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The effect of prolonged tracheal intubation on the association between patent ductus arteriosus and bronchopulmonary dysplasia (grades 2 and 3)

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Abstract

Objective: To determine if the need for mechanical ventilation alters the association between prolonged patent ductus arteriosus (PDA) exposure and bronchopulmonary dysplasia (grades 2 and 3) (BPD).

Study Design: Observational study of 407 infants (<28 weeks' gestation) with echocardiograms performed at planned intervals.

Results: Twelve percent (48/407) of study infants had BPD (grades 2 & 3). In a multivariable regression model, exposure to a moderate-to-large PDA shunt for ≥7 days was associated with an increased risk of BPD (grades 2 & 3) (from 16% to 35%: aRD=19% (6, 32%), p<0.005) when infants required ≥10 days of intubation (n=170). In contrast, there was no significant association between prolonged PDA exposure and BPD when infants required ≤9 days of intubation (aRD=4% (−1, 10%) (n=237).

Conclusion: Moderate-to-large PDAs are associated with an increased risk of BPD - but only when infants require intubation ≥10 days.

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Introduction:

Although a moderate-to-large patent ductus arteriosus left-to-right shunt (PDA) often causes hypotension, redistribution of organ blood flow, pulmonary edema and diminished pulmonary compliance in both preterm infants and nonhuman primates [1, 2, 3, 4, 5, 6, 7, 8], its role in the development of longer-term respiratory morbidities is still a matter of debate. In mechanically ventilated preterm baboons, exposure to a moderate-to-large PDA shunt for 2 weeks is associated with an arrest of alveolar development (the hallmark of bronchopulmonary dysplasia (BPD)) [8]. On the other hand, none of the randomized clinical trials (RCTs) performed to date in preterm human infants have found a relationship between therapies intended to close the PDA and the risk of developing BPD [9, 10, 11, 12, 13, 14].

Although the clinical RCTs suggest that the presence of a PDA is not related to BPD, there are several concerns that should be considered before trying to equate the design of the clinical RCTs with that of the preclinical trials performed in intubated preterm baboons. When the human RCTs were originally designed, little information was available to determine which infants might be at risk for developing BPD by being exposed to a PDA. As a result, little attention was paid to either the magnitude of the PDA shunt, the duration of shunt exposure, or the infants' need for respiratory support. This is an important concern since recent observational studies have shown that any association between a PDA and the risk of developing BPD depends not on the presence or absence of a PDA but on the magnitude of its shunt [15, 16, 17].

Another concern about the design of the clinical RCTs relates to the criteria that were used to determine when the outcome BPD was present or absent. The definitions for classifying BPD in the clinical RCTs were based on either the infant's need for oxygen (room air challenge test [18]) or the absolute amount of oxygen used to treat an infant at 36 weeks [19, 20] Unfortunately, these definitions do not accurately reflect lung function or pathology; nor do they characterize the wide spectrum of BPD severity [21]. In addition, they have been inconsistently associated with longer-term childhood morbidities [20, 21, 22, 23]. Recently, Jensen et al. [23] developed a severity-based definition of BPD that, while not being able to distinguish the pathophysiologic reasons for each infant's need for respiratory support, does have good discriminatory power for predicting clinically meaningful respiratory morbidity measured at 18–26 months' corrected age.

To address the above concerns, we designed the following observational study to determine if the duration of moderate-to-large PDA exposure affects the incidence of more severe grades of BPD as defined by Jensen et al. [23]. We were particularly interested in determining the duration of PDA exposure needed before one might expect to see an increase in the risk of BPD and in determining whether an infant's need for invasive respiratory support plays a role in shaping the relationship between PDA exposure and BPD.

Methods:

Patient Population and PDA treatment protocols:

This observational study utilizes data drawn from an ongoing database comprised of neonates <$28^{0/7}$ weeks of gestation born at University of California San Francisco, starting in 1992. A single neonatologist recorded all the demographic factors and outcome measures and reviewed all the echocardiograms with the attending cardiologists since the inception of the database. Institutional Review Board approval allows us to access these data without parental approval because all data are deidentified. Infants were eligible for the current study if they delivered before $28^{0/7}$ weeks of gestation between January 2005 and December 2019 and were admitted to the intensive care nursery within 24 hours of birth.

All infants had an echocardiogram performed on postnatal day 7. The echocardiographic studies included two-dimensional imaging, M-mode, color flow mapping, and Doppler interrogation as previously described [24, 25]. A moderate-to-large PDA was defined by a ductus diameter ≥1.5mm measured in 2D plus one or more of the following echocardiographic criteria: A) left atrium-to-aortic root ratio ≥1.6; B) mean pressure gradient across the ductus ≤8mm Hg; C) left pulmonary artery end-diastolic flow velocity >0.2 m/sec; and/or D) reversed diastolic flow in the descending aorta [24, 25]. Ductus that did not meet these criteria were considered to be “constricted” (small or closed).

Infants who had a moderate-to-large PDA on the echocardiogram performed on day 7 were followed with echocardiograms every 7 days for the next 2–3 weeks, then at least every other week until the PDA was no longer moderate-to-large in size. Infants with a “constricted” (small or closed) ductus on day 7 were examined daily for a change in clinical symptoms indicative of a reopened moderate-to-large PDA (systolic murmur or hyperdynamic precordium). If either of these occurred, an echocardiogram was performed within 24 hours. When a reopened moderate-to-large PDA was detected, echocardiograms were performed every 7 days for the next 2–3 weeks, and then at least every other week until the PDA was no longer moderate-to-large in size. Infants with a “constricted” ductus that never developed clinical signs of reopening had routine echocardiograms performed every 2–3 weeks to confirm ductus constriction until ductus closure or hospital discharge. Infants with a PDA at the time of discharge were followed as outpatients until spontaneous or device-induced PDA closure.

The duration of exposure to a moderate-to-large PDA that persisted beyond the first week was calculated and expressed in days. Infants with small or closed ductus at postnatal day 7 were assumed to have not been exposed to a moderate-to-large PDA during the first 7 days. Infants with moderate-to-large PDAs at postnatal day 7 were assumed to have been exposed to a moderate-to-large PDA for the entire 7 days. The time of ductus constriction was assigned as the halfway point between the last exam with a moderate-to-large PDA and the first exam with a constricted ductus. When reopening of the PDA occurred after documented ductus constriction, the exposure to the reopened moderate-to-large PDA shunt (calculated as the number of days from the echocardiogram demonstrating the reopened moderate-to-large shunt to the time of ductus constriction (i.e., the halfway point between the last exam

with a moderate-to-large PDA and the first exam with a constricted ductus)) was added to the duration of any prior moderate-to-large PDA shunt exposure.

Our primary outcome was the incidence of moderate-to-severe BPD (grades 2 and 3) defined by Jensen et al [23]. This definition categorizes BPD severity according to the mode of respiratory support administered at 36 weeks' postmenstrual age, regardless of the prior duration or current level of oxygen therapy. Infants with grades 2 or 3 BPD are reported to have a 47% chance of having late death or serious childhood respiratory morbidity compared with a risk of 10% in infants with no BPD or 19% in those with grade 1 BPD [23]. All study infants (except those requiring CPAP with ≥30% oxygen or mechanical ventilation), first underwent a modified room air challenge test between $36^{0/7}$ and $36^{6/7}$ weeks [18]. Those who failed the test (or who required CPAP with ≥30% oxygen or mechanical ventilation) were classified as "BPD-any grade" and were further classified by the severity graded diagnostic criteria of Jensen et al. [23]. Infants were classified as Grades 2 and 3 BPD if they required either nasal cannula flow rates >2 L/min, noninvasive positive airway pressure, or invasive mechanical ventilation between $36^{0/7}$ and $36^{6/7}$ weeks. None of the infants who passed the room air challenge test ever met the criteria for BPD (grades 2 or 3).

During the study period, two different protocols for PDA treatment were used. Between January 2005 and May 2011, all infants <28weeks of gestation were treated with a course of prophylactic indomethacin starting within 15 hours of birth [26, 27]. After May 2011, a more conservative PDA treatment approach was instituted: indomethacin was not given prophylactically, and pharmacologic treatment was delayed until at least postnatal day 8 to allow for spontaneous ductus closure. Infants with moderate-to-large PDAs could receive pharmacologic treatment after 8 days if they met prespecified "Rescue" criteria [14]. Moderate-to-large PDAs were ligated only if the infant's ventilatory support was escalating for 4 to 5 days or failed to improve during a 2-weeks interval. During both epochs, "constricted" (small or closed) ductus were never treated.

There were no changes to any of our other previously published, consensus driven protocols [26, 27, 28] for respiratory and hemodynamic support, or for fluid and feeding management during the study period.

Gestational age was determined by the date of last menstrual period and ultrasounds performed prior to 24 weeks gestation. Small for gestational age infants had birthweight-for-gestational age z scores <1.29 using the growth curves from Fenton and Kim [29]. Serious intraventricular hemorrhages were defined as grades 3 or 4 intraventricular hemorrhage (using the four-level grading system) [30]. The Net Fluid Gain during the first 96 hours was calculated by subtracting the total urine output during first 4 days from the total fluid intake during first 4 days. "Early" onset and "late" onset bacteremia were culture-positive bacteremia that occurred ≤3 days or ≥4 days after birth, respectively. Necrotizing enterocolitis was defined as Bell's classification II or greater [31]. This included necrotizing enterocolitis that was treated medically or surgically, and spontaneous intestinal perforations that occurred before 10 days.

Statistical Analysis:

Stata software (Release 14; StataCorp LP, College Station, Texas) was used for all statistical analysis. Chi-squared or Fisher's exact, and Student's t-tests were used to compare groups for categorical and parametric variables, respectively. Our primary goal was to examine the effect of invasive mechanical ventilation on the relationship between PDA exposure and the outcome BPD (grades 2 and 3). The variable "duration of PDA exposure" was defined as a binary categorical variable: ≤6 days and ≥7days (see Results). The variable "duration of invasive mechanical ventilation" was defined as a binary variable (tracheal intubation ≤9 and ≥10 days) since prior studies have shown that the variable tracheal intubation between 7 and 14 days is both strongly associated with the outcome moderate/severe BPD and more strongly associated than other neonatal variables [32].

We used multivariable logistic regression models to adjust for the possible confounding effects of other prenatal and postnatal demographic variables on the relationship between PDA exposure and the outcome BPD (grades 2 and 3). Since the observational period of our study spanned an interval of 15 years, we included a demographic variable that examined the effects of birth epoch (when infants were admitted to the nursery: 2005–08, 2009–14, and 2015–19) in our comparisons.

We first created a basic model for the outcome BPD (grades 2 and 3) that included our variable of interest "duration of PDA exposure ≥7days" and the variable "gestational age ≤25 weeks." Using these two variables, we performed a logistic regression to determine the odds ratio (OR) of BPD (grades 2 and 3) for the primary independent variable "duration of PDA exposure ≥7days"

Next, we added each of the demographic or birth epoch variables listed in Table 1 to the basic model and reran the logistic regression to determine how much the OR for the variable "duration of PDA exposure ≥7days" was altered by the addition of the new variable to the basic model. If the addition of the new variable altered the OR for the association between "duration of PDA exposure ≥7days" and BPD by more than 10% it was considered to be an "important demographic variable" that should be added to the Final Adjusted model. We repeated this step for each of the demographic variables in Table 1. Finally, we created the Final Adjusted model by adding all of the "important demographic variables" to the basic model. We used Stata's margins command to estimate the individual adjusted risks and the risk ratio for the final adjusted models.

Results:

During the study period 501 infants <28 weeks of gestation were admitted to the nursery. Sixty-four infants died before an echocardiogram could be performed at the end of the first week. Among the remaining 437 potential study infants, 30 infants died before being evaluated for BPD at 36 weeks (Figure 1). There was no difference in the death rates prior to 36 weeks between infants exposed to a moderate-to-large PDA for ≥7 days and those exposed for ≤6 days (Figure 1). Our study population was comprised of the 407 infants who were evaluated for BPD at 36 weeks (Table 1). Thirty-one percent (128/407) of the study

population had “BPD-any grade”; 12% (48/407) had moderate-to-severe BPD (grades 2 & 3) defined by Jensen et al. [23].

Infants who permanently constricted (closed or small shunt) their PDA during the first postnatal week had similar rates of BPD (grades 2 & 3) as those who transiently reopened their PDA after the first week (developing a moderate-to-large shunt for ≤6 days) (Figure 2). On the other hand, infants who were exposed to a moderate-to-large PDA for longer than 7 days had a significantly higher incidence of BPD (grades 2 & 3) than those who permanently constricted their ductus during the first week (Figure 2). It is interesting to note that once infants were exposed to a moderate-to-large shunt for 7 to 13 days, additional exposure (≥14 days) was not associated with any further increase in the incidence of BPD (grades 2 & 3): PDA exposure for 7 to 13 days (referent: OR=1); 14 to 34 days: OR (95% CI) =1.24 (0.47–3.28); ≥35 days: 1.54 (0.59–4.09).

We created multivariable models to adjust for the possible confounding effects of demographic characteristics (listed in Table 1) on the relationship between PDA exposure and the incidence of BPD (grades 2 & 3) (see Methods) (Table 2). A significant relationship between prolonged PDA exposure (≥7 days) and the incidence of BPD (grades 2 & 3) persisted even after adjusting for potential confounding variables (Table 2).

Our main objective was to determine if the amount of invasive respiratory support that infants required (tracheal intubation ≤9 or ≥10 days) affected the relationship between PDA exposure and BPD (grades 2 & 3). After adjusting for potential confounding variables (see legend Table 2), we found that infants who required tracheal intubation for ≤9 days (n=237) had a low incidence of BPD (grades 2 & 3), whether the ductus constricted during the first week (2%), or whether it remained open for several weeks (6%) (adjusted risk difference = 4% (−1, 10%), p=0.13). In contrast, when this relationship was examined among infants who required tracheal intubation for ≥10 days (n=170), exposure to a persistent PDA for ≥7 days was associated with a significant increase in the risk of developing BPD (grades 2 & 3) (from 16% to 35%: adjusted risk difference = 19% (6, 32%), p<0.005).

Although the association between PDA-duration and BPD was only present in infants who required intubation for ≥10 days, the length of intubation did not appear to account for the association between PDA-duration and BPD. When the variable “duration of intubation ≥10 days” was added to the Final Adjusted multivariable model, the OR of the relationship between PDA-duration ≥7 days and BPD was changed very little (Table 2). Both variables, “duration of PDA exposure ≥7 days” and “duration of intubation ≥10 days”, were significantly and independently associated with the outcome “incidence of BPD (grades 2 and 3)” (OR for “intubation ≥10 days” = 3.07 (1.89–4.99) (p<0.0001); OR for “PDA exposure ≥7 days” = 4.14 (1.87–9.19)).

Discussion:

Our study demonstrates that prolonged PDA exposure (≥7 days) is associated with an increased risk of developing moderate and severe forms of BPD (grades 2 & 3); however, the increased risk only seems to apply to the most critically ill infants - those who require

prolonged intubation and mechanical ventilation (≥10 days). Infants who require less ventilatory support have a low incidence of BPD (grades 2 & 3) whether the PDA constricts and closes during the first week, or whether it remains open and persists for several weeks. Our findings support recent studies that have found an association between the duration of PDA exposure and the incidence of BPD (any grade) [15, 17, 33]; they extend the prior studies' findings to more narrowly identify which infants with a moderate-to-large PDA are at greatest risk.

Our study has several limitations. As an observational study, it cannot distinguish between causation and association. We used data from a single center. Since the rates of moderate-to-large PDA vary widely by center [14] our results may not be generalizable to other centers where the rates of PDA differ from ours. We focused our study on infants who continued to have a persistent PDA beyond the first week. Therefore, we cannot address whether brief exposures to a moderate-to-large PDA during the first week could have altered the study outcomes. However, the effects of PDA exposure during the first week have been addressed by several prior RCTs and no noticeable effect on the incidence of BPD has been found [9, 10, 11, 12, 13]. Our study also took place over a 15 years interval. Even though we examined the effects of being born during different birth epochs, or having different demographic characteristics, unmeasured differences in practice could have affected the rates of BPD. In addition, the relatively small size of our study may have made it difficult to detect significant differences among some of our PDA exposure subgroups.

Nevertheless, our results may help to explain some of the differences between results reported from clinical RCTs and those reported from preclinical studies in baboons (where all animals were intubated for 2 weeks and where the PDA exposures in the two experimental groups were 2 days and 14 days, respectively). In the early prophylactic treatment RCTs, infants were exposed to a moderate-to-large PDA for less than 7 days and the two infant study groups ("prophylactic" and "conservative treatment") only differed in their duration of PDA exposure by 3 days [9, 10, 11, 12, 13]. Our current results suggest that the duration of PDA exposure in the two groups may not have been sufficient to detect a potential association between PDA exposure and BPD.

Similarly, our results may also affect how one interprets the findings of the recent PDA-TOLERATE RCT where no difference was found in the incidence of BPD between "early" and "late" PDA treatment. In the PDA-TOLERATE trial only 50% of the enrolled infants were intubated and both treatment groups had prolonged PDA exposures (median exposures were 16 days and 30 days, respectively) [14]. Our current study suggests that the PDA exposures in both treatment groups may have been too long to expect to see a difference in the risk of BPD. In our current study, we found that once infants have been exposed to a moderate-to-large PDA for 7–13 days, additional lengths of PDA exposure are not associated with further increases in the risk of BPD (Figure 2).

In conclusion, we found that prolonged exposure to a PDA (even for several weeks) does not appear to be associated with an increased risk of BPD (grades 2 & 3) as long as the infant requires <10 days of intubation. On the other hand, when infants require intubation for ≥10

days, the presence of a moderate-to-large PDA shunt that persists beyond 7–13 days is associated with an increased risk of BPD (grades 2 & 3).

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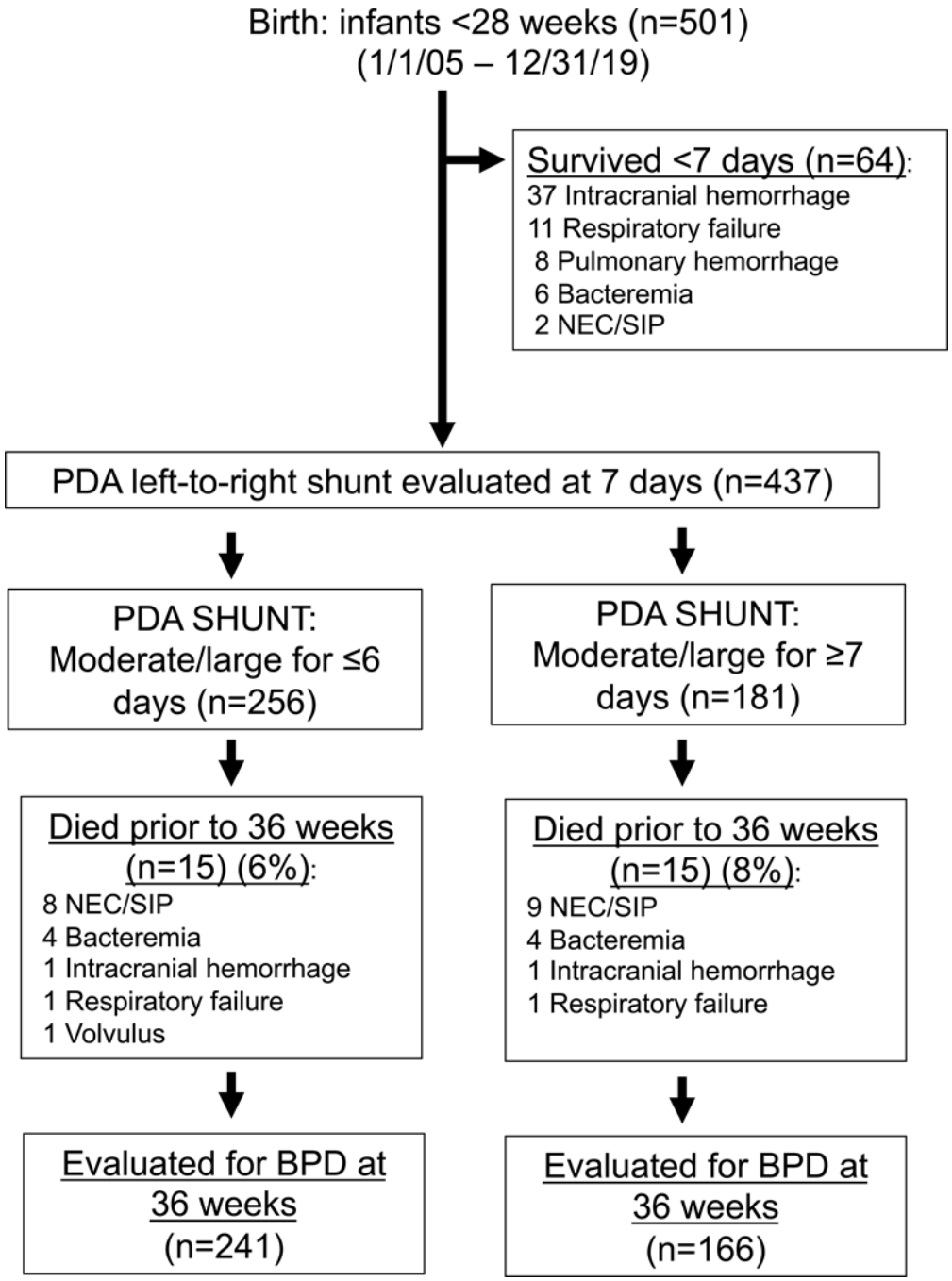

Figure 1: Flow diagram of patient entry into the study of BPD.

Sixty-four infants died before an echocardiogram could be performed at the end of the first week. After being evaluated by echocardiogram, 30 additional infants died before being evaluated for BPD

BPD, bronchopulmonary dysplasia (n=407).

NEC/SIP, necrotizing enterocolitis/spontaneous intestinal perforation

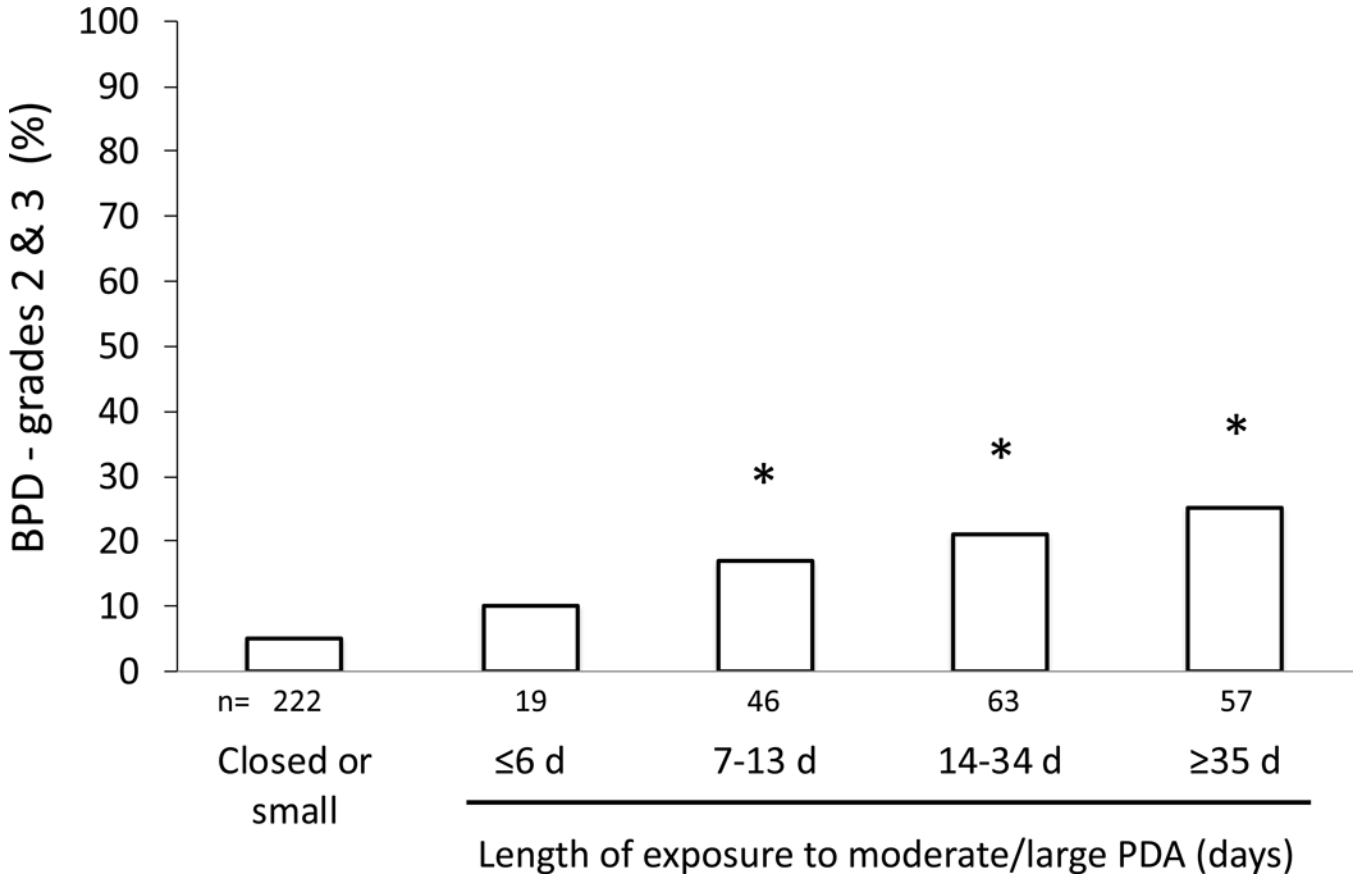

Figure 2: Relationship between PDA exposure and the outcome BPD (grades 2 & 3)

*, p-value <0.01, compared with infants who permanently constricted their ductus during the first week (Closed/Small PDA).

Closed/Small, infants who either closed their ductus permanently during the first week or had a small PDA at the end of the first week that either closed or remained small throughout the hospitalization.

≤6 days, infants with a constricted ductus during the first postnatal week (small or closed ductus at postnatal day 7) who subsequently reopened their PDA after the initial ductus constriction and were exposed to the reopened moderate-to-large PDA shunt for <7 days.

7–13 days, *14–34 days and ≥35 days*, total exposure to a moderate-to-large PDA for either 7–13 days, 14–34 days or ≥35 days, respectively: among infants who had a moderate-to-large PDA during the first week that persisted beyond 7 days and among infants with constricted ductus during the first week that later reopened, becoming moderate-to-large after the first week.

Table 1:

Demographic characteristics of infants who were evaluated for bronchopulmonary dysplasia at 36 weeks corrected age after being exposed to a moderate-to-large PDA shunt for ≤6 days or ≥7 days. Infants with a small or closed ductus at postnatal day 7 were assumed to have not been exposed to a moderate-to-large PDA during the first 7 days. Infants with a moderate-to-large PDA at postnatal day 7 were assumed to have been exposed to a moderate-to-large PDA for the entire 7 days.

	Duration of exposure to a moderate-to-large PDA		
Variable	**≤6 days** [1]	**≥7 days** [2]	**p-value**
N=	**241**	**166**	
Prenatal Variables:			
Multiple Gestation - %	29	35	
Preeclampsia - %	22	25	
Maternal Diabetes - %	12	15	
Chorioamnionitis - %	25	13	0.0450
Betamethasone ≥24 hours - %	76	72	
Caesarian Section - %	64	70	
Neonatal Variables:			
Gestation – weeks (m±sd)	26.4±1.0	26.0±1.1	0.0006
Gestation ≤25 weeks - %	32	46	0.0040
Birthweight – grams (m±sd)	857±195	794±189	0.0010
Small for Gestational Age - %	9	11	
Outborn - %	21	23	
Birth Epoch: (2005–08/2009–14/2015–19) - %	50/29/21	13/35/52	<0.0001
Caucasian - %	38	43	
Male - %	51	48	
5 minute Apgar ≤5 - %	30	38	
10 minute Apgar ≤5 - %	8	12	0.1330
Intubated during 1st 24 hours - %	83	81	
Still Intubated at 24 hours - %	51	64	0.0120
ICH (grades 3 or 4) - % [3]	10	10	
Net Fluid Gain 1st 96 hours – ml/kg (median (Interquartile range))	214 (146, 275)	183 (134, 267)	0.0900
Net Fluid Gain 1st 96 hours >250 ml/kg - %	34	30	
Bacteremia (early or late) - %	32	28	
Early Onset Bacteremia - %	5	4	
Late Onset Bacteremia - %	27	25	
Prophylactic Indomethacin - %	72	22	<0.0001
Any Pharmacologic PDA Treatment - % [4]	74	81	0.1400
PDA Ligation - %	5	19	0.0001
NEC/SIP - % [5]	11	12	

	Duration of exposure to a moderate-to-large PDA		
Variable	**≤6 days** [1]	**≥7 days** [2]	**p-value**
N=	**241**	**166**	
Duration of intubation ≥10 days - %	34	53	0.0002
Outcomes:			
BPD – any grade - %	22	45	<0.0001
BPD – Grades 2 & 3 - %	5	21	<0.0001
Discharged home in O2 or died from chronic lung disease after 37 weeks - % [6]	22	39	0.0004

p-values, only p-values ≤0.1500 are reported.

[1] *≤6 days*, ductus that were closed or small at the end of the first week and stayed closed or small throughout the hospitalization (n=222), plus ductus that reopened, becoming moderate-to-large after the first week, that had a moderate-to-large shunt for ≤6 days before closing permanently (n=19).

[2] *≥7 days*, exposure to a moderate-to-large PDA for ≥7 days: PDA shunts that were moderate-to-large during the first week that persisted beyond 7 days, plus ductus that were constricted during the first week, that later reopened, becoming moderate-to-large after the first week, and persisting for ≥7 days.

[3] *ICH (grades 3 or 4),* serious intraventricular hemorrhages

[4] *Any PDA Treatment*, infants who received prophylactic indomethacin and/or later pharmacologic PDA treatment

[5] NEC/SIP, Necrotizing enterocolitis/Spontaneous intestinal perforations.

[6] *Discharged home in O2 or died from chronic lung disease:* infants who were discharged home with oxygen (n=108) or died from progressive respiratory failure after 37 weeks (n=7) (n=397; 10 infants were not available for evaluation due to death from NEC after 36 weeks (n=2) or discharge information unavailable from the referral hospital (n=8).

Table 2:

Statistical models for examining the relationship between PDA exposure and the outcome BPD (grades 2 and 3).

Statistical Models	BPD (grades 2 & 3)		
	PDA duration ≤6 days (n=241)	PDA duration ≥7 days (n=166)	p-value
Unadjusted Model			
Risk	.05	0.21	<0.001
Odds Ratio (95% CI)	4.69 (2.39–9.17)		<0.001
Risk Ratio (95% CI)	3.91 (2.13–7.16)		<0.001
Risk Difference (95% CI)	0.16 (0.09–2.3)		<0.001
Final Adjusted Model *			
Risk	0.06	0.18	<0.001
Odds Ratio (95% CI)	4.22 (1.97–9.03)		<0.001
Risk Ratio (95% CI)	2.88 (1.61–5.14)		<0.001
Risk Difference (95% CI)	0.12 (0.05–0.18)		<0.001
Final Adjusted Model * **plus Need for Intubation ≥ 10 days** #			
Risk	0.07	0.17	<0.001
Odds Ratio (95% CI)	4.14 (1.87–9.19)		<0.001
Risk Ratio (95% CI)	2.60 (1.49–4.52)		<0.001
Risk Difference (95% CI)	0.11 (0.05–0.16)		<0.001

*, Final adjusted model was adjusted for all of the demographic variables from Table 1 that were considered to be “important demographic variables” (see Methods): gestational age, small for gestational age, tracheal intubation still required at 24 hours after birth, PDA ligation, bacteremia (either early or late onset).

#, statistical model includes all of the variables in the Final Adjusted model plus the variable “need for tracheal intubation for longer than 10 days”.