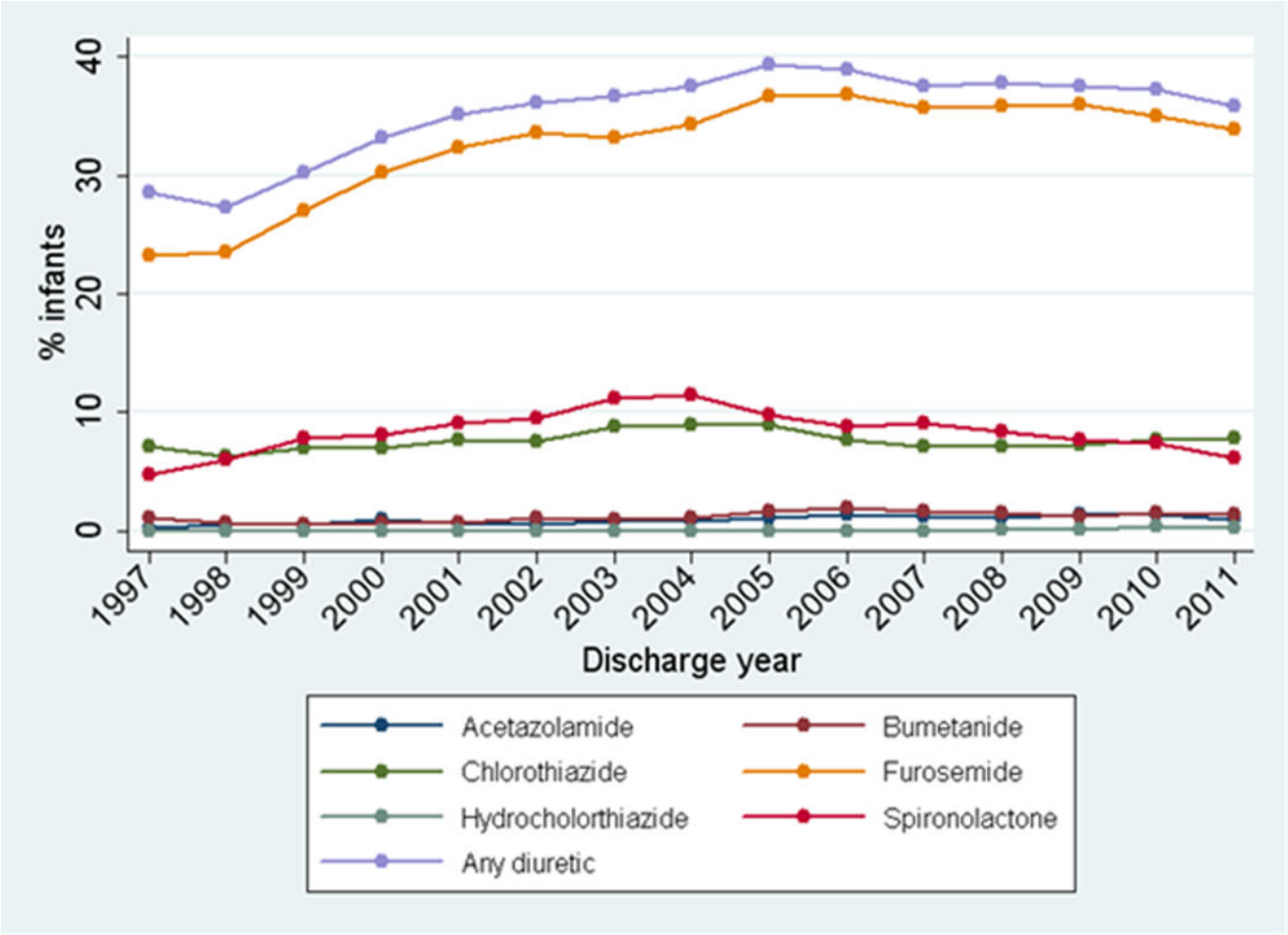

Figure 1.
Percentage of infants <32 weeks and <1500 g exposed to diuretics over time.

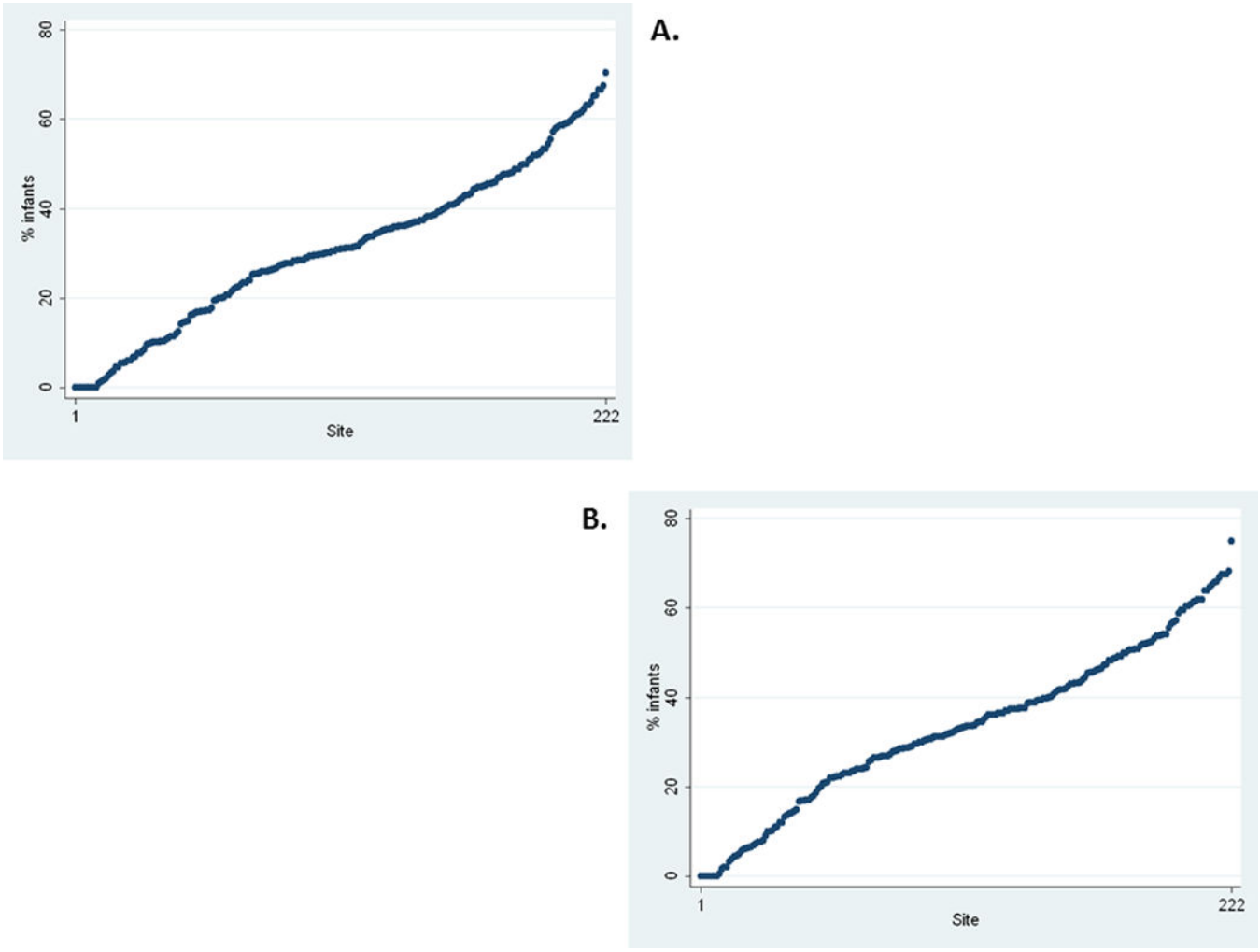

Figure 2.

Percentage of infants <32 weeks and <1500 g exposed to (A) furosemide and (B) any diuretic by site.

Table 1

Demographics, N (%, column percent)

	Exposed	Not exposed	All	P
	39,357	**68,185**	**107,542**	
Gestational age (weeks)				<0.001
<23	150 (<1)	498 (1)	648 (1)	
23–24	6697 (17)	6441 (10)	13,138 (12)	
25–26	12,537 (32)	9523 (14)	22,060 (21)	
27–28	11,892 (30)	17,346 (25)	29,238 (27)	
29–30	6728 (17)	24,501 (36)	31,229 (29)	
31–32	1353 (3)	9876 (15)	11,229 (10)	
Birth weight (g)				<0.001
<1000	25,975 (66)	25,371 (37)	51,196 (48)	
1000–1500	13,382 (34)	42,814 (63)	56,196 (52)	
Antenatal steroids	29,207 (74)	50,023 (73)	79,230 (74)	0.002
Male sex	21,821 (56)	33,752 (50)	55,573 (52)	<0.001
Race/ethnicity				<0.001
White	17,848 (47)	31,456 (48)	49,304 (48)	
Black	10,504 (28)	17,310 (26)	27,814 (27)	
Hispanic	8045 (21)	13,143 (20)	21,188 (20)	
Other	1767 (5)	3632 (6)	5399 (5)	

Table 2

Infants <32 Weeks and <1500 g Exposed to Diuretics by Type

Diuretic*	N (%)† Total N=39,357	Exposure‡	Courses‡	Days of exposure§
Furosemide	36,759 (93)	342	784	66
Spironolactone	9577 (24)	86	109	3
Chlorothiazide	8309 (21)	77	98	29
Hydrochlorothiazide	2473 (6)	22	26	7
Bumetanide	1443 (4)	13	17	2
Acetazolamide	1131 (3)	11	18	2

*Metolazone (n=147), hydrochlorothiazide/spironolactone (n=87), diazoxide (n=64), ethacrynic acid (n=61), mannitol (n=8), and amiloride (n=3) exposures were minimal.

†Infants could be exposed to more than 1 diuretic.

‡Per 1000 infants (all infants).

§Per 1000 infant days (all infants).

Table 3

Top 10 Simultaneous Diuretic Combinations in Infants <32 Weeks and <1500 g

Rank	Diuretic combination	Exposure*	Days of simultaneous exposure†
1	Chlorothiazide + spironolactone	36	12
2	Hydrochlorothiazide+ spironolactone	13	4.4
3	Furosemide + spironolactone	40	2.9
4	Furosemide + chlorothiazide	36	2.6
5	Furosemide + hydrochlorothiazide	11	0.9
6	Furosemide + bumetanide	8	0.6
7	Furosemide + acetazolamide	5	0.8
8	Acetazolamide + spironolactone	2	0.3
9	Chlorothiazide + acetazolamide	1	0.1
10	Hydrochlorothiazide + acetazolamide	0.7	0.1

*For at least one day, per 1000 infants (all infants).

†Per 1000 infant days (all infants).

Table 4

Respiratory Support on First Day of Each New Diuretic Course in Infants <32 Weeks and <1500 g, row percents

	No support	Nasal cannula	HFNC/ NCPAP	Mechanical ventilation	High-frequency ventilation	F_iO_2
	n (%)	n (%)	n (%)	n (%)	n (%)	Median, IQR
Furosemide	4886 (6)	12,935 (15)	21,324 (25)	32,811 (39)	12,053 (14)	35 (25, 50)
Spironolactone	626 (5)	3336 (29)	4073 (35)	3122 (27)	460 (4)	35 (27, 50)
Chlorothiazide	463 (4)	2867 (27)	3151 (30)	3418 (33)	613 (6)	36 (28, 50)
Hydrochlorothiazide	147 (5)	732 (27)	984 (36)	751 (27)	130 (5)	35 (26, 49)
Bumetanide	18 (1)	43 (2)	98 (5)	853 (47)	813 (45)	45 (30, 75)
Acetazolamide	40 (2)	178 (9)	636 (33)	917 (48)	153 (8)	35 (27, 48)

Abbreviations: HFNC, high-flow nasal cannula; NCPAP, nasal continuous positive airway pressure; IQR, interquartile range.

Table 5

Laboratory AEs and SAEs, per 1000 Infant Days, While Exposed to Any Diuretic and Furosemide in Infants <32 Weeks and <1500 g

	AE*			SAE*		
		Any diuretic	Furosemide		Any diuretic	Furosemide
Electrolytes						
Hyperglycemia	*> 250 mg/dL*	0.8	0.7	*> 400 mg/dL*	0.1	0.1
Hypoglycemia	*< 40 mg/dL*	2.1	1.8	*< 20 mg/dL*	0.4	0.3
Hypernatremia	*> 150 mmol/L*	2.2	1.8	*> 160 mmol/L*	0.2	0.2
Hyponatremia	*< 125 mmol/L*	2.9	1.8	*< 115 mmol/L*	0.1	0.1
Hyperkalemia	*> 6 mmol/L*	12.7	8.3	*> 7.5 mmol/L*	1.6	1.2
Hypokalemia	*< 3 mmol/L*	5.8	3.9	*< 2.5 mmol/L*	1.1	0.8
Hypocalcemia	*< 6mg/dL*	4.3	4.2	*<5 mg/dL*	4.2	2.4
Hypercalcemia	*> 12.5 mg/dL*	0.7	0.7	*> 13.5 mg/dL*	0.3	0.2
Hypophosphotemia	*<3.5 mg/dL*	6.2	5.2	*2.5 mg/dL*	1.7	1.5
Hyperphosphotemia	*> 9.5 mg/dL*	0.3	0.2	*> 10.5 mg/dL*	0.1	0.1
Renal dysfunction						
Elevated BUN	*> 70 mg/dL*	3.7	3.1	*> 100 mg/dL*	1.0	0.8
Elevated creatinine	*> 1.7 mg/dL*	5.4	4.3	*> 3.0 mg/dL*	1.0	0.8
Liver dysfunction						
Elevated AST	*>500 U/L*	0.1	0.1	*> 1000 U/L*	<0.1	<0.1
Elevated ALT	*> 500 U/L*	0.4	0.2	*> 1000 U/L*	<0.1	<0.1
Elevated GGT	*> 100 U/L*	4.0	2.4	*> 200 U/L*	1.8	1
Direct bilirubin	*> 5 mg/dL*	9.9	6.6	*>10 mg/dL*	2.6	1.8
Blood counts						
Leukocytosis	*> 25,000/mm^3*	13.4	11.2	*> 40,000/mm^3*	2.4	2.1
Leukopenia	*< 5000/mm^3*	5.6	4.8	*< 2000/mm^3*	0.4	0.3
Thrombocytopenia	*< 100,000/mm^3*	41.9	34.7	*< 30,000/mm^3*	3.8	3.2

		AE*			SAE*	
		Any diuretic	Furosemide		Any diuretic	Furosemide
Thrombocytosis	> *600,000/mm*^{3}	3.2	1.6	> *1,000,000/mm*^{3}	<0.1	<0.1

*Per 1000 infant days.

Abbreviations: BUN, blood urea nitrogen; GGT, gamma-glutamyl transpeptidase.