Association of Center-Specific Patient Volumes and Early Respiratory Management Practices with Death and Bronchopulmonary Dysplasia in Preterm Infants

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Objectives To describe variability in admission volumes and approach to early respiratory support between neonatal intensive care units in the Australian and New Zealand Neonatal Network and to evaluate whether these center-specific factors are associated with death and bronchopulmonary dysplasia.

Study design This retrospective cohort study included 19 099 neonates born between 25 and 32 weeks' gestation and admitted to 1 of 25 NICUs from 2007 to 2013. Center-specific factors evaluated were annual admission volume and rate of using continuous positive airway pressure (CPAP) rather than intubation as the first mode of respiratory support. Logistic regression was used to examine any association of these center-specific factors with death, BPD, and death or survival with BPD (death/BPD). Analysis was performed separately for 2 gestation groups (25-28 weeks and 29-32 weeks inclusive).

Results Admission volumes and rates of early CPAP use varied widely across centers. Higher admission volumes were associated with lower odds of death or survival with BPD in the 25-28 week group (aOR 0.93, 99% CI 0.88-0.99 per increase of 10 babies per center annually). Centers with higher early CPAP use did not have lower odds of death or BPD than centers that intubated more frequently.

Conclusions Higher admission volumes are associated with more favorable outcomes for the more preterm infants in the Australian and New Zealand Neonatal Network. Further investigation is required to explore why the individual benefits of early CPAP do not translate to better outcomes for centers that use this approach most frequently. *(J Pediatr 2019;210:63-8)*.

Prevention of mortality and significant morbidity is the primary aim of interventions that specialized neonatal intensive care units (NICUs) provide to preterm infants. Although this goal is clear, variation in the clinical outcomes of preterm infants has been described between NICUs and between multiple neonatal networks.[1-9] Studies that examine such differences suggest there are characteristics inherent to centers themselves that influence clinical outcomes in a manner distinct to the impact of individual patient management decisions. However, the contribution of these center-specific factors is ill-defined.[1,7,10,11]

Lower rates of death and neonatal morbidities are frequently reported in high volume NICUs[12,13] although some analyses suggest that high admission volumes have little impact,[7,14] or even a negative impact on these outcomes.[15] An evaluation of admission volumes in association with clinical outcomes in the Australian and New Zealand Neonatal Network (ANZNN) has not previously been performed. Variation in a variety of clinical practices is described between centers, one of which is the choice of first mode of respiratory support for preterm infants.[1,16,17] Risks of death and bronchopulmonary dysplasia (BPD) are lower when babies are initially supported by continuous positive airway pressure (CPAP) rather than intubated,[18-20] particularly if noninvasive support is maintained throughout the first 3 days.[21] Although the benefits of early CPAP are clear for individual infants, no recent study has investigated whether a center-specific practice of initiating CPAP from birth confers an advantage to that center's infant population after adjustment for confounding factors.

The first objective of this study was to identify and describe variation in 2 center-specific factors in the ANZNN: unit admission volume of infants within 2 preterm gestation ranges, and approach to early respiratory support (CPAP

ANZNN	Australia and New Zealand Neonatal Network
BPD	Bronchopulmonary dysplasia
CPAP	Continuous positive airway pressure
Death/BPD	Death or survival with bronchopulmonary dysplasia
NICU	Neonatal intensive care unit

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or intubation). The second objective was to evaluate the association between these center-specific factors and 2 clinical outcomes: death and bronchopulmonary dysplasia.

Methods

Data from a retrospective cohort study from the years 2007 to 2013 from the ANZNN were used. The ANZNN coordinates a collaborative, prospective audit through data collected for eligible infants admitted to each of the tertiary NICUs in the 2 countries.[22] A standardized data set is collected by audit officers at each site, and de-identified information is submitted to the ANZNN coordinator.[22] Collection of data is approved at each site by local ethics committees, and this study was approved by the Tasmanian Health Research Ethics Committee.

Infants registered to the ANZNN were included in this analysis if they were in the gestational age range $25^{0/7}$ weeks to $32^{6/7}$ weeks, inborn in a perinatal tertiary center (or co-located private facility), and admitted to a level III NICU within 60 minutes of birth. Exclusion criteria were: (1) congenital anomaly likely to affect respiratory function or early management, (2) prolonged premature rupture of membranes (≥14 days), (3) no requirement for respiratory support (intubation or CPAP) in the first 24 hours, and (4) insufficient information regarding early respiratory management.[21] The characteristics of this cohort, previously assembled to examine the influence of early respiratory management at an individual level,[21] ensured a group that was homogeneous with respect to clinician intent to deliver active intensive care and absence of congenital pulmonary morbidities that might preclude a standard approach to respiratory management. Outborn infants were excluded to ensure that decision making for the first mode of respiratory support was not altered by anticipated interhospital transfer and its attendant risks.[23] Infants born below 25 weeks were excluded as intubation rather than support with CPAP occurs at delivery for the vast majority of these infants resuscitated at delivery in the ANZNN.[24] As with the previous report,[21] infants were separated for analysis into 2 gestation ranges (25-28 weeks and 29-32 weeks, inclusive).

The average number of infants admitted per year (center volume) was calculated for each deidentified center for the 2 gestation ranges for all years where data were available. The proportion of infants who received CPAP as their first mode of respiratory support (primary CPAP) was determined for each center (CPAP start rate). Primary CPAP was defined as a CPAP trial of at least 30 minutes of duration from the time of delivery.[21] Centers were then grouped in low, medium, or high CPAP start categories by partitioning centers by their CPAP start rates in tertiles for each gestation range. Baseline data were compared between CPAP start categories using Pearson χ^2 test for categorical variables, 1-way ANOVA for normally distributed continuous variables, and the Kruskal-Wallis test for skewed data. Observed rates of death prior to hospital discharge, BPD, and the composite outcome of death or survival with BPD (death/BPD), were calculated for each gestation group and its CPAP start tertiles. BPD was defined as need for respiratory support and/or supplemental oxygen at 36 postmenstrual weeks.[25,26]

In the second stage of the analysis, a multivariate logistic regression model was used to investigate the impact of center volume and center-specific CPAP start rates on death, BPD, and death/BPD. Center volume was included in the model as a continuous variable, calculated as infants per year per center divided by 10 to allow interpretation of the influence of differing unit volume in 10 patient increments. CPAP start rate was included in the model as tertile-categorized groups, with the medium CPAP start category used as the reference group. The logistic regression model was also adjusted for the following patient characteristics: gestational age (completed weeks), birth weight (<10th percentile/≥10th percentile), sex (male/female), mode of delivery (cesarean delivery/vaginal birth), plurality (singleton/multiple), antenatal glucocorticoid exposure (incomplete/complete), and 5-minute Apgar score (<7/≥7).[21] As inherent similarities in population and outcome may occur within centers, clustering by NICU was incorporated in the model. Finally, an interaction term was separately added to the model specified above to assess the impact of any relationship between center volume and CPAP start category. Statistical analyses were performed in STATA v 14.2 (StataCorp, College Station, Texas) and figures generated with GraphPad Prism v 7.0c (GraphPad Software Inc, San Diego, California). Given the large cohort examined, the level of significance was set to $P < .01$ with corresponding 99% CIs.

Results

In total, 24 212 preterm infants born at 25-32 weeks' gestation were registered to the ANZNN during the study period. Of these, 962 had a congenital anomaly and 1294 had premature prolonged rupture of membranes, 2074 did not require ventilation or CPAP in the first 24 hours, and 779 had insufficient data on early respiratory management. Twenty-six ANZNN centers were identified as having admitted inborn infants born at 25-32 completed weeks. One center was excluded due to insufficient admissions for analysis (<10 over 7 years). Thus, the final cohort studied contained 19 099 infants from 25 centers: 6771 in the 25-28 week group and 12 328 in the 29-32 week group. The overall rates of death, BPD, and death/BPD were 8.1% (n = 547), 35.3% (n = 2385), and 42.5% (n = 2875) for infants at 25-28 weeks, and 1.0% (n = 117), 5.7% (n = 704) and 6.6% (n = 815) for infants at 29-32 weeks, respectively.

Center volume varied widely across the network, from 8 to 99 (median 32) infants per year at 25-28 weeks, and 5 to 196 (median 60) infants per year at 29-32 weeks (**Figure**). Center-specific CPAP start rates also varied, and ranged between 0.7% and 73.2% (median 22.5%, IQR 14.8%-36.2%) for infants at 25-28 weeks, and 18.8% to 95.8% (median 78.2%, IQR 67.1%-86.3%) for the 29-32 week group (**Figure**). The partitioning of ANZNN units as low, medium, and high CPAP start categories is shown in the **Figure**.

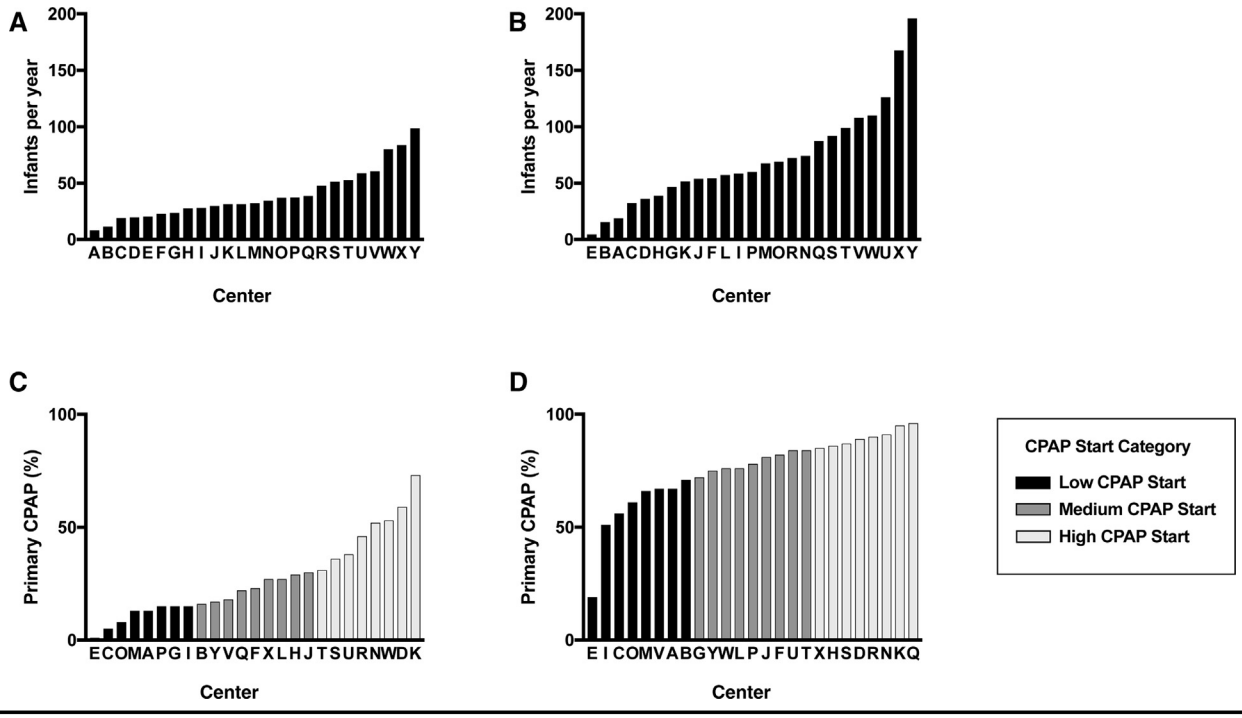

Figure. Variation in center volumes and CPAP start rates among ANZNN centers. **A,** Average center volume per year, 25-28 weeks. **B,** Average center volume per year, 29-32 weeks. **C,** CPAP start rate, 25-28 weeks. **D,** CPAP start rate, 29-32 weeks. Deidentified ANZNN centers labeled as A-Y, with labeling consistent in panels A-D.

Tables I and II (available at www.jpeds.com) show baseline characteristics of infants within units comprising the different CPAP start tertiles. Rates of cesarean delivery differed between CPAP start categories for both gestation groups, with the lowest rate seen in high CPAP start centers ($P < .001$). The proportion of babies with a 5-minute Apgar score less than 7 varied between the CPAP start categories in the 29-32 week group, with more observed in low CPAP start centers ($P = .005$). The proportion of multiple deliveries also differed between the CPAP start categories in both gestation groups (each $P < .01$). In the 29-32 week group, the proportion of infants who started on CPAP but required intubation within 72 hours differed between the 3 groups, with the highest proportion observed in the low CPAP start category ($P < .001$).

In the 25-28 week group, higher center volume was associated with lower odds of death/BPD: aOR for each increment of 10 infants per year was 0.93, 99% CI 0.88-0.99, $P = .003$. Although lower aORs for death and BPD were also observed with increased unit volume in both gestation groups, none met statistical significance (Table III). Table IV details the influence of CPAP start category on clinical outcomes. The high CPAP start category had the highest observed rates of death, BPD and death/BPD in the 25-28 week group, and of death and death/BPD in the 29-32 week group. No significant association was found for death, BPD, or death/BPD in any of the 3 CPAP start categories. The aORs for these outcomes were consistently higher for the high CPAP start category compared with the middle CPAP start category for the 25-28 week group. In the 29-32 week group the high CPAP start category's aOR for death was 1.56 (99% CI 0.93-2.62, $P = .03$), however, its aORs for BPD and death/BPD were lower than the middle CPAP start category. The addition of an interaction term to the logistic regression model did not reveal any significant interplay between center volume and CPAP start category for death, BPD or death/BPD in either gestation category (results not reported).

Discussion

Several studies have explored the influence that center-specific practices or characteristics can have on neonatal clinical outcomes. Our analysis assessed 2 center-specific factors

Table III. The contribution of center volume to clinical outcomes

	25-28 Wk		29-32 Wk	
Clinical outcomes	aOR* (99% CI)	*P*	aOR* (99% CI)	*P*
Death	0.95 (0.88-1.01)	.04	1.00 (0.94-1.06)	.92
BPD	0.95 (0.89-1.02)	.06	0.97 (0.94-1.01)	.06
Death/BPD	0.93 (0.88-0.99)	**.003**	0.98 (0.94-1.01)	.06

Volume was analyzed as a continuous variable in units of 10. Thus, the aORs presented reflect the impact of a center having an admission volume increased by 10 infants per year.
*Covariates adjusted for are gestation, birthweight (above or below the 10th percentile), sex, mode of delivery, plurality, antenatal glucocorticoid exposure, 5-minute Apgar score, and CPAP start category.

Table IV. Clinical outcomes by CPAP start category

Gestation groups	CPAP start category	Death			BPD			Death/BPD		
		n (%)	aOR* (99% CI)	P	n (%)	aOR* (99% CI)	P	n (%)	aOR* (99% CI)	P
25-28 wk (25 centers; 6771 infants)	Low CPAP Start (8 centers; 1413 infants)	122 (8.7)	1.09 (0.73-1.62)	.60	479 (34.1)	0.84 (0.57-1.24)	.25	593 (42.2)	0.87 (0.57-1.31)	.37
	Medium CPAP start (9 centers; 2725 infants)	186 (6.8)	Reference	-	929 (34.1)	Reference	-	1097 (40.3)	Reference	-
	High CPAP start (8 centers; 2633 infants)	239 (9.1)	1.20 (0.85-1.69)	.18	977 (37.1)	1.06 (0.74-1.54)	.65	1185 (45.0)	1.12 (0.76-1.65)	.44
29-32 wk (25 centers; 12 328 infants)	Low CPAP start (8 centers; 2532 infants)	19 (0.8)	0.78 (0.37-1.67)	.41	143 (5.7)	0.78 (0.5-1.21)	.15	161 (6.4)	0.77 (0.52-1.15)	.09
	Medium CPAP start (9 centers; 5860 infants)	47 (0.8)	Reference	-	343 (5.9)	Reference	-	388 (6.6)	Reference	-
	High CPAP start (8 centers; 3936 infants)	51 (1.3)	1.56 (0.93-2.62)	.03	218 (5.5)	0.77 (0.5-1.18)	.11	266 (6.8)	0.86 (0.59-1.26)	.31

*Covariates adjusted for are gestation, birthweight (above or below the 10th percentile), sex, mode of delivery, plurality, antenatal glucocorticoid exposure, 5-minute Apgar score, and center volume.

in the ANZNN: volume of preterm infant admissions and center-specific approach to early respiratory support (CPAP or intubation).

The impact of center volume or level of care has been examined in several countries, with most analyses demonstrating superior outcomes for preterm infants in NICUs that are larger or provide the highest level of care for their region.[2,12,13,27] Our analysis shows that centers with higher admission numbers in the ANZNN have more favourable clinical outcomes, though this effect was less stark compared with other analyses, and only apparent for the most preterm infants. There are several unique features of the ANZNN that play a role in the distribution of infant admissions. First, although a strongly positive effect of admission to a center which has high admission volumes and also provides a higher classified level of care has been demonstrated in other neonatal networks,[12,13] the level of clinical service provision was more homogenous in our study than others, as all units included in this analysis are classified at the highest level in the network.[22] Further, although no international standard for categorizing the size of units exists, the effect of unit volume in other analyses is most apparent in units with smaller volumes than the majority of centers in the ANZNN.[12,13] For example, an analysis of several regions in North America found that the greatest risk for death or severe morbidity in very low birth weight infants was in centers with fewer than 10 deliveries per year of very low birth weight infants.[13] There were only 2 ANZNN units with a volume level below 10 per year in each gestation group, one of which was excluded from our analysis. It is also important to note that by virtue of the region's unique geography, several neonatal units in the ANZNN serve relatively small populations in isolated regions, where distance to the nearest larger city exceeds 2 hours' flight. Thus, although the argument exists for the centralization of NICUs as a measure to improve clinical outcomes,[12] this must be tempered by the practicalities of providing of timely and effective neonatal intensive care to preterm infants born in centers in isolated regions.

Although the number of admissions to NICUs may not be easily modifiable, the center-specific effect of volume might be. In adult intensive care services, organizational factors such as staff-to-patient ratios and active involvement in tertiary education have been shown to mitigate the otherwise negative association with clinical outcomes ascribed to lower unit volumes.[28] Although a comparable analysis for NICUs was not possible in this database study, it is conceivable that such factors could positively influence outcomes in the ANZNN's smaller units.

Effective respiratory support is a cornerstone of optimal care for preterm infants.[29] Multiple studies have demonstrated the positive effects of noninvasive respiratory support with CPAP in preference to intubation for the prevention of death and BPD.[20] More than 30 years ago, Avery et al raised the notion that a NICU's respiratory practices could influence the rate of chronic lung disease among its preterm population.[1] Their analysis of 8 NICUs revealed a markedly lower rate of chronic lung disease in a center that promoted early

CPAP use for preterm infants.[1] Subsequent studies found a benefit for centers with a practice of using CPAP more frequently than intubation for the first mode of respiratory support, though to varying degrees.[10,30] Our finding that centers which used more CPAP from the outset did not have lower rates of death and/or BPD, and showed a potential trend to worse outcomes, was unexpected. A previous analysis of this study's population identified a beneficial influence of early CPAP application in comparison with intubation for individual preterm infants.[21] Although it is possible that high CPAP start centers might have used the therapy in infants with a higher likelihood of CPAP failure,[21,31] our results show that this is not the case. It would seem that there were additional influences on the trajectory of these infants which, in aggregate, negated the individual benefits of primary CPAP use in preterm infants. To explore the reasons behind this finding is beyond the scope of this retrospective analysis and requires an examination of the broader picture that creates a NICU's clinical environment.

In the 1987 study by Avery et al, in the highest performing unit investigated, a single clinician was responsible for ensuring optimal delivery of all aspects of respiratory care full time.[1] Thus, in addition to high CPAP frequency, this center also received the benefit of clinical cohesion and consistency. Although this model of practice would be considered impractical in many contemporary NICUs, the concept parallels well with quality improvement based on standardized initiatives.[32] It has also been suggested that the greatest gains in improving neonatal morbidity and mortality might be made with a focus on the highest performing centers.[33] Such an approach may greatly inform quality improvement projects across the ANZNN for respiratory practice and likely other elements of neonatal intensive care. Ideally, a suite of both organizational and clinical practice factors would be assessed amongst centers that excel. This could include a detailed exploration of the patterns of respiratory practice in such units, their use and efficacy of center-specific clinical guidelines, skill mix and available ratios of clinical staff, and consistency in respiratory practice amongst NICU clinicians.

There are several limitations to this study. With respect to patient volumes, although the population we have analyzed is representative of a specific and clinically homogenous group of patients, analyzed unit volumes comprise only infants who met the eligibility criteria rather than absolute numbers per center. The reported outcomes in this study are only for this homogenous population and do not necessarily reflect the trajectory of infants excluded from the analysis, including those with prolonged membrane rupture, congenital anomalies, or not receiving respiratory support in the first 24 hours. As all centers were deidentified, determining each center's early respiratory support practice from unit guidelines and direct inquiry was not possible, and was instead deduced from observed CPAP start rates. It is also possible that the introduction of new therapies in the study period such as high flow nasal cannula therapy may have influenced some treatment decisions. Further, any potential effect of temporal changes in the rates of BPD and death within centers was not part of this analysis. Finally, some elements which may influence individual likelihoods of death and BPD such as ethnicity, postnatal steroid therapy, and clinical course beyond the first 3 days were not able to be included in this analysis.[29,34]

Center-specific factors may influence the clinical trajectory of a neonatal unit's preterm population. In the ANZNN, this includes the positive impact of higher unit admission rates for infants born at 25-28 weeks. On the other hand, individual benefits of early CPAP did not translate to better unit performance for NICUs that used this therapy most frequently. This counterintuitive result should inform future efforts directed at quality improvement in the respiratory management of preterm infants. ■

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Appendix

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*Denotes the ANZNN Executive.

Table I. Demographic, clinical, and center-specific data for infants 25-28 weeks

Characteristics	All	Low CPAP start	Medium CPAP start	High CPAP start	P*
Centers, n	25	8	9	8	-
Infant number, n	6771	1413	2725	2633	-
Gestation (wk)					.18
25 wk, n (%)	1244 (18.4)	267 (18.9)	489 (17.9)	488 (18.5)	
26 wk, n (%)	1577 (23.3)	299 (21.2)	631 (23.2)	647 (24.6)	
27 wk, n (%)	1709 (25.2)	363 (25.7)	677 (24.8)	669 (25.4)	
28 wk, n (%)	2241 (33.1)	484 (34.3)	928 (34.1)	829 (31.5)	
Birthweight in g, mean (SD)	960 (236)	967 (245)	963 (232)	952 (234)	.09
Birthweight <10th percentile, n (%)	678 (10.0)	144 (10.2)	254 (9.3)	280 (10.6)	.27
Male sex, n (%)	3585 (53.0)	735 (52.1)	1445 (53.1)	1405 (53.4)	.73
Multiple delivery, n (%)	1927 (28.5)	402 (28.6)	716 (26.3)	809 (30.7)	**.002**
Delivery by cesarean delivery, n (%)	4423 (65.6)	967 (68.8)	1809 (66.5)	1647 (62.9)	**<.001**
Incomplete antenatal steroids, n (%)	2234 (33.2)	475 (34.0)	845 (31.3)	914 (34.8)	.02
Apgar score <7 at 5 min, n (%)	1673 (24.8)	349 (24.7)	639 (23.5)	685 (26.1)	.09
Center volume, median (IQR)	32 (24 to 51)	26 (20 to 35)	31 (28 to 61)	50 (33 to 56)	.10
Infants who received primary CPAP, n (%)	1989 (29.4)	154 (10.9)	613 (22.5)	1222 (46.4)	**<.001**
Proportion of infants who received primary CPAP who were intubated within 72 h, n (%)	862/1988 (43.4)	70/154 (45.5)	257/612 (42.0)	535/1222 (43.8)	.66

Values in bold are statistically significant.
*Comparisons made between low, medium, and high CPAP start categories using the Kruskal-Wallis test for center volume, one-way ANOVA for all other continuous variables and Pearson χ^2 test for all categorical variables.

Table II. Demographic, clinical, and center-specific data for infants 29-32 weeks

Characteristics	All	Low CPAP start	Medium CPAP start	High CPAP start	P*
Centers, n	25	8	9	8	-
Infant number, n	12 328	2532	5860	3936	-
Gestation (wk)					.06
29 wk, n (%)	2513 (20.4)	505 (19.9)	1148 (19.6)	860 (21.9)	
30 wk, n (%)	3052 (24.8)	623 (24.6)	1445 (24.7)	984 (25.0)	
31 wk, n (%)	3403 (27.6)	717 (28.3)	1611 (27.5)	1075 (27.3)	
32 wk, n (%)	3360 (27.3)	687 (27.1)	1656 (28.3)	1017 (25.8)	
Birthweight in g, mean (SD)	1538 (352)	1533 (354)	1546 (349)	1528 (354)	.03
Birthweight <10th percentile, n (%)	1224 (9.9)	261 (10.3)	547 (9.3)	416 (10.6)	.10
Male sex, n (%)	6826 (55.4)	1400 (55.3)	3259 (55.6)	2167 (55.1)	.87
Multiple delivery, n(%)	4352 (35.3)	819 (32.4)	2161 (36.9)	1372 (34.9)	**<.001**
Delivery by cesarean delivery, n (%)	8619 (70.3)	1884 (74.7)	4117 (70.4)	2618 (67.3)	**<.001**
Incomplete antenatal steroids, n (%)	4274 (34.9)	861 (34.5)	2048 (35.2)	1365 (34.8)	.813
Apgar score <7 at 5 min, n (%)	1423 (11.6)	332 (13.1)	626 (10.7)	465 (11.8)	**.005**
Center volume, median (IQR)	60 (47 to 92)	45 (17 to 68)	60 (54 to 126)	73 (45 to 90)	.15
Infants who received primary CPAP, n (%)	9693 (78.6)	1560 (61.6)	4606 (78.6)	3527 (89.6)	**<.001**
Proportion of infants who received primary CPAP who were intubated within 72 hours, n (%)	2060/9693 (21.3)	361/1560 (23.1)	1025/4606 (22.3)	674/3527 (19.1)	**<.001**

Values in bold are statistically significant.
*Comparisons made between low, medium, and high CPAP start categories using the Kruskal-Wallis test for center volume, one-way ANOVA for all other continuous variables and Pearson χ^2 test for all categorical variables.