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Association between postmenstrual age and furosemide dosing practices in very preterm infants

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Abstract

Objective: Furosemide renal clearance is slow after very preterm (VP) birth and increases with postnatal maturation. We compared furosemide dose frequency and total daily dose between postmenstrual age (PMA) groups in VP infants.

Study Design: Observational cohort study of VP infants exposed to a repeated-dose course of furosemide in Pediatrix neonatal intensive care units (NICU) from 1997 to 2016.

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Results: We identified 6565 furosemide courses among 4638 infants. There were no statistically significant differences between PMA groups on the odds of receiving more frequent furosemide dosing. Furosemide courses initiated at < 28 weeks PMA were associated with a higher total daily dose than those initiated at a later PMA.

Conclusions: Furosemide dosing practices in the NICU are similar across PMA groups, despite maturational changes in drug disposition. Research is needed to identify and test rational dosing strategies across the PMA spectrum for this commonly used but unproven pharmacotherapy.

Introduction

Furosemide use is common in neonatal medicine. Between 2005 and 2010, furosemide rose from the ninth to the sixth most frequently prescribed medication in Pediatrix Medical Group neonatal intensive care units (NICU).(1–3) Use is particularly common in preterm infants with established severe bronchopulmonary dysplasia (BPD) beyond 36 weeks postmenstrual age (PMA). In this older preterm population, furosemide is the most common pharmacotherapy in United States children's hospitals.(4)

Furosemide clearance depends on renal maturation. Pharmacokinetic studies in the 1980s identified slow furosemide clearance in very preterm infants, with elimination half-lives in excess of 24 hours among infants of PMA < 32 weeks.(5–7) These findings are reflected in the US Food and Drug Administration (FDA) label recommendation, which states the maximum intravenous furosemide dose in preterm infants should not exceed 1 milligram per kilogram per day (mg/kg/d) to avoid potentially toxic drug accumulation.(8) However, studies report a rapid increase in clearance and decrease in elimination half-life in preterm infants beyond 32 weeks PMA. This change is attributed to the maturation of renal tubular secretion driving renal clearance and furosemide elimination.(5,6) These developmental changes suggest a lower risk of drug accumulation with more frequent dosing in older preterm infants. Further, once daily dosing in older subjects may result in prolonged periods of subtherapeutic furosemide concentrations, facilitating rebound sodium and water retention between dose administrations.(9)

It is unknown if neonatal providers change their furosemide dosing practices with increasing PMA to account for these developmental changes in renal clearance. A recent descriptive study of infants discharged from Pediatrix Medical Group NICUs identified 1 mg/kg/d as the predominant intravenous dosing approach, consistent with the FDA label recommendation.(8,10) Differences in dosing as a function of PMA were not described. The objective of this study was to compare furosemide dosing practices across PMA groups in very preterm infants. Our primary outcome was dose frequency; we hypothesized this would be similar across PMA groups, suggesting these prior findings have limited influence on observed clinical practice. Our secondary outcome was cumulative daily dose; we again hypothesized similar dosing across PMA groups.

Methods

Study Design, Data Source & Study Population

We performed a cohort study and followed STROBE reporting guidelines.(11) Our data source was the Pediatrix Medical Group Clinical Data Warehouse. This database contains prospectively collected demographic and clinical data generated by clinicians and captured through integration with the electronic health record.(12) Approximately 20% of infants admitted to a NICU in the United States are represented in the database.(13) We included very preterm (gestational age (GA) < 32 weeks) infants discharged alive or deceased from NICUs managed by the Pediatrix Medical Group from 1997 to 2016 and prescribed a repeated-dose course of furosemide between admission and discharge. We excluded infants only prescribed single-dose or as needed furosemide, those with incomplete dosing data (e.g., missing route of administration, end date, or dose) and those receiving > 9 mg/kg/dose, as these were outlying values at risk of being reporting errors.(10) This was a convenience cohort without formal sample size calculation. This study was considered exempt from human subject research approval by the Duke University Institutional Review Board.

Variables

The primary predictor variable was PMA in completed weeks at the initiation of the furosemide course. We applied PMA as a categorical variable with 5 groups: <28, 28–31 6/7, 32–35 6/7, 36–39 6/7, and ≥ 40 weeks. We chose to assess PMA as a categorical rather than a continuous variable to facilitate between-group comparisons. Specific groupings reflect the prior identification of 32 weeks PMA as a time-point coinciding with the lower inflection point of rapidly increasing furosemide renal clearance, 36 weeks PMA as the time point when BPD is commonly classified, and an effort to balance the number of weeks among the PMA groups.(5,14,15) The decision to collapse all PMA values below 28 and above 40 weeks PMA reflects the expected distribution of PMA at furosemide initiation across the cohort, and a desire to limit the overall number of comparisons.

A repeated-dose furosemide course was defined as more than one administration with consistent weight-based dose, route of administration and frequency. A change in any of these dosing parameters was classified as a new, distinct furosemide course. For example, an infant exposed to a consistent dose and route of administration of furosemide every 24 hours, and then exposed to the same dose and route of administration every 12 hours contributed two distinct furosemide courses, with the second course initiated at the time of the dose frequency change. We focused on the PMA at course initiation (versus midpoint or cessation) as this reflects the infant's developmental maturity when the dosage practice decision was made by the prescriber.

The primary outcome was furosemide dose frequency. We assessed dose frequency as a categorical variable with 5 groups: every 6 hours, every 8 hours, every 12 hours (q12h), every 24 hours (q24h) and every 48 hours. We chose these specific values based on preliminary data from a broader neonatal cohort showing these frequencies made up > 99% of all prescribed courses.(10) We then dichotomized dose frequency groups into q12h or more frequent vs q24h or less frequent, as values other than q12h or q24h contributed

fewer than 10% of all courses in the cohort. Our secondary outcome was total daily dose, assessed for each course, as a continuous variable with units of mg/kg/d. Doses were rounded to the nearest 0.5 mg/kg/d value, and reported as intravenous-equivalent doses, assuming a bioavailability of 50% for enteral formulations, such that a 2 mg/kg enteral dose was reported as a 1 mg/kg intravenous equivalent.(8,16)

We identified candidate covariates that were plausibly associated with both the PMA at furosemide prescription and provider dosing decisions. All covariates were ascertained at the initiation of the furosemide course. These were postnatal age in days, exposure to furosemide in the seven days preceding the course, route of administration, and type of respiratory support as a surrogate measure of lung disease severity. We considered postnatal age because renal function matures with both PMA and postnatal age, and furosemide use may be guarded in the immediate postnatal period when renal function and furosemide clearance is most compromised.(17) For example, furosemide use may be less frequent in a 1 day old infant born at 29 and 6/7 weeks GA than in a 6 week infant born at 24 weeks GA, despite an equivalent PMA of 30 weeks. We described postnatal age as both a continuous variable and as a dichotomous variable comprised of 0–3 days vs greater than 3 days, using the dichotomous variable for multivariable models. Three days reflects the typical postnatal age associated with improving renal function in preterm infants(18,19). We considered prior exposure to furosemide in the seven days preceding the course as furosemide diuresis may be subject to tolerance, such that greater effective drug concentrations are required to achieve the same diuretic response over time with sustained treatment.(20) As such, dosage selection for a new course, which would include a change in dose or frequency as defined in our methods, may be greater following recent furosemide exposure in an effort to compensate for the evolution of tolerance. We considered route of administration as enteral administrations likely increase with PMA as feed volumes increase and intravenous lines become less common, while more frequent dose intervals during intravenous administration may be discouraged by quality improvement efforts to limit the frequency of line accesses and risk for infection. Lastly, neonatal lung disease tends to improve with increasing PMA, and furosemide dosage practices may be influenced by the severity of lung disease motivating its use, with greater use in infants requiring higher levels of support. We reported respiratory support as a categorical variable with values of none, non-invasive and invasive, the latter reflecting tracheal intubation and mechanical ventilation of any type.

Statistical Analyses

We described cohort variables with summary statistics, such as counts (percentages) and medians [interquartile range (IQR)]. Logistic regression with cluster-robust variance estimates to account for multiple courses within the same subject were used for both unadjusted bivariable and adjusted multivariable statistical analyses. We first examined the unadjusted association between PMA and dose frequency. We then performed analogous bivariable analyses for each candidate covariate and the outcome of dose frequency, including characteristics associated with the outcome at $p < 0.10$ as covariates in a multivariable model testing the adjusted association between PMA and dose frequency. We used an analogous statistical approach for the secondary outcome of total daily dose but applying a linear regression model. To facilitate clinical interpretation, estimates of the

association between predictor variables and total daily dose were reported as post-estimation marginal means. We considered the unadjusted analysis after accounting for within-subject clustering to be our primary analysis, under the rationale that while included covariates may help explain provider dosage decisions, they do not obviate the developmental changes in furosemide pharmacology that influence drug disposition and motivate our study. For example, while greater severity of lung disease at a younger PMA may help explain more frequent furosemide use during these developmental periods, it does not directly alter the rate of furosemide clearance and potential appropriateness of less frequent dosing in younger preterm infants. We therefore presented adjusted multivariable models as secondary analyses exploring explanatory factors. In consideration of the 20 year study period, we conducted a post-hoc sensitivity analysis to assess whether the association between PMA and our primary outcome of dose frequency varied across two time period strata: 1997–2006 and 2007–2016. We considered $p < 0.05$ to be statistically significant throughout without adjustment for multiple comparisons. All analyses were performed with Stata 16 (StataCorp, College Station, Texas, USA).

Results

A total of 1,249,466 infants were admitted to one of 392 participating NICUs during the study period. A total of 200,611 (16%) infants were <32 weeks. Of these, 38,183 (19%) received at least one dose of furosemide and 10,868 (28%) had complete dosing data. Our final cohort included 4,638 very preterm infants from 185 NICUs who received at least one qualifying multiple-dose furosemide course. The infants had a median birth GA of 27 weeks, a median birth weight of 915 grams, and were predominantly exposed to a single course of furosemide (Table 1).

The 4,638 infants contributed a total of 6565 furosemide courses. Dosing practices as a function of PMA at course initiation are summarized in Table 2. Dose frequencies of q12h or more frequent (45% of courses) and q24h or less frequent (55% of courses) were both common. The dose frequency distribution was similar across PMA groups, with q12h or more frequent dosing present in a narrow range of 52% to 56% across all five PMA groups. The median intravenous dose was 1 mg/kg, as were both values describing the interquartile range. The median enteral dose, unadjusted for a presumed bioavailability of 50%, was 1.5 mg/kg, with an interquartile range of 1 to 2 mg/kg. The median (intravenous equivalent) total daily dose was 1 mg/kg/d, though an exposure of 2 mg/kg/d or greater occurred in >25% of courses. The median value for total daily dose (1 mg/kg/day) was the same in all 5 groups, with an interquartile range of 1 to 2 mg/kg/day for all groups except 32 – 35 6/7 weeks PMA, in which a range of 0.5 to 1.5 mg/kg/day was identified.

Covariates characteristics as a function of PMA at course initiation are summarized in Table 3. There were large differences in the proportion of courses administered enterally between the PMA groups, ranging from 16% at < 28 weeks to 70% in the 36–39 6/7 weeks PMA group. Similarly, furosemide was initiated during invasive respiratory support in 90% of courses at < 28 weeks versus 19% of courses in the 36–39 6/7 weeks PMA group.

For our primary analysis, there were no statistically significant differences between PMA groups on the odds of receiving more frequent furosemide after adjusting for within-subject clustering. Point estimates suggested slightly lower odds of receiving more frequent dosing in higher PMA groups compared to < 28 weeks PMA as the reference group (Table 4). This finding was consistent when assessed for 1997–2006 versus 2007–2016 in separate strata (Table SA1). For the outcome of furosemide total daily dose, courses initiated at < 28 weeks PMA weeks were associated with higher mean values compared to all groups except > 40 weeks PMA after adjusting for within-subject clustering.

In explanatory analyses, the odds of receiving more frequent furosemide dosing was slightly higher for all PMA groups relative to < 28 weeks PMA, with the differences reaching statistical significance for the 32 – 35 6/7 and 36 – 39 6/7 weeks PMA groups (Table 5). Furosemide exposure in the 7 days preceding the course and enteral route of administration were associated with significantly lower odds of receiving more frequent furosemide dosing in multivariable modeling. For the outcome of furosemide total daily dose, courses initiated at < 28 weeks PMA were associated with lower mean total daily doses compared to courses initiated at 36 – 39 6/7 weeks and > 40 weeks PMA, with no statistically significant difference noted between <28 weeks PMA and the remaining two groups. Enteral route of administration was associated with a statistically significant lower total daily dose compared to intravenous administration, while non-invasive and invasive respiratory support were associated with greater total daily doses compared to no respiratory support.

Discussion

The objective of this study was to compare furosemide dosing practices across PMA groups in very preterm infants. We found that furosemide dosing frequency was similar across PMA groups. In turn, total daily dose differed modestly across groups, with slightly higher values in the youngest (< 28 weeks) and oldest (> 40 weeks) PMA groups.

Our study was motivated by prior research describing maturational changes in furosemide clearance following preterm birth. These suggest the elimination half-life of furosemide may exceed 24 hours in preterm infants prior to 32 weeks PMA, but shortens beyond this developmental window as renal tubular secretion, the primary mechanism of renal clearance and furosemide elimination, matures.(5–7) In a longitudinal study evaluating changes in furosemide pharmacokinetics in 10 very low birth weight infants over 3 months, the elimination half-life was estimated to decline to 4 hours by term corrected age.(5) Among NICU populations, this is particularly relevant to infants with established severe BPD, who are older than 36 weeks PMA by definition and for whom furosemide is the most common pharmacotherapy.(4,14) Once daily dosing in this population may led to prolonged periods of subtherapeutic furosemide concentrations between dose administrations, challenging efforts to minimize edema by facilitating rebound sodium and water retention between dose administrations.(9) We did not find an association between increasing PMA and more frequent dosing, and paradoxically observed the highest mean total daily dose in the least mature PMA group.

We speculate that disease severity may have a greater influence on furosemide dosing practices than maturation. In contrast to our primary analysis, our secondary explanatory analysis identified statistically significant greater odds of more frequent furosemide dosing at 32 – 35 6/7 and 36 – 39 6/7 weeks PMA compared to < 28 weeks PMA following multivariable adjustment, with point estimates in the opposite direction of those observed in our primary analysis. Similarly, the 36 – 39 6/7 weeks PMA group had a statistically significant higher mean total daily dose compared to the < 28 weeks PMA group following multivariable adjustment, again with a reversal in the direction of the point estimate observed in the primary analysis. Our interpretation of these findings is that while dosage practices are similar between PMA groups (Table 2), the 36 – 39 6/7 group is observed to receive greater than expected furosemide after adjusting for between-group differences in covariates reflecting disease severity. As summarized in Table 3, the 36 – 39 6/7 PMA group had the lowest proportion of courses initiated through intravenous administration and during invasive mechanical ventilation, suggesting greater clinical stability in this group. The strong association between enteral route of administration and both less frequent furosemide use and lower total daily dose suggests this variable may act as a surrogate of clinical stability. Though degree of respiratory support was less strongly associated with both furosemide dose frequency and total daily dose compared to route of administration, a statistically significant association between less respiratory support and lower total daily dose was observed in explanatory models. Lastly, an association between furosemide use and disease severity may help explain the seemingly paradoxical finding of greatest furosemide total daily dose at the extremes of the PMA group values: < 28 weeks and > 40 weeks (Table 4). One interpretation is this reflects disease severity cohort enrichment beyond 40 weeks, when healthier preterm infants have been discharged. This possibility is supported by the observation that this group contributed the fewest number of furosemide courses to the study, yet the proportion of courses occurring via intravenous route and during invasive respiratory support increase considerably after consistently down-trending from < 28 weeks to 36 – 39 6/7 weeks PMA (Table 3). We recently observed a similar pattern in an analysis of loop diuretic exposure as a function of PMA in the Pediatric Health Information System database, with the percentage of exposed subjects decreasing between 35 and 40 weeks PMA and then gradually rising beyond this age.(21) Although the use of more furosemide with greater disease severity is understandable, the risk of drug accumulation and toxicity is not lower in sicker infants. Indeed, the opposite may often be true.

As expected, we found unadjusted furosemide doses to be greater for enteral versus intravenous administrations across the cohort (Table 2). However, our data suggest that an assumed 50% bioavailability and a 1:2 intravenous to enteral conversion is not consistently applied, with a 1 mg/kg unadjusted dose noted in over 25% of enteral courses. Our secondary outcome of total daily dose reports intravenous equivalent doses, such that a 1 mg/kg enteral dose is adjusted to 0.5 mg/kg (8,16). As such, an inconsistent conversion practice would contribute bias to the association between PMA group and total daily dose, decreasing the overall estimates for PMA groups with higher enteral administrations. This may also help explain the lower total daily dose estimates observed among the 28 – 31 6/7, 32 – 35 6/7 and 36 – 39 6/7 weeks PMA groups relative to < 28 weeks PMA group (Table 4), and the attenuation of these differences in multivariable explanatory models

(Table 5). This finding of inconsistent practice highlights the importance of research to better characterize furosemide bioavailability.

Our study has additional limitations. Several of these are common to large retrospective cohort studies that use real-world data from databases. Our study includes a large sample of very preterm infants from hundreds of NICUs across the United States. Although the statistical confidence allowed by this large sample is a strength, the population is likely heterogenous and inclusive of subjects exposed to furosemide for various reasons. Importantly, the indication for furosemide use was unavailable, and exposure may have been motivated by various conditions, including congestive heart failure, respiratory distress syndrome, bronchopulmonary dysplasia, oliguric renal failure and/or edema of various etiologies. It is possible that our estimates would have differed if restricted to more specific populations and indications. Further, 72% of furosemide exposures were excluded for a lack of complete dosing data, which reflects our conservative inclusion criteria. While this improved the accuracy of the included data, it limits the generalizability of our findings. It is possible that furosemide dosing practices differed among subjects that had complete dosing data and those that did not, raising the possibility of bias in our estimates. Nonetheless, our report is the first to describe furosemide dosing practices in preterm infants across a postnatal developmental spectrum, making our findings novel and valuable. Efforts to corroborate our findings with alternative data sources are needed.

Our findings suggest that furosemide dosing practices are not influenced by prior data reporting higher clearance and shorter elimination half-lives among older PMA infants. However, FDA labeling does not provide PMA-based dosage recommendations, and hesitancy to increase exposure among these groups may be justified. First, the existing data is sparse. Though a few studies have reported pharmacokinetics in very preterm subjects beyond 32 weeks PMA, all but Mirochnick et al. (n = 10) enrolled four or fewer such subjects.(5,6,22) Second, furosemide drug disposition is influenced by various factors and a risk of drug accumulation with frequent dosing may remain in some older PMA subjects. For example, Vert et al. reported elimination half-lives in excess of 30 hours in two of four very preterm subject evaluated beyond 32 weeks PMA.(6) Identifying appropriate individualized dosage regimens will likely require consideration of parameters beyond PMA. Further, these data are now more than 30 years old and may not reflect improved analytical techniques for pharmacokinetic studies nor contemporary neonatal populations. A recent Japanese study of 10 extremely preterm infants evaluated in the first two weeks of life reported faster furosemide clearance (16.5 ml/kg/h) and a shorter elimination half-life (15.3 hours) than older studies despite a lower PMA among study participants, emphasizing the importance of revisiting earlier estimates.(23) Lastly, though faster furosemide clearance may allow more frequent dosing with lower risk of drug accumulation in older PMA infants, the benefit-harm profile of this approach remains uncertain. Furosemide harm can result from toxic drug accumulation at off-target sites (e.g. ototoxicity) or from undesired sequalae of on-target effects, such as nephrocalcinosis or metabolic bone disease following antagonism of renal water and electrolyte reabsorption. As such, achieving a more consistent diuretic effect through more frequent dosing may also increase harms. Of note, despite common practice, evidence to support the routine use of furosemide in BPD is lacking, with sparse data from clinical trials and inconsistent conclusions from cohort studies.(21,24,25)

In summary, our findings suggest that modern furosemide dosing practices in very preterm infants do not reflect prior studies describing rapid postnatal maturation of furosemide renal clearance beyond 32 weeks PMA. This underscores the importance of education to better inform providers of existing knowledge, as well as research to further characterize the developmental pharmacology of furosemide and translate rational dosage strategies to much needed trials of furosemide efficacy and safety in preterm populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Abbreviations:

BPD	bronchopulmonary dysplasia
FDA	United States Food and Drug Administration
GA	gestational age
IQR	interquartile range
NICU	neonatal intensive care unit
PMA	postmenstrual age
q12h	every twelve hours
q24h	every twenty-four hours
VP	very preterm

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Table 1.

Infant characteristics

	(N = 4638)
Receipt of antenatal steroids, No. (%)	3475 (75)
Gestational age, median [IQR], weeks	27 [25–29]
Birth weight, median [IQR], grams	915 [735–1160]
Female, No. (%)	2059 (44)
Maternal race/ethnicity, No. (%) [a]	
White	2127 (47)
Black	1142 (25)
Hispanic	1078 (24)
Other	163 (4)
Small for gestational age, No. (%)	694 (15)
Furosemide courses per infant, median [IQR]	1 [1–2]

Abbreviations: IQR, interquartile range

[a]N = 4510, represents greatest degree of missingness for subject characteristics

Table 2.

Furosemide dosing by postmenstrual age at course initiation

		PMA at course initiation, weeks				
	Total	**< 28**	**28 – 31 6/7**	**32 – 35 6/7**	**36 – 39 6/7**	**≥ 40**
Courses, No. (%) [a]	6565 (100)	932 (14)	2545 (39)	2158 (33)	684 (10)	246 (4)
Dose frequency, No. (%)						
Every 24 hours or less frequent	3589 (55)	487 (52)	1379 (54)	1214 (56)	375 (55)	134 (54)
Every 12 hours or more frequent	2976 (45)	445 (48)	1166 (46)	944 (44)	309 (45)	112 (46)
Dose, IV equivalent, mg/kg, median [IQR] [b]	1 [0.5–1]	1 [1–1]	1 [0.5–1]	1 [0.5–1]	1 [0.5–1]	1 [1–1]
IV [c]	1 [1–1]	1 [1–1]	1 [1–1]	1 [1–1]	1 [1–1]	1 [1–1]
Enteral, without IV equivalent adjustment [d]	1.5 [1–2]	1.5 [1–2]	1 [1–2]	1 [1–2]	2 [1–2]	1.5 [1–2]
Total daily dose, IV equivalent mg/kg/day, median [IQR] [b]	1 [1–2]	1 [1–2]	1 [1–2]	1 [0.5 – 1.5]	1 [1–2]	1 [1–2]
Course duration, days, median [IQR]	3 [2–8]	4 [2–10]	3 [2–9]	3 [2–5]	3 [2–5]	3 [2–8]

Abbreviations: PMA, postmenstrual age, IQR, interquartile range, mg, milligram; kg, kilogram; IV, intravenous

[a] Subjects may contribute multiple courses to study cohort; data are descriptive across cohort without adjustment for within-subject clustering.

[b] Includes both intravenous and enteral doses, reported as intravenous equivalents using a 1:2 intravenous to enteral ratio to convert for presumed bioavailability, and rounded to nearest 0.5 mg/kg increment.

[c] Restricted to intravenous courses, $n = 3743$. Doses rounded to nearest 0.5 mg/kg increment

[d] Restricted to enteral courses, $n = 2822$. Doses rounded to nearest 0.5 mg/kg increment as prescribed for enteral administration without intravenous conversion

Table 3.

Furosemide course covariate characteristics by postmenstrual age at course initiation

		PMA at course initiation, weeks				
	All	**< 28**	**28 – 31 6/7**	**32 – 35 6/7**	**36 – 39 6/7**	**≥ 40**
Courses, No. (%) [a]	6565 (100)	932 (14)	2545 (39)	2158 (33)	684 (10)	246 (4)
Age at course initiation, median [IQR], days	29 [15–50]	12 [8–17]	21 [12–30]	42 [29–54]	70 [58–84]	119 [101–137]
Age at course initiation, No. (%)						
0–3 days [b]	244 (4)	105 (11)	139 (5)	0 (0)	0 (0)	0 (0)
> 3 days	6321 (96)	827 (89)	2406 (95)	2158 (100)	684 (100)	246 (100)
Furosemide exposure in prior 7 days, No. (%)	2000 (30)	293 (31)	846 (33)	625 (29)	165 (24)	71 (29)
Route of administration, No. (%)						
Intravenous	3743 (57)	779 (84)	1787 (70)	839 (39)	204 (30)	134 (54)
Enteral	2822 (43)	153 (16)	758 (30)	1319 (61)	480 (70)	112 (46)
Respiratory support at course initiation, No. (%) [c, d]						
None	424 (7)	1 (0)	58 (2)	236 (11)	112 (17)	17 (7)
Non-invasive	3193 (49)	100 (11)	1063 (42)	1470 (69)	436 (65)	124 (51)
Invasive	2859 (44)	820 (90)	1385 (55)	427 (20)	125 (19)	102 (42)

Abbreviations: PMA, postmenstrual age, IQR, interquartile range

[a] Subjects may contribute multiple courses to study cohort; data are descriptive across cohort without adjustment for within-subject clustering.

[b] As cohort is restricted to very preterm infants born < 32 weeks gestational age, 0–3 days age group is not applicable to older PMA age groups.

[c] N = 6476, represents greatest degree of missingness for course characteristics

[d] Non-invasive respiratory support is inclusive of nasal cannula, continuous positive airway pressure and bilevel, irrespective of type or modality. Invasive respiratory support inclusive of all delivered through tracheal intubation and mechanical ventilation, irrespective of type or modality.

Table 4.

Estimates of the association between furosemide course characteristics, dose frequency and total daily dose.

	Odds ratio (95% CI) for more frequent furosemide dosing [a]	*P* value	Marginal means (95% CI) for total daily dose (mg/kg/d) [b]	*P* value
PMA in weeks at course initiation				
<28 (reference)	-		1.42 (1.36 – 1.48)	-
28 – 31 6/7	0.93 (0.79 – 1.08)	0.33	1.26 (1.23 – 1.29)	<0.001
32 – 35 6/7	0.85 (0.72 – 1.00)	0.05	1.17 (1.13 – 1.20)	<0.001
36 – 39 6/7	0.90 (0.73 – 1.11)	0.33	1.20 (1.15 – 1.25)	<0.001
> 40	0.91 (0.80 – 1.23)	0.56	1.42 (1.29 – 1.55)	0.98
Age at course initiation				
0–3 days	-		1.59 (1.42 – 1.75)	-
> 3 days	0.77 (0.59 – 1.00)	0.05	1.24 (1.22 – 1.26)	<0.001
Furosemide exposure in prior 7 days				
No (reference)	-		1.26 (1.24 – 1.28)	-
Yes	0.90 (0.8 – 1.00)	0.06	1.24 (1.20 – 1.28)	0.38
Route of administration				
Intravenous (reference)	-		1.47 (1.44 – 1.50)	-
Enteral	0.51 (0.46 – 0.57)	<0.001	0.97 (0.94 – 0.99)	<0.001
Respiratory support at course initiation				
None (reference)	-		1.06 (0.99 – 1.13)	-
Non-invasive	0.79 (0.65 – 0.98)	0.03	1.14 (1.12 – 1.17)	0.03
Invasive	1.11 (0.90 – 1.37)	0.34	1.41 (1.37 – 1.44)	<0.001

Abbreviations: PMA, postmenstrual age

[a] Results of bivariable logistic regression analyses applying cluster-robust variance estimates to account for multiple courses within subjects, odds ratio of furosemide frequency of every 12 hours or more vs every 24 hours or less

[b] Results of bivariable linear regression analyses applying cluster-robust variance estimates to account for multiple courses with subjects

Table 5.

Estimates of the association between furosemide course characteristics, dose frequency and total daily dose in explanatory multivariable models

	Odds ratio (95% CI) for more frequent furosemide dosing [a]	*P* value	Marginal means (95% CI) for total daily dose (mg/kg/d) [b]	*P* value
PMA in weeks at course initiation				
<28 (reference)	-		1.23 (1.17 – 1.29)	-
28 – 31 6/7	1.08 (0.91 – 1.27)	0.39	1.18 (1.15 – 1.21)	0.17
32 – 35 6/7	1.28 (1.06 – 1.54)	0.01	1.29 (1.25 – 1.32)	0.10
36 – 39 6/7	1.44 (1.14 – 1.82)	0.002	1.38 (1.32 – 1.43)	0.001
> 40	1.20 (0.88 – 1.64)	0.25	1.44 (1.31 – 1.56)	0.003
Age at course initiation				
0–3 days	-		1.40 (1.23 – 1.56)	-
> 3 days	1.03 (0.79 – 1.35)	0.83	1.25 (1.23 – 1.27)	0.08
Furosemide exposure in prior 7 days				
No (reference)	-		-	-
Yes	0.79 (0.71 – 0.89)	<0.001	-	-
Route of administration				
Intravenous (reference)	-		1.46 (1.43 – 1.49)	-
Enteral	0.47 (0.42 – 0.53)	<0.001	0.97 (0.95 – 1.00)	<0.001
Respiratory support at course initiation				
None (reference)	-		1.13 (1.06 – 1.20)	-
Non-invasive	0.79 (0.64 – 0.98)	0.03	1.21 (1.19 – 1.24)	0.02
Invasive	0.94 (0.74 – 1.19)	0.60	1.32 (1.28 – 1.35)	<0.001

Abbreviations: PMA, postmenstrual age, IQR, interquartile range

[a] Odds ratio of furosemide frequency of every 12 hours or more vs every 24 hours or less; results of multivariable logistic regression analyses applying cluster-robust variance estimates to account for multiple courses within subjects and adjusting for course characteristics included as model covariates following association with furosemide dosing frequency at $p < 0.10$ in bivariable analysis; all met criteria.

[b] Results of multivariable linear regression analyses applying cluster-robust variance estimates to account for multiple courses within subjects and adjusting for course characteristics included as model covariates following association with furosemide cumulative daily dose at $p < 0.10$ in bivariable analysis; all but furosemide exposure in prior 7 days met criteria