Title

Prolonged Tracheal Intubation and the Association Between Patent Ductus Arteriosus and Bronchopulmonary Dysplasia: A Secondary Analysis of the PDA-TOLERATE trial

Authors

Clyman, Ronald I
Kaempf, Joseph
Liebowitz, Melissa
et al.

Publication Date

2021-02-01

DOI

10.1016/j.jpeds.2020.09.047

Peer reviewed

Published in final edited form as:

J Pediatr. 2021 February ; 229: 283–288.e2. doi:10.1016/j.jpeds.2020.09.047.

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

Ronald I. Clyman, MD[1,2], **Joseph Kaempf, MD**[3], **Melissa Liebowitz, MD**[1], **Omer Erdeve, MD**[4], **Ali Bulbul, MD**[5], **Stellan Håkansson, MD**[6], **Johanna Lindqvist, MD**[6], **Aijaz Farooqi, MD**[6], **Anup Katheria, MD**[7], **Jason Sauberan, PharmD**[7], **Jaideep Singh, MD**[8], **Kelly Nelson, MD**[8], **Andrea Wickremasinghe, MD**[9], **Lawrence Dong, MD**[9], **Denise C. Hassinger, MD**[10], **Susan W. Aucott, MD**[11], **Madoka Hayashi, MD**[11], **Anne Marie Heuchan, MD**[12], **William A. Carey, MD**[13], **Matthew Derrick, MD**[14], **Erika Fernandez, MD**[15], **Meera Sankar, MD**[16], **Tina Leone, MD**[17], **Jorge Perez, MD**[18], **Arturo Serize, PA**[18], **PDA-TOLERATE (PDA: TO LEave it alone or Respond And Treat Early) Trial Investigators***

[1]Department of Pediatrics, University of California San Francisco

[2]Department of Cardiovascular Research Institute, University of California San Francisco

[3]Department of Pediatrics of Providence St. Vincent Medical Center, Portland, OR

[4]Department of Pediatrics of Ankara University School of Medicine Children's Hospital, Ankara, Turkey

[5]Department of Pediatrics of Sisli Hamidiye Etfal Training and Research Hospital, İstanbul, Turkey

[6]Department of Pediatrics of Umea University Hospital, Umea, Sweden

[7]Department of Pediatrics of Sharp Mary Birch Hospital, San Diego, CA

[8]Department of Pediatrics of University of Chicago, Chicago, IL

[9]Department of Pediatrics of Kaiser Permanente Santa Clara Medical Center, Santa Clara, CA

[10]Department of Pediatrics of Morristown Medical Center, Morristown, NJ

[11]Department of Pediatrics of Johns Hopkins University, Baltimore, MD

[12]Department of Pediatrics of University of Glasgow, Royal Hospital for Sick Children, Glasgow, Scotland, UK

[13]Department of Pediatrics of Mayo Clinic, Rochester, MN

[14]Department of Pediatrics of Northshore University Health System, Evanston, IL

Address for correspondence: Ronald Clyman, MD, University of California San Francisco, 513 Parnassus Ave., UCSF Box 0734, San Francisco, CA 94143-0734; phone:415-353-1565; clymanr@peds.ucsf.edu.

*List of additional PDA-TOLERATE Trial investigators available at www.jpeds.com (Appendix)

[15]Department of Pediatrics of University of California San Diego and Rady Children's Hospital, San Diego, CA

[16]Department of Pediatrics of Good Samaritan Hospital, San Jose, CA

[17]Department of Pediatrics of Columbia University Medical Center, New York, NY

[18]Department of Pediatrics of South Miami Hospital/Baptist Health South Florida, Miami, FL

Keywords

premature birth; bronchopulmonary dysplasia; patent ductus arteriosus

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 ≥10 days, prolonged PDA exposures (≥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 [1]. 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 [2–6]. 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 [5, 7–12]. 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 [13–17]. 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 ≥10 days [17]. 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 [17]. 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 [11]. The trial enrolled infants ≤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 (<$28^{0/7}$ 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 [11]. Rescue surgical ligation was used in both trial groups only if pharmacologic agents failed to constrict the PDA or were contraindicated [18, 19]. 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 [11].

Echocardiographic studies in the PDA-TOLERATE trial were performed according to the study protocol and schedule for examinations [11] and included two-dimensional imaging, M-mode, color flow mapping and Doppler interrogation as previously described [19, 20]. A moderate-to-large PDA was defined by a ductus internal diameter ≥ 1.5mm (or PDA:left pulmonary artery diameter ratio ≥0.5) and one or more of the following echocardiographic criteria: a) left atrium-to-aortic root ratio ≥1.6, b) ductus flow velocity ≤2.5m/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 [21]. 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 [21]. 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 [22]. 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. [21]. 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).

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 [15, 17]. 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 ≥11 days. Similarly, the variable "duration of invasive mechanical ventilation" was defined as a binary variable (tracheal intubation <10 and ≥10 days) because prior studies have shown that the variable "tracheal intubation ≥10 days" was both significantly associated with the outcome BPD [17] and more strongly associated with the outcome BPD than other neonatal variables [23]. 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 ≥11 days; 26 infants died before being evaluated for BPD at 36 weeks (Figure 1; available at 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 ≥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 ≥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 [23], the incidence of BPD was significantly greater among infants who received tracheal intubation for ≥10 days than those who received shorter periods of intubation (BPD-any grade: intubated <10 days=27% (24/88), intubated ≥10 days=75% (66/88), p<0.0001; BPD (grades 2 & 3): intubated <10 days=11% (10/88), intubated ≥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 [13–17], 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 [5, 7–10]. 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 ≥11days 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) [11, 12]. 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 ≥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 ≥11 days [11]. Similarly, only 20% of the infants in the early treatment arm of the "Nonintervention vs Oral Ibuprofen" trial constricted their ductus before 2 weeks [12]. 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 (≥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.

Acknowledgments

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.

Appendix: Additional PDA-TOLERATE Investigators

Study Coordinating Center:

University of California San Francisco, San Francisco, CA

Scott Fields, PharmD

Providence St. Vincent Medical Center, Portland, OR

Lora Whitten, RN

Stefanie Rogers, MD

Ankara University School of Medicine Children's Hospital, Ankara, Turkey

Emel Okulu, MD

Gaffari Tunc, MD

Tayfun Ucar, MD

Sisli Hamidiye Etfal Training and Research Hospital, İstanbul, Turkey

Ebru Türkoglu Ünal, MD

Sharp Mary Birch Hospital, San Diego, CA

Jane Steen, RN

Kathy Arnell, RN

University of Chicago, Chicago, IL

Sarah Holtschlag, RN

Michael Schreiber, MD

Morristown Medical Center, Morristown, NJ

Caryn Peters, RN

Johns Hopkins Hospital, Baltimore, MD

Maureen Gilmore, MD

University of Glasgow, Royal Hospital for Sick Children, Glasgow, Scotland, UK

Lorna McKay, RN

Dianne Carole, RN

Annette Shaw, RN

Mayo Clinic, Rochester, MN

Malinda Harris, MD

Amy Amsbaugh, RRT

Lavonne M. Liedl, RRT

Northshore University Health System, Evanston, IL

Sue Wolf, RN

Avi Groner, MD

University of California San Diego and Rady Children’s Hospital, San Diego, CA

Amy Kimball, MD

Jae Kim, MD

Renee Bridge, RN

Ellen Knodel, RN

Good Samaritan Hospital, San Jose, CA

Chrissy Weng, RN

South Miami Hospital/Baptist Health South Florida, Miami, FL

Magaly Diaz Barbosa, MD

Columbia University Medical Center, New York, NY

Richard Polin, MD

Marilyn Weindler, RN

Data Safety Monitoring Committee:

Shahab Noori, MD, University of Southern California, Los Angeles, CA

Jeffrey Reese, MD, Vanderbilt University, Nashville, TN

Yao Sun, MD, University of California San Francisco, San Francisco, CA

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

References

[1]. Sung SI, Chang YS, Chun JY, Yoon SA, Yoo HS, Ahn SY, et al. Mandatory Closure Versus Nonintervention for Patent Ductus Arteriosus in Very Preterm Infants. J Pediatr. 2016;177:66–71 [PubMed: 27453374]

[2]. Kluckow M, Jeffery M, Gill A, Evans N. A randomised placebo-controlled trial of early treatment of the patent ductus arteriosus. Arch Dis Child Fetal Neonatal Ed. 2014;99:F99–F104. [PubMed: 24317704]

[3]. Aranda JV, Clyman R, Cox B, Van Overmeire B, Wozniak P, Sosenko I, et al. A randomized, double-blind, placebo-controlled trial on intravenous ibuprofen L-lysine for the early closure of nonsymptomatic patent ductus arteriosus within 72 hours of birth in extremely low-birth-weight infants. Am J Perinatol. 2009;26:235–45. [PubMed: 19067286]

[4]. Al Faleh K, Smyth J, Roberts R, Solimano A, Asztalos E, Schmidt B. Prevention and 18-month outcome of serious pulmonary hemorrhage in extremely low birth weight infants: results from the triall of indomethacin prophylaxis in preterms. Pediatrics. 2008;121:e233–8. [PubMed: 18245398]

[5]. Cooke L, Steer P, Woodgate P. Indomethacin for asymptomatic patent ductus arteriosus in preterm infants. Cochrane Database Syst Rev. 2003:CD003745. [PubMed: 12804488]

[6]. Liebowitz M, Koo J, Wickremasinghe A, Allen IE, Clyman RI. Effects of Prophylactic Indomethacin on Vasopressor-Dependent Hypotension in Extremely Preterm Infants. J Pediatr. 2017;182:21–7 [PubMed: 27915200]

[7]. Fowlie PW, Davis PG. Prophylactic intravenous indomethacin for preventing mortality and morbidity in preterm infants. Cochrane Database Syst Rev. 2010:CD000174. [PubMed: 20614421]

[8]. Ohlsson A, Walia R, Shah SS. Ibuprofen for the treatment of patent ductus arteriosus in preterm or low birth weight (or both) infants. Cochrane Database Syst Rev. 2015;2:CD003481.

[9]. Ohlsson A, Shah SS. Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants. Cochrane Database Syst Rev. 2011:CD004213. [PubMed: 21735396]

[10]. Benitz WE. Treatment of persistent patent ductus arteriosus in preterm infants: time to accept the null hypothesis? J Perinatol. 2010;30:241–52. [PubMed: 20182439]

[11]. Clyman RI, Liebowitz M, Kaempf J, Erdeve O, Bulbul A, Hakansson S, et al. PDA-TOLERATE Trial: An Exploratory Randomized Controlled Trial of Treatment of Moderate-to-Large Patent Ductus Arteriosus at 1 Week of Age. J Pediatr. 2019;205:41–8. [PubMed: 30340932]

[12]. Sung SI, Lee MH, Ahn SY, Chang YS, Park WS. Effect of Nonintervention vs Oral Ibuprofen in Patent Ductus Arteriosus in Preterm Infants: A Randomized Clinical Trial. JAMA Pediatr. 2020; 174:1–9

[13]. Schena F, Francescato G, Cappelleri A, Picciolli I, Mayer A, Mosca F, et al. Association between Hemodynamically Significant Patent Ductus Arteriosus and Bronchopulmonary Dysplasia. J Pediatr. 2015;166:1488–92. [PubMed: 25882876]

[14]. Sellmer A, Bjerre JV, Schmidt MR, McNamara PJ, Hjortdal VE, Host B, et al. Morbidity and mortality in preterm neonates with patent ductus arteriosus on day 3. Arch Dis Child Fetal Neonatal Ed. 2013;98:F505–10. [PubMed: 23893268]

[15]. Clyman RI, Hills NK, Liebowitz M, Johng S. Relationship between Duration of Infant Exposure to a Moderate-to-Large Patent Ductus Arteriosus Shunt and the Risk of Developing Bronchopulmonary Dysplasia or Death Before 36 Weeks. Am J Perinatol. 2020;37:216–23. [PubMed: 31600791]

[16]. Mirza H, Garcia J, McKinley G, Hubbard L, Sensing W, Schneider J, et al. Duration of significant patent ductus arteriosus and bronchopulmonary dysplasia in extremely preterm infants. J Perinatol. 2019;39:1648–55. [PubMed: 31554913]

[17]. Clyman RI, Hills NK. The effect of prolonged tracheal intubation on the association between patent ductus arteriosus and bronchopulmonary dysplasia (grades 2 and 3). J Perinatol. 2020;online ahead of press. doi: 10.1038/s41372-020-0718-x.

[18]. Wickremasinghe AC, Rogers EE, Piecuch RE, Johnson BC, Golden S, Moon-Grady AJ, et al. Neurodevelopmental Outcomes Following Two Different Treatment Approaches (Early Ligation and Selective Ligation) for Patent Ductus Arteriosus. J Pediatr. 2012; 161:1065–72. [PubMed: 22795222]

[19]. Jhaveri N, Moon-Grady A, Clyman RI. Early surgical ligation versus a conservative approach for management of patent ductus arteriosus that fails to close after indomethacin treatment. J Pediatr. 2010;157:381–7. [PubMed: 20434168]

[20]. El Hajjar M, Vaksmann G, Rakza T, Kongolo G, Storme L. Severity of the ductal shunt: a comparison of different markers. Arch Dis Child Fetal Neonatal Ed. 2005;90:F419–22. [PubMed: 16113155]

[21]. Jensen EA, Dysart K, Gantz MG, McDonald S, Bamat NA, Keszler M, et al. The Diagnosis of Bronchopulmonary Dysplasia in Very Preterm Infants. An Evidence-based Approach. Am J Respir Crit Care Med. 2019;200:751–9. [PubMed: 30995069]

[22]. Walsh MC, Yao Q, Gettner P, Hale E, Collins M, Hensman A, et al. Impact of a physiologic definition on bronchopulmonary dysplasia rates. Pediatrics. 2004;114:1305–11. [PubMed: 15520112]

[23]. Laughon MM, Langer JC, Bose CL, Smith PB, Ambalavanan N, Kennedy KA, et al. Prediction of bronchopulmonary dysplasia by postnatal age in extremely premature infants. Am J Respir Crit Care Med. 2011;183:1715–22. [PubMed: 21471086]

[24]. Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. BMC Pediatr. 2013;13:59. [PubMed: 23601190]

[25]. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weight < 1500 grams. J Pediatr. 1978;92:529–34. [PubMed: 305471]

[26]. Bell MJ, Ternberg JL, Feigin RD, Keating JP, Marshall R, Barton L, et al. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. Ann Surg. 1978;187:1–7. [PubMed: 413500]

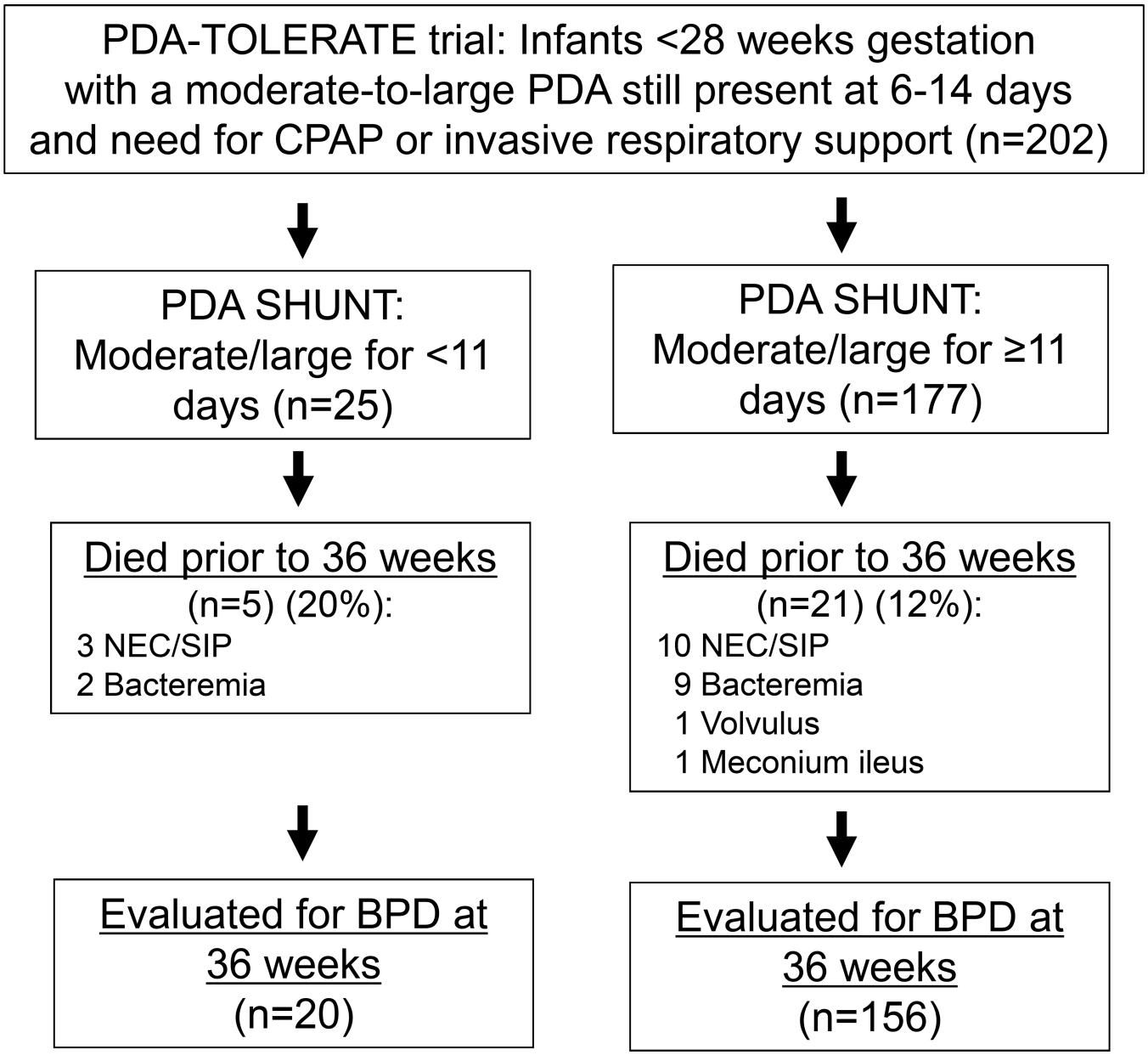

Figure 1;
online: Flow diagram of patient distribution in the PDA-TOLERATE trial: number of infants exposed to a moderate-to-large PDA shunt for <11 days or ≥11 days who were evaluated for BPD at 36 weeks post menstrual age.

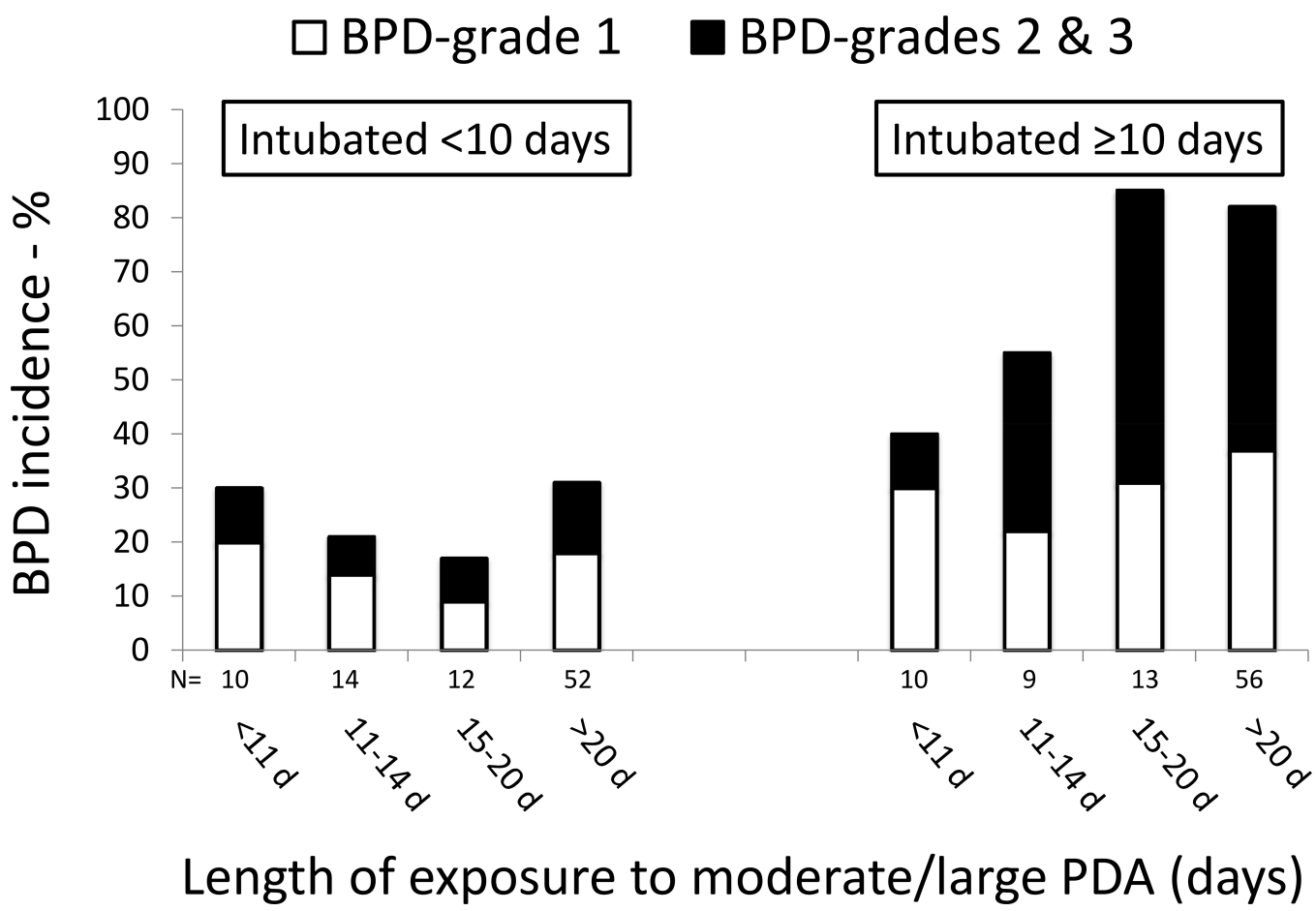

Figure 2:

Relationship between PDA exposure and the outcomes BPD-any grade and BPD-grades 2 & 3 among infants intubated for <10 days or ≥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 ≥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.

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 <11 days or ≥11 days.

	Duration of exposure to a moderate-to-large PDA		
Variable	**<11 days**	**≥11 days**	**p-value**
N=	**20**	**156**	
Prenatal Variables:			
Multiple Gestation - %	30	32	
Preeclampsia - %	20	18	
Maternal Diabetes - %	10	4	
Chorioamnionitis - %	15	15	
Antenatal Betamethasone <24 hours - %	45	33	
Caesarian Section - %	70	71	
Neonatal Variables:			
Gestation – weeks (m±sd) [1]	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 - % [2]	0	8	
Caucasian - %	45	51	
Male - %	50	45	
5 minute Apgar ≤5 - %	40	32	
Intubated in the delivery room - %	65	67	
Intubated during 1st 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) - % [3]	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 - % [4]	10	2	
Late Onset Bacteremia - % [5]	20	22	
SIP/NEC - % [6]	10	14	
Any Pharmacologic PDA Treatment - % [7]	90	71	
PDA Ligation - %	0	13	
Duration of moderate/large PDA exposure -days median (IQR) [8]	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 exposure to a moderate-to-large PDA		
Variable	**<11 days**	**≥11 days**	**p-value**
N=	**20**	**156**	
Duration of intubation ≥10 days - %	50	50	

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

[1] Gestational age was determined by the date of last menstrual period and ultrasounds performed prior to 24 weeks gestation.

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

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

[4] *Early onset,* culture-positive bacteremia that occurred ≤3 days after birth.

[5] *Late onset bacteremia,* culture-positive bacteremia that occurred ≥4 days after birth.

[6] *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) [26].

[7] *Any PDA Treatment,* infants who received PDA treatment as part of the Early PDA treatment protocol or later Rescue PDA treatment.

[8] *IQR,* interquartile range.