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Prolonged tracheal intubation and the association between patent ductus arteriosus and bronchopulmonary dysplasia: a secondary analysis of the PDA-TOLERATE trial

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PII: S0022-3476(20)31180-X

DOI: <https://doi.org/10.1016/j.jpeds.2020.09.047>

Reference: YMPD 11797

To appear in: *The Journal of Pediatrics*

Received Date: 8 July 2020

Revised Date: 16 August 2020

Accepted Date: 17 September 2020

Please cite this article as: Clyman RI, Kaempf J, Liebowitz M, Erdeve O, Bulbul A, Håkansson S, Lindqvist J, Farooqi A, Katheria A, Sauberan J, Singh J, Nelson K, Wickremasinghe A, Dong L, Hassinger DC, Aucott SW, Hayashi M, Heuchan AM, Carey WA, Derrick M, Fernandez E, Sankar M, Leone T, Perez J, Serize A, PDA-TOLERATE (PDA: TO LEave it alone or Respond And Treat Early) Trial Investigators, Prolonged tracheal intubation and the association between patent ductus arteriosus and bronchopulmonary dysplasia: a secondary analysis of the PDA-TOLERATE trial, *The Journal of Pediatrics* (2020), doi: <https://doi.org/10.1016/j.jpeds.2020.09.047>.

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**Title: Prolonged tracheal intubation and the association between patent ductus arteriosus and bronchopulmonary dysplasia: a secondary analysis of the PDA-TOLERATE trial**

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**Reprint requests:** none available

Supported by the Gerber Foundation, U.S. Public Health Service National Heart, Lung and Blood Institute (HL109199), National Center for Advancing Translational Sciences, National Institutes of Health, through (UL1 TR001872, UL1 TR000004 and UL1TR001873), and a gift from the Jamie and Bobby Gates Foundation. The authors declare no conflicts of interest.

**key words:** premature birth, bronchopulmonary dysplasia, patent ductus arteriosus

**Abbreviations:**

PDA, patent ductus arteriosus

RCT, randomized clinical trials PDA

BPD, bronchopulmonary dysplasia

PDA-TOLERATE trial, the PDA: TO LEave it alone or Respond And Treat Early trial

NEC/SIP, necrotizing enterocolitis or spontaneous intestinal perforation

In the PDA-TOLERATE trial, persistent, moderate-to-large PDAs (even for several weeks) were not associated with an increased risk of BPD when infants required <10 days of intubation. However, if infants required intubation for  $\geq 10$  days, prolonged PDA exposures ( $\geq 11$  days) were associated with an increased risk of moderate/severe BPD.

Between 50-70% of infants <28 weeks' gestation have a patent ductus arteriosus (PDA) that persists for weeks after birth<sup>1</sup>. Early PDA closure can decrease the incidence of several neonatal morbidities that occur during the first week after birth, such as dopamine-dependent hypotension, early hemorrhagic pulmonary edema, and the intensity of respiratory support<sup>2-6</sup>. Whether exposure to a PDA shunt increases the risks of later neonatal morbidities, like bronchopulmonary dysplasia (BPD), is still unclear. None of the randomized clinical trials (RCTs) performed to date have found a relationship between therapies intended to close the PDA and the risk of developing BPD<sup>5,7-12</sup>. Unfortunately, when these trials were initially designed there was little information available to determine which infants with a PDA were actually at risk for BPD and might benefit from enrollment in such a trial. Little attention was paid to either the magnitude of the PDA shunt, the duration of shunt exposure, or the infant's need for respiratory support.

Several recent single-center observational studies have shown that infants with small PDA shunts do not appear to be at increased risk for developing BPD. Instead, an association between PDA and BPD only appears to occur when moderate-to-large shunts persist beyond 7-14 days<sup>13-17</sup>. An infant's need for invasive respiratory support also may play an important role in determining whether prolonged PDA exposure is associated with BPD. A recent single center study found that the association between BPD and exposure to a moderate-to-large PDA was only observed when infants required mechanical ventilation and intubation for  $\geq 10$  days<sup>17</sup>. The incidence of BPD among infants who required intubation for shorter durations ( $< 10$  days) was the same whether the ductus closed soon after birth or whether it persisted as a moderate-to-large shunt for several weeks<sup>17</sup>. The results of these single center studies need to be confirmed by other centers before they can be thought of as useful, consistent criteria for identifying infants at risk for developing BPD if the ductus fails to close after birth.

The PDA-TOLERATE trial (NCT01958320) was a prospective randomized controlled trial conducted between January 2014 and June 2017 at 17 international neonatal intensive care centers<sup>11</sup>. The trial enrolled infants  $\leq 28$  weeks' gestation to determine if routine pharmacologic PDA treatment at the end of the first postnatal week would reduce neonatal morbidity compared with a conservative approach that delayed PDA drug treatment for at least another 7-10 days. The trial demonstrated that routine PDA treatment at the end of the first week did not reduce PDA ligations or any of the pre-specified secondary outcomes like BPD.

We performed a secondary analysis of the data from the PDA-TOLERATE trial to determine if an infant's need for invasive respiratory support plays a role in shaping the relationship between PDA exposure and BPD. We were particularly interested in determining whether the association between PDA exposure and BPD depended on the length of time that an infant required tracheal intubation.

### **Methods:**

We utilized deidentified data from the multicenter PDA-TOLERATE trial (NCT01958320). Institutional review board approval and written informed parental consent were obtained before patient enrollment into the trial. The trial enrolled 202 infants (<28<sup>0/7</sup> weeks' gestation) at the end of the first week (between 6-14 days) who still had a persistent moderate-to-large PDA and who required continuing respiratory support with either nasal CPAP or intubation and mechanical ventilation. Infants were randomized to receive either "early routine" pharmacologic PDA treatment (n=104) or a "conservative approach" (n=98) that delayed pharmacologic treatment until at least 7 days after randomization. Infants randomized to the conservative approach were not eligible for pharmacologic PDA treatment unless one or more pre-specified respiratory and/or cardiovascular "rescue" criteria were met<sup>11</sup>. Rescue surgical ligation was used in both trial groups only if pharmacologic agents failed to constrict the PDA or were contraindicated<sup>18,19</sup>. The decision to use rescue ligation was left to the attending neonatologist. Full details of the PDA-TOLERATE trial including screening, echocardiographic analyses, inclusion and exclusion criteria, enrollment, drug treatment protocols, rescue criteria, and definitions of study variables and outcomes have been published elsewhere<sup>11</sup>.

Echocardiographic studies in the PDA-TOLERATE trial were performed according to the study protocol and schedule for examinations<sup>11</sup> and included two-dimensional imaging, M-mode, color flow mapping and Doppler interrogation as previously described<sup>19,20</sup>. A moderate-to-large PDA was defined by a ductus internal diameter  $\geq 1.5$ mm (or PDA:left pulmonary artery diameter ratio  $\geq 0.5$ ) and one or more of the following echocardiographic criteria: a) left atrium-to-aortic root ratio  $\geq 1.6$ , b) ductus flow velocity  $\leq 2.5$ m/sec, c) left pulmonary artery diastolic flow velocity  $>0.2$  m/sec, and/or d) reversed diastolic flow in the descending aorta. PDAs that did not meet these criteria were considered to be "*constricted*" (small or closed) and not eligible for enrollment or treatment. The cardiologists or echocardiography-trained neonatologists reading the echocardiograms were unaware of the infants' treatment assignments.

All infants had an echocardiogram performed at the time of randomization. A repeat echocardiogram was performed in both the Conservative and Early treatment groups between five-to-seven days after randomization. Infants with a “constricted” (small or closed) ductus 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. In addition, routine echocardiograms were performed every 2-3 weeks in infants with a “constricted” PDA until ductus closure or hospital discharge. Infants with a persistent moderate-to-large PDA were followed with frequent (every 7-14 days) echocardiograms to determine when ductus constriction occurred. Echocardiograms were performed until ductus closure or hospital discharge.

The duration of exposure to a moderate-to-large PDA was calculated and expressed in days. The day of birth was considered day 0. All infants in the trial had a persistent moderate-to-large PDA at the time of enrollment and were assumed to have been exposed to a moderate-to-large PDA since birth. The time of ductus constriction was assumed to have occurred at the halfway point between the last examination with a moderate-to-large PDA and the first examination with a constricted ductus. When reopening of the PDA occurred after documented ductus constriction, the additional exposure to the reopened moderate-to-large PDA shunt was 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 examination with a moderate-to-large PDA and the first examination with a constricted ductus). The duration of exposure to the reopened PDA was added to the initial moderate-to-large PDA shunt exposure.

Our primary outcome for this secondary analysis was the incidence of BPD (both “any grade” and the incidence of moderate-to-severe BPD (grades 2 and 3) as defined by Jensen et al<sup>21</sup>. 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 <sup>21</sup>. All study infants (except those requiring CPAP with  $\geq 30\%$  oxygen or mechanical ventilation), first underwent a modified room air challenge test between 36<sup>0/7</sup> and 36<sup>6/7</sup> weeks <sup>22</sup>. Those who failed the test (or who required CPAP with  $\geq 30\%$  oxygen or mechanical ventilation) were classified as "BPD-any grade" and were further classified by the severity graded diagnostic criteria of Jensen et al. <sup>21</sup>. 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<sup>0/7</sup> and 36<sup>6/7</sup> weeks. None of the infants who passed the room air challenge test ever met the criteria for BPD (grades 2 or 3).

#### **Statistical Analyses:**

Chi-squared, Fisher exact, Mann-Whitney, and Student 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 the variable "duration of PDA exposure" and the outcome BPD (both "any grade" and grades 2 and 3). Prior single center, observational studies reported that infants  $<28$  weeks' gestation, who were exposed to a moderate-to-large PDA for longer than 7-14 days, had a significantly higher incidence of BPD than those exposed to shorter durations of ductus patency; in addition, once the threshold exposure of 7-14 days was reached, additional exposures ( $>15$  days) were not associated with additional increases in the incidence of BPD <sup>15, 17</sup>. Therefore, in our study, the variable "duration of PDA exposure" was defined as a binary categorical variable: exposure to a moderate-to-large PDA for  $<11$  days and  $\geq 11$  days. Similarly, the variable "duration of invasive mechanical ventilation" was defined as a binary variable (tracheal intubation  $<10$  and  $\geq 10$  days) because

prior studies have shown that the variable “tracheal intubation  $\geq 10$  days” was both significantly associated with the outcome BPD<sup>17</sup> and more strongly associated with the outcome BPD than other neonatal variables<sup>23</sup>. The variable “duration of tracheal intubation” included both consecutive and non-consecutive days of intubation.

### **Results:**

Among the 202 infants in the PDA-TOLERATE trial, 25 infants were exposed to a moderate-to-large PDA for  $< 11$  days and 177 for  $\geq 11$  days; 26 infants died before being evaluated for BPD at 36 weeks (Figure 1; available at [www.jpeds.com](http://www.jpeds.com)). There was no difference in the death rates prior to 36 weeks between infants exposed to a moderate-to-large PDA for  $< 11$  days and those exposed for  $\geq 11$  days (Figure 1).

Our study population was comprised of the 176 infants who were evaluated for BPD at 36 weeks (Table). Among the perinatal or neonatal demographic characteristics listed in the Table only two characteristics were significantly different between the two PDA exposure groups: infants exposed to a moderate-to-large PDA for  $\geq 11$  days were more likely to be randomized to the conservative approach and were more likely to be randomized at a later postnatal age (Table).

Overall, 51% (90/176) of the study population had BPD-any grade; 26% (46/176) had moderate-to-severe BPD (grades 2 & 3). As has been previously observed<sup>23</sup>, the incidence of BPD was significantly greater among infants who received tracheal intubation for  $\geq 10$  days than those who received shorter periods of intubation (BPD-any grade: intubated  $< 10$  days=27% (24/88), intubated  $\geq 10$  days=75% (66/88),  $p < 0.0001$ ; BPD (grades 2 & 3): intubated  $< 10$  days=11% (10/88), intubated  $\geq 10$  days=41% (36/88),  $p < 0.0001$ ).

Our main objective was to determine if the amount of invasive respiratory support that infants received also affected the relationship between PDA exposure and BPD. Among infants who received  $< 10$  days of intubation, prolonged exposure to a moderate-to-large PDA (even for

several weeks) did not appear to be associated with an increased risk of BPD (Figure 2): *BPD-any grade*: PDA <11 days=30% (3/10), PDA ≥11 days=27% (21/78),  $p=1.00$ ; *BPD (grades 2 & 3)*: PDA <11 days=10% (1/10), PDA ≥11 days=12% (9/78),  $p=1.00$ .

On the other hand, when this relationship was examined among infants who required tracheal intubation for ≥10 days, prolonged exposure to a moderate-to-large PDA was associated with a significant increase in the risk of developing BPD (Figure 2): *BPD-any grade*: PDA <11 days=40% (4/10), PDA ≥11 days=79% (62/78),  $p=0.01$ ; *BPD (grades 2 & 3)*: PDA <11 days=10% (1/10), PDA ≥11 days=45% (35/78),  $p=0.04$ .

### **Discussion:**

Our secondary analysis of the multi-center PDA-TOLERATE trial agrees with the findings from prior single center observational studies that have reported an association between the duration of PDA exposure and the incidence of BPD<sup>13-17</sup>, and extends the prior studies' findings to more narrowly identify which infants with a moderate-to-large PDA are at greatest risk for developing BPD. In our study, prolonged PDA exposure (≥11 days) was associated with an increased incidence of both BPD-any grade and moderate/severe forms of BPD (grades 2 & 3). However, the increased risk of BPD that was associated with prolonged PDA exposure only occurred in infants who also received prolonged intubation and mechanical ventilation (≥10 days). The incidence of BPD among infants who received less ventilatory support (intubation for <10 days) was the same whether the ductus closed shortly after birth or whether it persisted as a moderate-to-large shunt for several weeks. Although our results do not prove a cause-and-effect relationship, they do indicate that the presence of a moderate-to-large PDA shunt, that persists beyond 10 days in infants requiring prolonged intubation, may be a useful biomarker for identifying infants at increased risk for BPD. In addition, our results suggest that if a clinician's sole purpose for wanting to close a PDA is to decrease the incidence of BPD, then infants who require shorter durations of intubation (<10 days) may not need to have their

ductus closed even if they do have a moderate-to-large PDA shunt that persists for several weeks.

Our study has several limitations. As an observational study, it cannot distinguish between causation and association. Because echocardiograms were performed every 7 days during the first three weeks, the exact duration of exposure to the moderate-to-large PDA was an assumption based on the halfway point between the last examination with a moderate-to-large PDA and the first examination with a constricted ductus. In addition, 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<sup>5,7-10</sup>. The relatively small size of our study may have made it difficult to detect significant differences among some of our PDA exposure subgroups. Even though there were no significant differences in any of the neonatal demographic characteristics between infants exposed to a moderate-to-large PDA for <11 days and ≥11 days unmeasured differences in practice might have affected the rates of BPD.

Our results may help to interpret the findings of two recently reported PDA treatment RCTs (PDA-TOLERATE trial and “Nonintervention vs Oral Ibuprofen” trial)<sup>11,12</sup>. In contrast with earlier PDA treatment RCTs, where PDA shunt magnitude was usually unknown, both trials were designed to exclusively enroll infants with moderate-to-large PDAs. Although the infants enrolled in these trials were the ones most likely to be affected by the presence of a persistent PDA, neither trial found that the drugs used to close the PDA had any effect on the risk of BPD. We speculate that one possible explanation for the failure of both trials to detect a causal relationship between PDA exposure and BPD is that infants in the early treatment arms of both trials may have been exposed to moderate-to-large PDA shunts for too long an interval for the

infants to receive any benefit from treatment. Both studies suffered from having a low rate of PDA closure in the early treatment arm of the trial. In the PDA-TOLERATE trial, among the infants most likely to develop BPD (those ventilated for  $\geq 10$  days), only 22% of the early treatment enrollees constricted their ductus before 11 days and 78% of the early treatment group ultimately were exposed to a prolonged moderate-to-large PDA shunt that persisted for  $\geq 11$  days <sup>11</sup>. Similarly, only 20% of the infants in the early treatment arm of the “Nonintervention vs Oral Ibuprofen” trial constricted their ductus before 2 weeks <sup>12</sup>. Successful closure was even less among infants born between 23-to-26 weeks’ gestation in the “Nonintervention vs Oral Ibuprofen” trial where only 8% constricted their ductus before 2 weeks. In both studies, the failure of early routine PDA treatment to decrease the incidence of BPD might be attributable to the low therapeutic efficacy of the drugs used for closing the PDA. Future RCTs will need to find reliable treatments that can close the PDA before 11 days if we are ever to learn whether early closure of the PDA will or will not decrease the incidence of BPD.

In conclusion, in the PDA-TOLERATE trial, which tolerated moderate-to-large PDAs for the first week in infants  $< 28^{0/7}$  weeks’ gestation, the presence of a PDA shunt was associated with an increased risk of BPD when it persisted beyond 10 days and the infant also required prolonged intubation ( $\geq 10$  days). On the other hand, prolonged exposure to a PDA (even for several weeks) did not appear to be associated with an increased risk of BPD if the infant only required  $< 10$  days of intubation.

**Figure 1; online:** Flow diagram of patient distribution in the PDA-TOLERATE trial: number of infants exposed to a moderate-to-large PDA shunt for  $<11$  days or  $\geq 11$  days who were evaluated for BPD at 36 weeks post menstrual age.

**Figure 2:** Relationship between PDA exposure and the outcomes BPD-any grade and BPD-grades 2 & 3 among infants intubated for  $<10$  days or  $\geq 10$  days. The height of the bars represents the incidence of BPD-any grade. The clear portion of the bar represents the incidence of BPD grade 1. The solid portion of the bar represents the incidence of BPD grades 2 & 3. Infants exposed to a moderate-to-large PDA for  $\geq 11$  days were arbitrarily divided into 3 exposure subgroups (11-14 days, 15-20 days, and  $>20$  days) to illustrate how incremental increases in exposure (beyond 10 days) affects the association between BPD and the presence of a persistent PDA.

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Table 1

Variable	Duration of exposure to a moderate-to-large PDA		
	<11 days	≥11 days	p-value
N=	20	156	
<b>Prenatal Variables:</b>			
Multiple Gestation - %	30	32	
Preeclampsia - %	20	18	
Maternal Diabetes - %	10	4	
Chorioamnionitis - %	15	15	
Antenatal Betamethasone <24 hours - %	45	33	
Caesarian Section - %	70	71	
<b>Neonatal Variables:</b>			
Gestation - weeks (m±sd) <sup>1</sup>	25.7±1.2	25.9±1.1	
Gestation ≤25 weeks - %	60	49	
Birthweight - grams (m±sd)	818±125	810±175	
Small for Gestational Age - % <sup>2</sup>	0	8	
Caucasian - %	45	51	
Male - %	50	45	
5 minute Apgar ≤5 - %	40	32	
Intubated in the delivery room - %	65	67	
Intubated during 1 <sup>st</sup> 24 hours - %	95	90	
Still Intubated at 24 hours - %	50	65	
Dopamine during 1st 72 hours after birth - %	35	33	
ICH (grades 3 or 4) - % <sup>3</sup>	10	11	
PDA-TOLERATE-Age at randomization -days	6.3±1.1	8.5±2.1	<0.001
PDA-TOLERATE-Conservative group - %	10	56	<0.001
Intubated at enrollment - %	60	45	
Postnatal steroids - %	30	44	
Early Onset Bacteremia - % <sup>4</sup>	10	2	
Late Onset Bacteremia - % <sup>5</sup>	20	22	
SIP/NEC - % <sup>6</sup>	10	14	
Any Pharmacologic PDA Treatment - % <sup>7</sup>	90	71	
PDA Ligation - %	0	13	
Duration of moderate/large PDA exposure -days median (IQR) <sup>8</sup>	10 (9-10)	26 (19-49)	<0.001
Duration of intubation - days median (IQR)	8.5 (0-16.5)	9.0 (0-27)	
Duration of intubation ≥10 days - %	50	50	

Table 1 legend: 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 <11 days or ≥11 days.

p-values, only p-values ≤0.150 are reported.

<sup>1</sup> Gestational age was determined by the date of last menstrual period and ultrasounds performed prior to 24 weeks gestation.

<sup>2</sup> *Small for Gestational Age*, infants with birthweight-for-gestational age z scores <-1.29 using the growth curves from Fenton and Kim <sup>24</sup>.

<sup>3</sup> *ICH (grades 3 or 4)*, serious intraventricular hemorrhages defined as grades 3 or 4 intraventricular hemorrhage using the four-level grading system <sup>25</sup>.

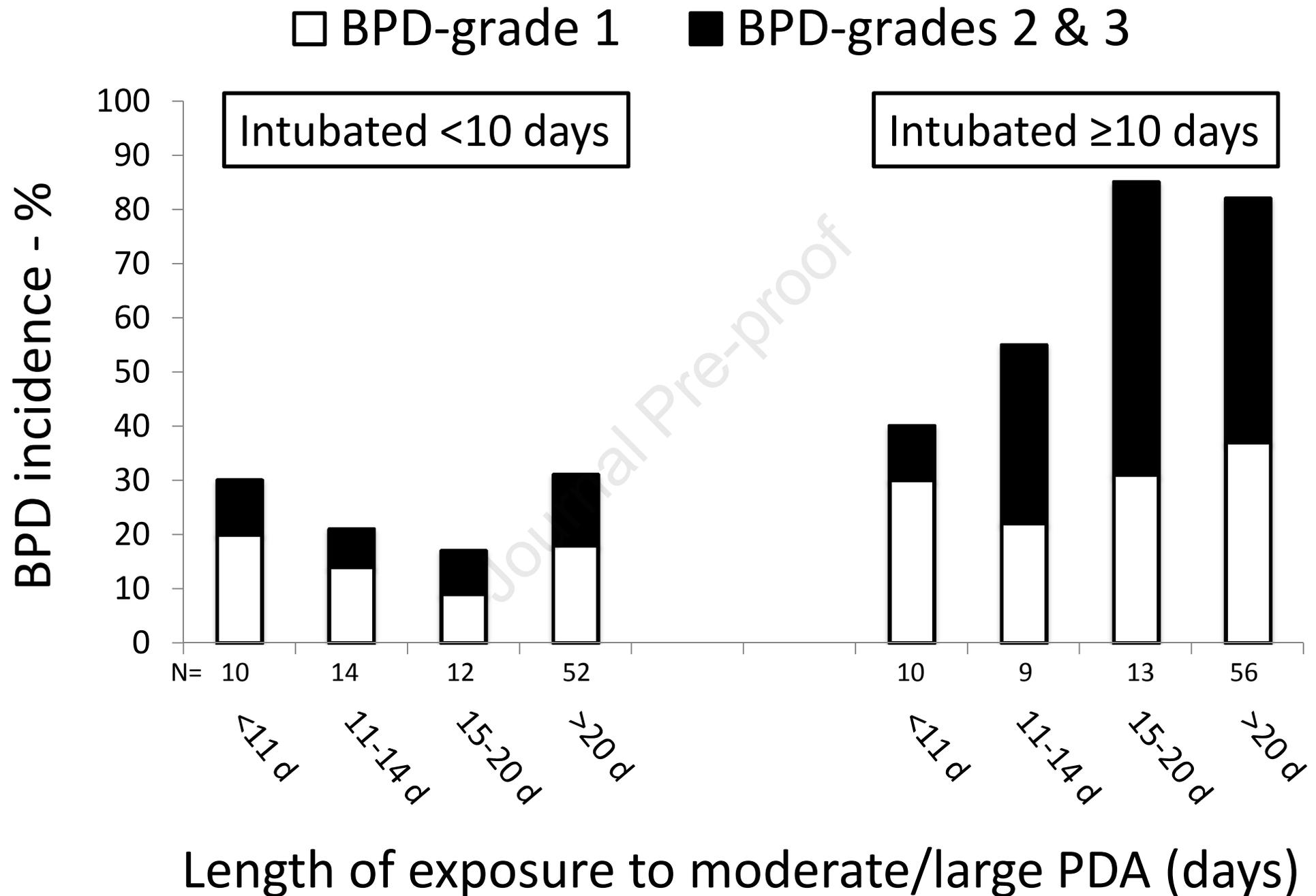
<sup>4</sup> *Early onset*, culture-positive bacteremia that occurred  $\leq 3$  days after birth.

<sup>5</sup> *Late onset bacteremia*, culture-positive bacteremia that occurred  $\geq 4$  days after birth.

<sup>6</sup> *SIP/NEC*, spontaneous intestinal perforation that occurred before 10 days, or necrotizing enterocolitis, defined as Bell's classification II or greater (either medically or surgically treated) <sup>26</sup>.

<sup>7</sup> *Any PDA Treatment*, infants who received PDA treatment as part of the Early PDA treatment protocol or later Rescue PDA treatment.

<sup>8</sup> *IQR*, interquartile range.



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PDA-TOLERATE trial: Infants <28 weeks gestation with a moderate-to-large PDA still present at 6-14 days and need for CPAP or invasive respiratory support (n=202)



PDA SHUNT:  
Moderate/large for <11  
days (n=25)

PDA SHUNT:  
Moderate/large for ≥11  
days (n=177)



Died prior to 36 weeks  
(n=5) (20%):  
3 NEC/SIP  
2 Bacteremia

Died prior to 36 weeks  
(n=21) (12%):  
10 NEC/SIP  
9 Bacteremia  
1 Volvulus  
1 Meconium ileus



Evaluated for BPD at  
36 weeks  
(n=20)

Evaluated for BPD at  
36 weeks  
(n=156)