

Morbidity Associated with Patent Ductus Arteriosus in Preterm Newborns: A Retrospective Case-Control Study

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Abstract

Introduction: Association between persistency of a patent ductus arteriosus (PDA) and morbidity in preterm newborns is still controversial. We aimed to investigate the relation between PDA and morbidity in a large retrospective study.

Methods: A case-control study including neonates consecutively admitted to the Neonatal Intensive Care Unit (NICU), with gestational age (GA) \leq 32 weeks or body birth weight (BW) \leq 1500 g, over a 5-year period. Newborns were divided into Cases and Controls, according with the presence or absence of a hemodynamically significant PDA (hs-PDA).

Results: We enrolled 85 Cases and 193 Controls. Subjects with hs-PDA had significantly ($p < 0.001$) lower GA (26.7 w, 95%CI 27.1-28.0 vs. 30.1 w, 95%CI 29.7-30.4), BW (1024 g, 95% CI 952-1097 vs. 1310 g 95%CI 1263-1358) and an increased morbidity (60.0% vs. 18.7%). In a sub-group of extremely preterm newborns (GA $<$ 29 weeks and BW $<$ 1000 g), the rate of BPD was significantly increased in Cases (31.7%) compared with Controls (5.9%, $p = 0.033$). Multivariate analysis showed that morbidity significantly depended on hs-PDA, GA and BW, and that, in extremely preterms, the hs-PDA represented an independent risk factor for BPD.

Conclusions: The presence of hs-PDA seemed to increase the risk of morbidity in very low birth weight (VLBW) infants. In extremely preterm newborns, the risk of bronchopulmonary dysplasia (BPD) depended on the occurrence of hs-PDA.

Introduction

The ductus arteriosus is a vascular structure that connects the proximal descending aorta to the roof of the main pulmonary artery near the origin of the left branch pulmonary artery [1]. The ductus arteriosus normally constricts after birth and becomes functionally closed by the first days of life [2]. Persistency of a patent ductus arteriosus (PDA) is a common issue in preterm newborns. Particularly, in very low birth weight (VLBW) infants, the ducts fails to close leading to a left heart volume overload and systemic hypoperfusion [2]. Clinical consequences of this hemodynamic condition are still largely undefined. If a body of evidence suggested an increase in the morbidity associated with PDA, recent randomized controlled studies and metanalysis have failed to demonstrate a causal relationship [2–5].

The purpose of this study was to investigate the association between the presence of PDA and the occurrence of morbidities of prematurity.

Methods

Study design and population

This is a case-control study including all neonates consecutively admitted to the Neonatal Intensive Care Unit (NICU) of Policlinico Umberto I Hospital, La Sapienza University of Rome, from April 2015 to March 2020, with gestational age (GA) \leq 32 weeks or body birth weight (BW) \leq 1500 g. We excluded newborns with incomplete clinical data, major congenital malformations, inborn errors of metabolism, intestinal and extra-intestinal congenital diseases, familiar history of allergy, use of pre-or probiotics, transfer to other hospital or death within the first 72 hours of life [6–11].

The enrolled subjects were divided into 2 groups according to the presence (Cases) or absence (Controls) of a hemodynamically significant PDA (hs-PDA), confirmed by echocardiographic evaluation. We defined PDA, as hemodynamically significant, when we observed at least one of the following criteria: 1) PDA diameter at its narrowest part ≥ 1.5 mm; 2) unrestrictive pulsatile transductal flow; 3) left atrial-to-aortic root ratio ≥ 1.5 ; 4) absent diastolic flow in descending aorta; 5) abnormal diastolic flow in middle cerebral artery [5, 12–14]. Newborns were classified as Cases when affected by hs-PDA, confirmed by echocardiographic evaluation performed within 1 week of life. We classified as Controls all newborns without PDA during hospital stay. Pediatric cardiologists performed ultrasound studies and the treatment was eventually decided after an agreement between cardiologists and neonatologists on duty.

The study was conducted in conformity with World Medical Association Declaration of Helsinki for medical research involving human subjects. We obtained a written informed consent from all parents of enrolled newborns.

Outcomes

We considered as primary outcome the rate of newborns with at least one of the following morbidities, before discharge from the NICU: prolonged mechanical ventilation (more than 7 days), bronchopulmonary dysplasia (BPD), intraventricular haemorrhage (IVH) stage ≥ 2 , necrotizing enterocolitis (NEC) Bell-Stage ≥ 2 , retinopathy of prematurity (ROP) stage ≥ 3 , hypotension [1, 2, 15–17]. We considered as secondary outcomes the mortality and the duration of hospital stay.

Data collection

Investigators who were not involved in the enrollment phases, recorded clinical data using a structured data form, from birth to discharge, transfer to another hospital or death of the patient. We collected data about gender, GA, BW, twin pregnancies, type of delivery, use of antenatal steroids, pregnancy-induced hypertension, alteration of Doppler velocimetry on uterine arteries, pH on cord blood and Apgar score at 5 minutes.

Diagnosis of the main neonatal morbidities were performed according to the standard criteria, by physicians unaware of the study design and aims, as previously described [18–20]. Nutritional management was performed as previously described [18, 21–23]. We collected data on morbidity and duration of hospital stay in a separate and codified data form.

Statistics

Statistical analysis was performed per protocol, using Statistical Package for Social Science software for Microsoft Windows (SPSS Inc, Chicago, IL), and version 25.0. We checked for normality using Shapiro-Wilk test. The mean and 95% confidence interval (CI) summarised continuous variables. We compared the Cohorts using chi-square test for categorical variable and t-test or Mann-Whitney for paired and unpaired variables.

We performed a sensitivity analysis, including a sub-group of patients with GA < 29 g (Sub-group A) and BW < 1000 (Sub-group B). We performed a binary logistic regression analysis to evaluate whether gender (female or male), GA (< 29 or ≥ 29 weeks of PMA), use of prenatal steroids, pH at birth (< 7.1 or ≥ 7.1), and Group (Case or Control) or Sub-Group assignment (A or B) influenced primary outcome. We performed linear regression analysis to evaluate if gender, GA, antenatal steroids influenced duration of hospitalization. The level of significance for all statistical tests was 2-sided ($p < 0.05$).

Results

We considered eligible for the study 343 newborns. We excluded 65 neonates because of congenital malformations, congenital infections, maternal autoimmune diseases ($n = 29$), early transfer to other hospital ($n = 21$) or death ($n = 15$). Thus, we included 278 infants, 85 as Cases (30.6%) and 193 as Controls (69.4%).

The main clinical characteristics of participating Cases and Controls subjects were summarized in Table 1. We observed that infants with PDA had lower GA, BW, Apgar scores, rate of administration of antenatal steroids and pH on cord blood. The overall morbidity was significantly increased in Cases compared with Controls (Table 2). The risk of prolonged mechanical ventilation, BPD, IVH, ROP and hypotension were increased in Cases compared with Controls (Table 2).

The rate of mortality was increased in Cases (10.6%) compared with Controls (3.6%, $p = 0.025$). Mean duration of hospital stay was increased in newborns with hs-PDA (80.4 days, 95%CI 69.4 to 91.4) compared with Controls (54.9 days, 95%CI 50.9 to 58.9, $p < 0.001$).

Multivariate analysis showed that morbidity was independently and significantly related to the occurrence of a hs-PDA, in both models including GA and BW, respectively (Table 3). Mortality was not influenced by the presence of a hs-PDA, but depended only on GA and BW (Table 3). Multivariate linear regression analysis showed that duration of hospital stay was influenced by the occurrence of hs-PDA along with GA < 28 weeks, BW < 1000 g and the use of antenatal steroids (Table 4).

When we analyzed Sub-group of children with GA < 28 weeks and BW < 1000 g, we found similar baseline characteristics, between Cases and Controls (**Table S1**), but an increased rate of newborns with BPD in those with hs-PDA compared with Controls (Table 5). The mortality rate was similar between Cases (19.5%) and Controls (27.8%). In this Sub-Group of patients, we observed that the mean length of hospital stay was significantly increased in Cases (98.8%, 95%CI 79.0 to 118.7) compared with Controls (64.4%, 95%CI 44.6 to 84.2), ($p = 0.034$).

In a sensitivity logistic regression analysis, including newborns of Sub-groups A and B, hs-PDA was a significant and independent factor associated with occurrence of BPD (**Table S2**).

We observed, in a linear logistic regression analysis, that hs-PDA was not an independent and significant risk factor for length of hospitalization (**Table S3**).

Table 1
Clinical characteristics of study population.

	Case Group <i>(n = 85)</i>	Control Group <i>(n = 193)</i>	<i>p</i>
Female sex, <i>N. (%)</i>	41 (48.2)	87 (45.1)	0.696
Gestational Age, <i>weeks</i>	27.6 (27.1 to 28.0)	30.1(29.7 to 30.4)	< 0.001
Birth weight, <i>g</i>	1024 (952 to 1097)	1310 (1263 to 1358)	< 0.001
Twins, <i>N. (%)</i>	23 (27.1)	54 (28.0)	1.000
Cesarean Section, <i>N. (%)</i>	69 (82.1)	168 (88.4)	0.181
Antenatal steroids ^a , <i>N. (%)</i>	49 (59.8)	139 (73.5)	0.031
Pregnancy-induced hypertension, <i>N. (%)</i>	20 (26.3)	46 (24.1)	0.754
Alteration of doppler velocimetry of uterine arteries, <i>N. (%)</i>	14 (19.4)	35 (18.5)	0.861
pH on cord blood	7.2 (7.2 to 7.3)	7.3 (7.2 to 7.3)	0.016
5-min Apgar score	7 (6 to 7)	8 (7 to 8)	< 0.001
Notes. (a) Intramuscular steroid cycle in two doses of 12 mg over a 24-hour period. Data were expressed as mean (95% CI), when not specified.			

Table 2
Morbidity associated with hemodynamic significant patent ductus arteriosus.

	Case Group <i>(n = 85)</i>	Control Group <i>(n = 193)</i>	<i>p</i>
Prolonged Mechanical Ventilation	19 (22.4)	11 (5.7)	< 0.001
Bronchopulmonary Dysplasia	13 (15.3)	6 (3.1)	0.001
Intraventricular Hemorrhage	17 (20.0)	8 (4.1)	< 0.001
Retinopathy of prematurity	18 (21.2)	5 (2.6)	< 0.001
Necrotizing Enterocolitis	1 (1.2)	5 (2.6)	0.406
Hypotension	27 (31.8)	11 (5.7)	< 0.001
Overall Morbidity ¹	51 (60.0)	36 (18.7)	< 0.001
Notes. Data were expressed as No. (%), when not specified.			

Table 3
Multivariate analysis evaluating confounding variables on morbidity and mortality.

	Covariates (Model 1)				Covariates (Model 2)			
<i>Dependent variables</i>	hs-PDA	Gender	GA < 28 weeks	Antenatal steroids ^a	hs-PDA	Gender	BW < 1000 g	Antenatal steroids ^a
Prolonged Mechanical Ventilation								
<i>OR (95%CI)</i>	2.567 (1.063 to 6.202)	1.498 (0.650 to 3.454)	6.471 (2.385 to 17.561)	1.171 (0.474 to 2.892)	2.335 (0.953 to 5.721)	1.411 (0.603 to 3.305)	7.441 (2.919 to 18.969)	1.094 (0.440 to 2.720)
<i>p</i>	0.036	0.343	< 0.001	0.733	0.063	0.427	< 0.001	0.846
Bronchopulmonary Dysplasia								
<i>OR (95%CI)</i>	4.358 (1.386 to 13.702)	1.744 (0.594 to 5.117)	3.121 (0.951 to 10.241)	10.698 (1.350 to 84.789)	2.188 (0.661 to 7.240)	1.646 (0.538 to 5.037)	13.270 (3.235 to 54.441)	9.937 (1.240 to 79.634)
<i>p</i>	0.012	0.311	0.061	0.025	0.199	0.383	< 0.001	0.031
Intraventricular Hemorrhage								
<i>OR (95%CI)</i>	3.184 (1.170 to 8.666)	1.223 (0.488 to 3.065)	7.182 (2.219 to 23.244)	0.518 (0.204 to 1.316)	3.850 (1.427 to 10.390)	1.138 (0.457 to 2.834)	4.214 (1.591 to 11.162)	0.498 (0.197 to 1.258)
<i>p</i>	0.023	0.667	0.001	0.167	0.008	0.781	0.004	0.141
Retinopathy of Prematurity								
<i>OR (95%CI)</i>	4.083 (1.339 to 12.447)	1.028 (0.387 to 2.729)	12.174 (2.621 to 56.552)	1.077 (0.379 to 3.057)	4.594 (1.496 to 14.102)	0.927 (0.349 to 2.463)	6.178 (2.016 to 18.936)	0.977 (0.347 to 2.749)
<i>p</i>	0.013	0.956	0.001	0.890	0.008	0.879	0.001	0.965
Hypotension								
<i>OR (95%CI)</i>	4.834 (2.047 to 11.418)	0.793 (0.357 to 1.760)	7.563 (2.874 to 19.899)	1.455 (0.607 to 3.490)	5.723 (2.446 to 13.393)	0.732 (0.334 to 1.604)	3.798 (1.676 to 8.605)	1.373 (0.589 to 3.204)
<i>p</i>	< 0.001	0.568	< 0.001	0.400	< 0.001	0.436	0.001	0.463
Morbidity [°]								
Notes. hs-PDA: hemodynamically significant Patent Ductus Arteriosus. (a) Intramuscular steroid cycle in two doses of 12 mg over a 24-hour period;								
[°] BPD or NEC or IVH or PLV or ROP or Prolonged mechanical ventilation or Hypotension requiring treatment.								

	Covariates (Model 1)				Covariates (Model 2)			
<i>OR (95%CI)</i>	4.058 (2.145 to 7.677)	1.072 (0.581 to 1.979)	5.227 (2.814 to 9.708)	0.974 (0.502 to 1.890)	4.109 (2.160 to 7.819)	1.023 (0.548 to 1.912)	6.596 (3.441 to 12.643)	0.986 (0.507 to 1.919)
<i>p</i>	< 0.001	0.823	< 0.001	0.937	< 0.001	0.942	< 0.001	0.967
Mortality								
<i>OR (95%CI)</i>	1.307 (0.414 to 4.126)	1.205 (0.396 to 3.664)	26.178 (3.210 to 213.479)	0.475 (0.154 to 1.468)	1.519 (0.470 to 4.908)	1.148 (0.373 to 3.540)	10.977 (2.787 to 43.230)	0.473 (0.153 to 1.460)
<i>p</i>	0.648	0.743	0.002	0.196	0.485	0.810	0.001	0.193
Notes. hs-PDA: hemodynamically significant Patent Doctus Arteriosus. (a) Intramuscular steroid cycle in two doses of 12 mg over a 24-hour period;								
° BPD or NEC or IVH or PLV or ROP or Prolonged mechanical ventilation or Hypotension requiring treatment.								

Table 4
Multivariate analysis evaluating confounding variables on duration of hospital stay.

		B	Std. Err.	β	p
Overall newborns					
Model 1	<i>Gender</i>	0.873	4.111	0.012	0.832
	<i>GA</i>	-5.259	0.888	-0.368	< 0.001
	<i>Antenatal steroids^a</i>	11.497	4.507	0.144	0.011
	<i>hs-PDA</i>	12.062	5.020	0.150	0.017
Model 2	<i>Gender</i>	2.329	4.046	0.032	0.565
	<i>BW</i>	-0.040	0.006	-0.394	< 0.001
	<i>Antenatal steroids^a</i>	12.440	4.430	0.156	0.005
	<i>hs-PDA</i>	14.508	4.689	0.181	0.002
Notes. hs-PDA: hemodynamically significant Patent Doctus Arteriosus; GA: Gestational Age; BW: Birth weight; (a) Intramuscular steroid cycle in two doses of 12 mg over a 24-hour period.					

Table 5
Morbidity in study population with gestational age < 28 weeks and birth weight < 1000 g.

	Case Group <i>(n = 41)</i>	Control Group <i>(n = 18)</i>	<i>p</i>
Bronchopulmonary displasia	13 (31.7)	1 (5.9)	0.033
Prolonged Mechanical Ventilation	17 (41.5)	3 (16.7)	0.079
Intraventricular Hemorrhage	12 (29.3)	4 (22.2)	0.412
Necrotizing Enterocolitis	1 (2.4)	1 (5.6)	0.521
Retinopathy of Prematurity	14 (34.1)	2 (11.1)	0.060
Hypotension	19 (46.3)	6 (33.3)	0.403
Overall Morbidity ¹	34 (82.9)	12 (66.7)	0.148
Notes. (1) BPD or Prolonged mechanical ventilation or IVH or NEC or ROP or Hypothension. Data were expressed as No. (%), when not specified			

Discussion

In a population of VLBW newborns, morbidity and mortality were related with hs-PDA, along with GA and BW. When we corrected data for confounding variables, we observed that hs-PDA associated with GA and BW, were risk factors for the occurrence of prolonged mechanical ventilation, BPD, IVH, ROP, and hypotension. We also observed in a univariate analysis, performed in a subgroup of extremely low gestational age neonates (ELGAN) and extremely low birth weight (ELBW) newborns, an increased risk of BPD in patients with hs-PDA. We found a significant relation between hs-PDA and BPD in multivariate analysis for ELGAN and ELBW. Finally, we showed that the presence of hs-PDA may increase the duration of hospitalization in enrolled newborns.

It has been hypothesized that hemodynamic condition generated by hs-PDA may induce different organs injuries, leading to an increased risk of clinical complications [24]. Despite it is clinical plausible, there is still uncertainty from current evidence regarding possible association between hs-PDA, morbidity and mortality in VLBW infants. Randomized controlled trials (RCTs) did not clarify whether PDA may have clinical consequences in this population [25], whereas, several not controlled studies found a relation between symptomatic hs-PDA, morbidity and mortality [26–28]. A retrospective study, exploring the impact of PDA on survival, found that mortality rate was higher among preterm infants with PDA [2]. In this study, all patients enrolled had a PDA and confidence intervals for the odds for mortality were relatively wide. We found that hs-PDA influenced morbidity in a more complex regression model, solely in association with GA and BW. Contemporarily, we observed that hs-PDA did not independently affect survival, neither in VLBW nor in ELGAN and ELBW infants. It is worth mentioning that the presence of a hs-PDA could, in turn, depend on GA and BW. This aspect may limit the clinical validity of the multivariate model.

Our results suggest that the presence of hs-PDA may prolong the duration of mechanical ventilation. A persistent shunt, increasing the pulmonary blood flow, can lead to pulmonary edema, loss of lung compliance, and deterioration of respiratory status. In a retrospective cohort study was assessed the relation between PDA and prolonged mechanical ventilation in preterm newborns [29, 30]. Although a causal association has not been proven, the link was greatest among infants born at lower gestational age who were treated with mechanical ventilation in the presence of a large ductal shunt [29]. In addition, authors did not perform a multivariate analysis in order to

confirm their findings adjusted for other covariates. We did not find any association between hs-PDA and occurrence of prolonged mechanical ventilation in ELGAN and ELBW enrolled in our study, neither in univariate analysis nor in multivariate analysis. However, the difference in the rate of patients with prolonged mechanical ventilation, observed between Cases and Controls, might become significant in a larger population of ELGAN and ELBW newborns.

Prolonged mechanical ventilation could be also a condition that may have increased the risk of BPD in enrolled newborns affected by hs-PDA. A causative relation between the PDA and the development of BPD was suggested by observational retrospective evidence [28, 31]. Schena et al. estimated that occurrence of BPD depended on severity of hs-PDA exposure. El-Khuffash et al. in a study exploring possible prognostic values of a PDA score based on echocardiography measurements found that association between PDA and BPD strengthens with decreasing gestational age [24]. On the other hand, in a recent study comparing mandatory closure vs. a non-interventional approach to manage hs-PDA in preterm newborns, despite longer PDA exposure, the non-interventional approach was associated with significantly less BPD [32]. However, all newborns with hs-PDA enrolled in this study required ventilatory treatment, which could have influenced the occurrence of BPD. We observed a relation between hs-PDA and BPD still when we corrected the data for confounding variables including GA and BW. This association was observed in a multivariate analysis performed in the sub-group of ELGAN and ELBW subjects. However, the significance of multivariate model suggests that further studies, including a larger number of preterm newborns, should be performed to confirm these findings.

We observed a relation between hs-PDA and IVH as suggested by previous retrospective studies. A large retrospective cohort study on VLBW infants demonstrated that the rate of spontaneous closure before hospital discharge occurs in the majority of patients. However, the Authors excluded the deceased infants from the analysis, whose cause of death was reported to be potentially related to PDA, including IVH and all of them had documented PDA [33]. Our multivariate analysis showed that hs-PDA was a risk factor in association with GA and BW for IVH. Further studies are needed to establish the causality between hemodynamic consequences of PDA and occurrence of IVH.

We showed the association between PDA and ROP, as observed in previous studies. Results from recent wide prospective study showed that PDA requiring medication significantly correlated with the development of ROP. This research, as well as our study, found that PDA was significantly correlated with ROP in the multivariate logistic regression analysis adjusted for GA and BW [34]. Taking these results into account, it is possible to hypothesize that hs-PDA, in critical ill newborns, may increase the risk of ROP due to hemodynamic instability that, in turn, may influence development of the immature and incompletely vascularized retina [35]. We did not observe the association between hs-PDA and ROP in ELGAN and ELBW patients. Probably, in these subjects, the extremely immaturity of retina vascularization represents a major risk factor for ROP independently by the presence of hs-PDA.

We observed a significant increased risk of hypotension in newborns with hs-PDA. Our findings are in keeping with the results of Ratner et al. who showed that a hs-PDA was associated with a reduction in systolic and diastolic blood pressure [36]. Although it is true that a moderate-to-large PDA can lower systemic blood pressure [37] and is associated with the presence of hypotension at the end of the first week [14, 38], no studies to date has determined whether the PDA actually is responsible for the hypotension or whether its presence is just a surrogate for nonspecific causes related to immaturity/illness. Our multivariate analysis suggested that hypotension in preterm newborns depend contemporarily on hs-PDA, BW and GA. However, the hs-PDA does not seem to influence the occurrence of hypotension in ELGAN and ELBW subjects. Clinical validity of these results should be confirmed in a specifically designed clinical trial focused on hypotension.

A causal relationship between pregnancy-induced hypertension and occurrence of PDA has been described in previous studies. According with a recent cohort research, we demonstrated a higher rate of pregnancy-induced hypertension in Cases compared with Controls. That increased risk for developing PDA in newborns of women with preeclampsia has been attributed to the likelihood of shared angiogenic imbalance between the mother and fetus [39–41].

A large number of previous piece of research have included infants with PDA regardless of hemodynamic significance [42–44]. Therefore, any effect of PDA may have been masked by the absence of clinical consequences of a physiological condition.

Our results should be interpreted considering study limitations. The association between hs-PDA and morbidity outcome in VLBW may be related to the effects of chance, random error, bias or confounding factors. We verified that effect on the main outcome of the study persisted even after correction for confounding variables. Despite of everything, other confounding variables, unknown or not considered in our statistical analysis, may have influenced the study results. In addition, covariate “hs-PDA” could dependent by GA and BW. To limit observer bias, researchers unaware for study aims collected the data for the analysis, a third party observer was involved to collect data on the outcome of the study, and a blinded statistician performed the data analysis. Finally, Results regarding population of ELGAN and ELBW newborns should be interpreted considering the small number of subjects enrolled as Controls compared with Cases.

Conclusion

In conclusion, the presence of hs-PDA does not seem to influence the clinical course of VLBW newborns. Potential association between hs-PDA and BPD encourages designing a randomized trial, that should include an adequate number of critical newborns, with GA < 28 weeks and BW < 1000 g.

Abbreviations

PDA
patent ductus arteriosus;
NICU
neonatal intensive care unit;
GA
gestational age;
BW
birth weight;
VLBW
very low birth weight;
hs-PDA
hemodynamic significant patent ductus arteriosus;
BPD
bronchopulmonary dysplasia;
IVH
intraventricular hemorrhage;
NEC

necrotizing enterocolitis;
ROP
retinopathy of prematurity;
ELGAN
extremely low gestational age;
ELBW
extremely low birth weight;
RCTs
randomized clinical trials.

Declarations

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

G.T., M.D.C. (Maria Di Chiara), G.B., V.M. conceptualized and designed the study, organized the acquisition of data and reviewed and revised both analyses and the manuscript; G.T., M.D.C. (Maria Di Chiara), G.B., V.M., F.F., E.O., A.G., V.D.D., V.C. and M.D.C. (Mario De Curtis) drafted the article and revised it critically for important intellectual content; all the authors approved the final manuscript to be published.

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References

1. Bhat R, Das UG. Management of Patent Ductus Arteriosus in Premature Infants. *Indian J Pediatr.* 2015;82:53–60.
2. Benitz WE. Treatment of persistent patent ductus arteriosus in preterm infants: time to accept the null hypothesis? *J Perinatol.* 2010;30:241–52.
3. 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:F99–104.
4. <http://doi.wiley.com/10.1002/14651858.CD004213.pub5>
Ohlsson A, Shah SS. Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants. *Cochrane Neonatal Group, editor. Cochrane Database Syst Rev [Internet].* 2020 [cited 2020 Jul 23];

Available from: <http://doi.wiley.com/10.1002/14651858.CD004213.pub5>.

5. EL-Khuffash A, James AT, Corcoran JD, Dicker P, Franklin O, Elsayed YN, et al. A Patent Ductus Arteriosus Severity Score Predicts Chronic Lung Disease or Death before Discharge. *J Pediatr*. 2015;167:1354–61.e2.
6. Canani RB, Terrin G. Recent Progress in Congenital Diarrheal Disorders. *Curr Gastroenterol Rep*. 2011;13:257–64.
7. Passariello A, Terrin G, et al. Diarrhea in neonatal intensive care unit. *World J Gastroenterol*. 2010;16:2664.
8. Ferreira CR, van Karnebeek CDM. Inborn errors of metabolism. *Handb Clin Neurol* [Internet]. Elsevier; 2019 [cited 2020 Jul 29]. p. 449–81. Available from: <https://linkinghub.elsevier.com/retrieve/pii/B9780444640291000229>.
9. Nocerino R, Paparo L, Terrin G, Pezzella V, Amoroso A, Cosenza L, et al. Cow's milk and rice fermented with *Lactobacillus paracasei* CBA L74 prevent infectious diseases in children: A randomized controlled trial. *Clin Nutr* [Internet]. 2017 [cited 2020 Aug 4];36:118–25. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0261561415003416>.
10. Berni Canani R, Di Costanzo M, Pezzella V, Cosenza L, Granata V, Terrin G, et al. The Potential Therapeutic Efficacy of *Lactobacillus* GG in Children with Food Allergies. *Pharmaceuticals* [Internet]. 2012 [cited 2020 Aug 4];5:655–64. Available from: <http://www.mdpi.com/1424-8247/5/6/655>.
11. 10.1542/peds.107.2.416
Salvia G, Cascioli CF, Ciccimarra F, Terrin G, Cucchiara S. A Case of Protein-Losing Enteropathy Caused by Intestinal Lymphangiectasia in a Preterm Infant. *PEDIATRICS* [Internet]. 2001 [cited 2020 Aug 4];107:416–7. Available from: <http://pediatrics.aappublications.org/cgi/doi/10.1542/peds.107.2.416>.
12. Kindler A, Seipolt B, Heilmann A, Range U, Rüdiger M, Hofmann SR. Development of a Diagnostic Clinical Score for Hemodynamically Significant Patent Ductus Arteriosus. *Front Pediatr*. 2017;5:280.
13. Mellander M, Larsson LE, Ekström-Jodal B, Sabel K-G. Prediction of Symptomatic Patent Ductus Arteriosus in Preterm Infants Using Doppler and M-mode Echocardiography. *Acta Paediatr*. 1987;76:553–9.
14. Keusters L, Purna J, Deshpande P, Mertens L, Shah P, McNamara PJ, et al. Clinical validity of systemic arterial steal among extremely preterm infants with persistent patent ductus arteriosus. *J Perinatol* [Internet]. 2020 [cited 2020 Jul 23]; Available from: <http://www.nature.com/articles/s41372-020-0663-8>.
15. Terrin G, Conte F, Oncel MY, Scipione A, McNamara PJ, Simons S, et al. Paracetamol for the treatment of patent ductus arteriosus in preterm neonates: a systematic review and meta-analysis. *Arch Dis Child - Fetal Neonatal Ed*. 2016;101:F127–36.
16. <http://doi.wiley.com/10.1002/14651858.CD000174>
Fowlie PW, Davis PG. Prophylactic intravenous indomethacin for preventing mortality and morbidity in preterm infants. In: The Cochrane Collaboration, editor. *Cochrane Database Syst Rev* [Internet]. Chichester, UK: John Wiley & Sons, Ltd; 2002 [cited 2020 Jul 23]. p. CD000174. Available from: <http://doi.wiley.com/10.1002/14651858.CD000174>.
17. Rolland A, Shankar-Aguilera S, Diomandé D, Zupan-Simunek V, Boileau P. Natural evolution of patent ductus arteriosus in the extremely preterm infant. *Arch Dis Child - Fetal Neonatal Ed*. 2015;100:F55–8.
18. Terrin G, Coscia A, Boscarino G, Faccioli F, Di Chiara M, Greco C, et al. Long-term effects on growth of an energy-enhanced parenteral nutrition in preterm newborn: A quasi-experimental study. *Gebremedhin S, editor. PLOS ONE*. 2020;15:e0235540.
19. Terrin G, Boscarino G, Di Chiara M, Iacobelli S, Faccioli F, Greco C, et al. Nutritional Intake Influences Zinc Levels in Preterm Newborns: An Observational Study. *Nutrients*. 2020;12:529.

20. Terrin G, Berni Canani R, Di Chiara M, Pietravalle A, Aleandri V, Conte F, et al. Zinc in Early Life: A Key Element in the Fetus and Preterm Neonate. *Nutrients*. 2015;7:10427–46.
21. Berni Canani R, Passariello A, Buccigrossi V, Terrin G, Guarino A. The Nutritional Modulation of the Evolving Intestine: *J Clin Gastroenterol* [Internet]. 2008 [cited 2020 May 6];42:S197–200. Available from: <http://journals.lww.com/00004836-200809002-00013>.
22. <http://doi.wiley.com/10.1111/j.1651-2227.2008.00987.x>
Terrin G, Passariello A, Canani RB, Manguso F, Paludetto R, Cascioli C. Minimal enteral feeding reduces the risk of sepsis in feed-intolerant very low birth weight newborns. *Acta Paediatr* [Internet]. 2009 [cited 2020 Jan 11];98:31–5. Available from: <http://doi.wiley.com/10.1111/j.1651-2227.2008.00987.x>.
23. Terrin G, De Nardo MC, Boscarino G, Di Chiara M, Cellitti R, Ciccarelli S, et al. Early Protein Intake Influences Neonatal Brain Measurements in Preterms: An Observational Study. *Front Neurol*.
24. Elsayed YN, Fraser D. Patent Ductus Arteriosus in Preterm Infants, Part 1: Understanding the Pathophysiologic Link Between the Patent Ductus Arteriosus and Clinical Complications. *Neonatal Netw*. 2017;36:265–72.
25. Clyman RI. Patent ductus arteriosus, its treatments, and the risks of pulmonary morbidity. *Semin Perinatol*. 2018;42:235–42.
26. Brown ER. Increased risk of bronchopulmonary dysplasia in infants with patent ductus arteriosus. *J Pediatr*. 1979;95:865–6.
27. Dani C, Mosca F, Cresi F, Lago P, Lista G, Laforgia N, et al. Patent ductus arteriosus in preterm infants born at 23–24 weeks' gestation: Should we pay more attention? *Early Hum Dev*. 2019;135:16–22.
28. 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.
29. Clyman RI. The role of patent ductus arteriosus and its treatments in the development of bronchopulmonary dysplasia. *Semin Perinatol*. 2013;37:102–7.
30. Clyman RI. Patent ductus arteriosus, its treatments, and the risks of pulmonary morbidity. *Semin Perinatol*. 2018;42:235–42.
31. Marshall DD, Kotelchuck M, Young TE, Bose CL, Kruyer L, O'Shea TM, et al. Risk Factors for Chronic Lung Disease in the Surfactant Era: A North Carolina Population-based Study of Very Low Birth Weight Infants. *PEDIATRICS*. 1999;104:1345–50.
32. 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.e1.
33. Semberova J, Sirc J, Miletin J, Kucera J, Berka I, Sebkova S, et al. Spontaneous Closure of Patent Ductus Arteriosus in Infants \leq 1500 g. *Pediatrics*. 2017;140:e20164258.
34. Hwang JS, Rehan VK. Recent Advances in Bronchopulmonary Dysplasia: Pathophysiology, Prevention, and Treatment. *Lung*. 2018;196:129–38.
35. Abu-Shaweesh JM, Almidani E. PDA: Does it matter? *Int J Pediatr Adolesc Med*. 2020;7:11–4.
36. Noori S, McCoy M, Friedlich P, Bright B, Gottipati V, Seri I, et al. Failure of Ductus Arteriosus Closure Is Associated With Increased Mortality in Preterm Infants. *PEDIATRICS*. 2009;123:e138–44.
37. Verma RP, Dasnadi S, Zhao Y, Chen HH. Complications associated with the current sequential pharmacological management of early postnatal hypotension in extremely premature infants. *Bayl Univ Med Cent Proc*. 2019;32:355–60.

38. Ruoss JL, Bazacliu C, Giesinger RE, McNamara PJ. Patent ductus arteriosus and cerebral, cardiac, and gut hemodynamics in premature neonates. *Semin Fetal Neonatal Med.* 2020;101120.
39. Auger N, Fraser WD, Healy-Profitós J, Arbour L. Association Between Preeclampsia and Congenital Heart Defects. *JAMA.* 2015;314:1588.
40. Yilgwan CS, Pam VC, Ige OO, Golit WN, Anzaku S, Imade GE, et al Profile of congenital heart disease in infants born following exposure to preeclampsia. Xie L, editor. *PLOS ONE.* 2020;15:e0229987.
41. Boyd HA, Basit S, Behrens I, Leirgul E, Bundgaard H, Wohlfahrt J, et al. Association Between Fetal Congenital Heart Defects and Maternal Risk of Hypertensive Disorders of Pregnancy in the Same Pregnancy and Across Pregnancies. *Circulation.* 2017;136:39–48.
42. Sosenko IRS, Fajardo MF, Claire N, Bancalari E. Timing of Patent Ductus Arteriosus Treatment and Respiratory Outcome in Premature Infants: A Double-Blind Randomized Controlled Trial. *J Pediatr.* 2012;160:929–35.e1.
43. Mahony L, Carnero V, Brett C, Heymann MA, Clyman RI. Prophylactic Indomethacin Therapy for Patent Ductus Arteriosus in Very-Low-Birth-Weight Infants. *N Engl J Med.* 1982;306:506–10.
44. Van Overmeire B, Van de Broek H, Van Laer P, Weyler J, Vanhaesebrouck P. Early versus late indomethacin treatment for patent ductus arteriosus in premature infants with respiratory distress syndrome. *J Pediatr.* 2001;138:205–11.

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