Patent Ductus Arteriosus, Low Platelets, Cyclooxygenase Inhibitors, and Intraventricular Hemorrhage in Very Low Birth Weight Preterm Infants

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Objective To assess the risk for intraventricular hemorrhage (IVH) in very low birth weight preterm infants with patent ductus arteriosus (PDA) and low platelet count with treatment with cyclooxygenase (COX) inhibitors.

Study design Diagnosis and treatment of PDA, as well as risk factors for IVH, were assessed using prospectively collected data of all infants born at a gestational age <32 weeks and with a birth weight ≤1500 g at Innsbruck University Hospital (January 2003-December 2009). Infants with severe thrombocytopenia (<50 × 10^9/L) were excluded from analysis.

Results Sixty-five (20%) of the 325 infants had IVH, and 149 (45.9%) of the 325 were treated with COX inhibitors. Treatment of PDA with COX inhibitors was not an independent risk predictor for IVH in preterm infants with platelets ≥100 × 10^9/L. However, COX inhibitors amplified the risk of bleeding in the presence of moderately decreased platelets (50-99 × 10^9/L) on days of life 2-7. Multivariable OR for IVH were 0.89 [95% CI 0.43-1.87] for patients with platelets ≥100 × 10^9/L and treatment with COX inhibitors, 3.40 [95% CI 1.13-10.29] for those with moderately decreased platelets without treatment, and 53.3 [95% CI 5.9-484] for patients with both moderately decreased platelets and COX inhibitor treatment compared with those with platelets ≥100 × 10^9/L and no treatment (reference group) ($P < .001$).

Conclusion In very low birth weight infants with moderate thrombocytopenia treatment with COX inhibitors increased the risk for intracerebral bleeding. Any benefits of this therapy should be carefully balanced against this potential hazard. *(J Pediatr 2013;■:■-■)*.

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Patent ductus arteriosus (PDA) is a common complication related to gestational age of preterm birth. In infants born at less than 32 weeks of gestation, the frequency of PDA ranges from 50% to more than 80%.[1,2] Untreated PDA is associated with increased mortality and morbidity in preterm infants, especially in those of less than 32 weeks of gestation and in those weighing less than 1500 g (very low birth weight infants).[3,4] In order to avoid these morbidities, a variety of management strategies to induce closure of PDA have been developed. Presymptomatic PDA treatment with cyclooxygenase (COX) inhibitors, either using indomethacin or ibuprofen, is most frequently used, but there is no consensus on treatment strategies for PDA.

Treatment with COX inhibitors inhibits prostaglandin synthesis and, thus, platelet function.[5,6] Moreover, a low platelet count may be a risk factor for IVH,[7] and neonatal platelets have hyporeactivity during the first days of life.[8,9] Therefore, a decreased platelet count might potentiate the risk of cerebral bleeding in the presence of COX inhibitors. Severe thrombocytopenia is considered a contraindication for medical treatment of a patent duct in many neonatal intensive care units, but cut-off values for platelet counts vary between centers.[10] The time of occurrence of thrombocytopenia is of importance because the platelet nadir typically occurs after the first day of life (DOL), reaching a nadir on days 4 to 5 of life with recovery by 7 to 10 days.[11-13]

The association between IVH, thrombocytopenia, and COX inhibitors has been minimally studied. We therefore investigated whether early presymptomatic treatment of PDA with COX inhibitors is associated with an increased risk for IVH in preterm infants with moderately low platelet counts (50-99 × 10^9/L).

COX	Cyclooxygenase
DOL	Day of life
IVH	Intraventricular hemorrhage
PDA	Patent ductus arteriosus
RDS	Respiratory distress syndrome

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The authors declare no conflicts of interest.

0022-3476/$ - see front matter. http://dx.doi.org/10.1016/j.jpeds.2012.12.035

Methods

We analyzed a prospective database of all infants with a birth weight of ≤1500 g, born at <32 completed weeks of pregnancy, and treated at Innsbruck Medical University, the only neonatal intensive care unit in Tyrol. Infants who had at least 1 ultrasound examination of the brain were included (2003-2009). Infants with major congenital anomalies and those who had received PDA prophylaxis with a COX inhibitor within 6 hours were excluded from analysis. Treatment with COX inhibitors was considered contraindicated with severe thrombocytopenia ($<50 \times 10^9$/L) and, therefore, these patients were also excluded.

Clinical data for infants with and without PDA were prospectively collected (Table I). Fertility treatment was classified as yes versus no, irrespective of the mode of treatment. Maternal hypertension in pregnancy was defined according to the Working Group on High Blood Pressure in Pregnancy.[14] Gestational age was calculated from the first day of the last menstrual period. This was compared with assessment of gestational age by ultrasound scans that had to be performed before 24 weeks. If the estimated gestational age differed from the calculated one, the scan assessment was used. Umbilical cord artery pH was graded as <7.1 or ≥7.1 and 5-minute Apgar score as <7 or ≥7. Growth charts developed by Alexander et al[15] were used to classify infants as small for gestational age at birth, defined as a birth weight lower than to 10th percentile for sex and gestational age. Severe respiratory distress syndrome (RDS) was defined as the need for ventilation or postnatal surfactant treatment because of clinical signs of tachy-/dyspnea, requirement for supplemental oxygen to maintain a pulse oximeter saturation over 85%, and reticulogranular appearance to lung fields with or without low lung volumes and air bronchograms within the first DOL. Severe arterial hypotension was defined as the need for catecholamine treatment. A diagnosis of early-onset (≤72 hours after birth) or late-onset (>72 hours) sepsis required signs of generalized infection, a positive blood culture and antibiotic therapy for five or more days. IVH was classified according to the method of Papile et al.[16] The term IVH was used to summarize hemorrhages grades 1-4, the term severe IVH for grades 3 and 4 bleedings.

Ultrasound examinations were routinely performed on DOL 2 and DOL 5 in the second and third weeks of life, and thereafter every other week. The first cranial ultrasound was performed before treatment with COX inhibitors was started.

PDA was diagnosed by echocardiography. Echocardiography was routinely performed on DOL 2 in infants who had severe RDS and on DOL 4-7 in those who were not ventilated,[17] and treatment, if indicated, was started immediately after diagnosis of PDA.

First-line therapy for PDA was treatment with COX inhibitors in the presymptomatic stage. The COX inhibitors indomethacin (0.1 mg/kg per dose) or ibuprofen (loading dose 10 mg/kg followed by 2 × 5 mg/kg at 24-hour intervals) were used if there were no contraindications (oliguria [urine output below 0.6 mL/kg per hour], severe thrombocytopenia, severe or progressive IVH and persistent pulmonary hypertension with right-to-left shunt). Fifteen of 164 patients (9.1%) received no therapy. Twelve patients had a small PDA, which was expected to close spontaneously, and 3 patients had a contraindication to treatment (Figure).

Platelet count was categorized to: $\geq 100 \times 10^9$/L or $99\text{-}50 \times 10^9$/L (moderate thrombocytopenia). We measured platelet counts on DOL 1 and from DOL 2-7. If blood count was measured more than once per time period, the lowest count was recorded. In each patient, at least 1 blood count was measured before the beginning of COX inhibitor therapy.

Table I. Characteristics of VLBW preterm infants with a gestational age <32 weeks with and without PDA (n = 322*)

Variable	PDA (n = 164) n (%) or median (range)	No PDA (n = 158) n (%) or median (range)	*P* value†
Gestational age (wk)	**28 (24-31)**	**29 (23-31)**	**.001**
Birth weight (g)	1160 (485-1500)	1190 (420-1500)	.206
Male sex	79 (48.2)	84 (53.2)	.370
Fertility treatment (any)	21 (12.8)	25 (15.8)	.450
Maternal hypertension	25 (15.2)	28 (17.7)	.549
Multiple birth	50 (30.5)	48 (30.4)	.983
Antenatal steroids	134 (81.8)	137 (86.7)	.135
pH < 7.1	3 (1.8)	5 (3.2)	.426
5-Min Apgar <7	**22 (13.4)**	**11 (7.0)**	**.037**
SGA	13 (7.9)	23 (14.6)	.059
Severe RDS	**105 (64.0)**	**66 (41.8)**	**<.001**
Severe arterial hypotension	**33 (30.1)**	**14 (8.9)**	**<.001**
Early-onset sepsis	7 (4.3)	3 (1.9)	.220
Late-onset sepsis	27 (16.5)	18 (11.4)	.197
IVH	**41 (25.0)**	**22 (14.0)**	**.012**
$50\text{-}99 \times 10^9$/L platelets DOL 1	7 (4.3)	2 (1.3)	.173
$50\text{-}99 \times 10^9$/L platelets DOLs 2-7	17 (10.4)	16 (10.1)	.854

SGA, small for gestational age; *VLBW*, very low birth weight.
Significant variables are marked in bold.
*Three patients had no echocardiography (Figure) and were not considered.
†*P* values are from the Mann–Whitney U test, χ^2, or Fisher exact test, as appropriate.

Statistical Analyses

Analyses were performed using SPSS software, v. 20.0 for Windows (SPSS Inc, Chicago, Illinois). Categorical and continuous data were compared with the χ^2 test, Fisher exact test, and the Mann–Whitney U test, respectively. In order to assess risk factors for IVH, multivariable unconditional logistic regression models were fitted. A four-category variable platelet count ($\geq 100 \times 10^9$/L and no treatment, platelet count $\geq 100 \times 10^9$/L and treatment with COX inhibitors, platelet count $50\text{-}99 \times 10^9$/L and no treatment, platelet count $50\text{-}99 \times 10^9$/L and treatment of PDA with COX inhibitors) was forced into these models, and other predictors of IVH were selected with a forward

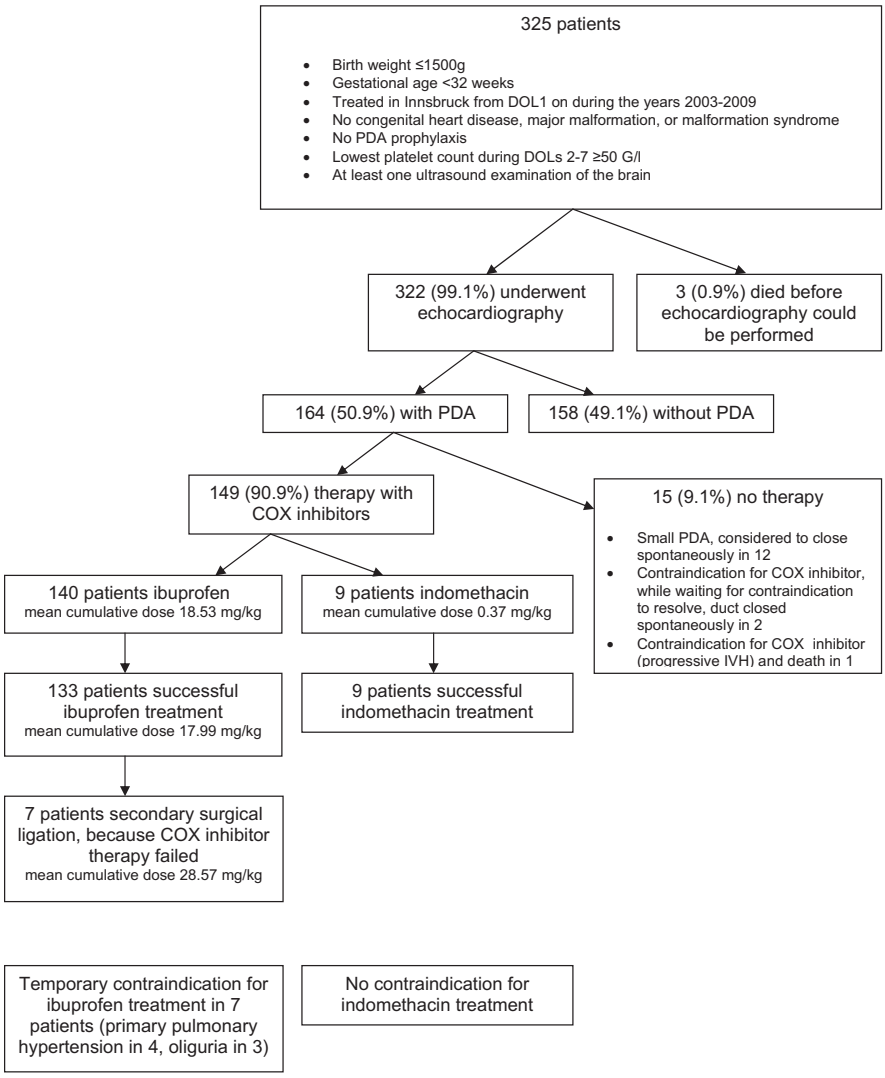

Figure. Mode of PDA treatment.

step-wise selection procedure (default inclusion and exclusion criteria) allowing for all variables in **Table I** with a univariate $P < .05$. P values for interaction between COX inhibitor therapy and moderately low platelet count were calculated by means of an appropriate interaction term. Post hoc analysis was performed with PASS statistical software (v. 11.0; NCSS LCC, Keysville, Utah).

Results

A total of 358 consecutive infants with a gestational age of less than 32 weeks and a birth weight at or below 1500 g were admitted to the neonatal intensive care unit. Ten infants were excluded because they had received PDA prophylaxis, 7 because of major congenital anomalies, and 16 infants because of severe thrombocytopenia ($<50 \times 10^9$/L) during DOLs 2-7.

Thus, 325 infants formed the study population (**Figure**). Median gestational age of participants was 29 weeks (range 23-31), median birth weight was 1170 g (range 420-1500). Comparing infants with and without COX inhibitor treatment, those without had a significantly higher gestational age ($P = .001$), were less likely small for gestational age ($P = .037$), suffered less frequently from severe RDS ($P < .001$), severe arterial hypotension ($P = .024$), and late-onset sepsis ($P = .044$). Comparing patients with PDA receiving COX inhibitor treatment according to the platelet count on DOL 2-7, those with a platelet count between 50 and 99 $\times 10^9$/L had a lower birth weight ($P = .030$), had more frequently a low 5-minute Apgar score ($P = .006$), severe arterial hypotension ($P = .007$), and IVH ($P < .001$) than those with a lower platelet count of ≥100 P 10^9/L.

Three hundred twenty-two (99.1%) of the 325 infants had echocardiography. Three patients died before

echocardiography, 1 because of severe sepsis, 2 because of severe IVH. PDA was found in 164 infants (50.5%). The treatment of PDA is given in the Figure.

Ultrasound examinations showed that IVH occurred in 65 (20%) of the 325 infants: 37 infants (11.3%) had grade 1 IVH, 7 infants (2.1%) grade 2 IVH, 12 infants (3.7%) grade 3 IVH, and 9 infants (2.8%) grade 4 IVH. The rate of IVH did not significantly differ between patients with or without treatment with COX inhibitors ($P = .242$).

In the majority of the 19 patients with IVH and platelets between 50-99 $\times$ 10^9/L on DOL 2-7, moderate thrombopenia (15 of 19; 79%) and initiation of COX inhibitor therapy (8 of 11; 73%) antedated the identification of IVH. In 1 patient IVH preceded COX inhibitor therapy, and in the remainder the temporal sequence could not be defined.

Univariate analysis showed a significant association between a higher IVH rate and low gestational age (median 27 vs 29 weeks, $P < .001$), low birth weight (median 1080 vs 1190 g, $P = .003$), and male sex (63.1% vs 47.3%, $P = .023$). The proportion of patients who received antenatal steroids was significantly lower in patients with IVH (77.8% vs 91.1%, $P = .003$). A pH < 7.1 and a 5-minute Apgar score <7 were associated with a higher rate of IVH (7.4% vs 2.1%, $P = .038$ and 19% vs 0.8%, $P < .001$, respectively). Severe RDS was more frequent in patients with IVH (76.9% vs 47.7%, $P < .001$), as were severe arterial hypotension (36.5% vs 9.8%, $P < .001$), early-onset sepsis (10.8% vs 1.5%, $P = .002$), and PDA (65.1% vs 47.5%, $P = .012$). When focusing on DOL 1, no significant association was observed between IVH and moderate thrombocytopenia, whereas on DOL 2-7 IVH was significantly associated with moderate thrombocytopenia (30.6% vs 6.7%, $P < .001$). In addition, IVH was not related to treatment with COX inhibitors (52.3% vs 44.2%, $P = .242$). Results of univariate analysis are given in Table II.

Comparing bleeding risk in patients receiving a COX inhibitor with a platelet count between 50 and 99 $\times$ 10^9/L and $\geq$100 $\times$ 10^9/L, OR was calculated as follows: 1.23 [95% CI 0.64-2.36] and 67.10 [95% CI 8.21-548.50], respectively. OR for patients with moderately low platelet counts without treatment was 3.05 [95% CI 1.15-8.06], P for interaction .014 (Table III).

In multivariate analysis, results were similar. Treatment of PDA with COX inhibitors was not an independent risk predictor for IVH in preterm infants with a platelet count of $\geq$100 $\times$ 10^9/L, but increased the risk of bleeding with moderately low platelet counts on DOL 2-7. Multivariable OR for IVH were 0.89 [95% CI 0.43-1.87] for patients with a platelet count $\geq$100 $\times$ 10^9/L and treatment with COX inhibitors, 3.40 [95% CI 1.13-10.3] for those with moderately low platelets without treatment, and 53 [95% CI 5.9-484] for patients with both moderately low platelet counts and COX inhibitor treatment compared with those with a platelet count $\geq$100 $\times$ 10^9/L and no treatment (reference group) ($P < .001$) (Table III). The association remained significant when only patients with severe IVH were analyzed and also when patients with early- and late-onset sepsis were excluded from analysis (data not shown). When excluding patients in whom IVH presented prior to assessment of platelet count or initiation of COX inhibitor treatment or the temporal sequence could not be defined for sure, findings were quite similar: multivariable OR of IVH for those with moderately low platelet counts alone was 3.33

Table II. Characteristics of VLBW preterm infants with a gestational age <32 weeks according to risk factors for IVH

Variable	IVH (n = 65) n (%) or median (range)	No IVH (n = 260) n (%) or median (range)	*P* value*
Gestational age (wk)	**27 (23-31)**	**29 (24-31)**	**<.001**
Birth weight (g)	**1080 (485-1490)**	**1190 (420-1500)**	**.003**
Male sex	**41 (63.1)**	**123 (47.3)**	**.023**
Fertility treatment (any)	10 (15.9)	37 (14.5)	.785
Maternal hypertension	9 (13.8)	44 (16.9)	.548
Multiple birth	18 (27.7)	81 (31.2)	.588
Antenatal steroids	**49 (77.8)**	**224 (91.1)**	**.003**
pH < 7.1	**4 (7.4)**	**5 (2.1)**	**0.038**
5-Min Apgar <7	**11 (19)**	**2 (0.8)**	**<.001**
SGA	8 (12.3)	29 (11.2)	.793
Severe RDS	**50 (76.9)**	**124 (47.7)**	**<.001**
Severe arterial hypotension	**23 (36.5)**	**25 (9.8)**	**<.001**
Early-onset sepsis	**7 (10.8)**	**4 (1.5)**	**.002**
Late-onset sepsis	13 (20.6)	32 (12.4)	.092
PDA	**41 (65.1)**	**123 (47.5)**	**.012**
COX inhibitor therapy	34 (52.3)	115 (44.2)	.242
50-99 $\times$ 10^9/L platelets DOL 1	4 (6.9)	6 (2.6)	.115
50-99 $\times$ 10^9/L platelets DOLs 2-7	**19 (30.6)**	**17 (6.7)**	**<.001**

Significant variables are marked in bold.
*P values are from the Mann–Whitney U test, χ^2, or Fisher exact test, as appropriate.

Table III. Risk for IVH in the 4 categories: platelet count $\geq$100 $\times$ 10^9/L and no treatment (reference group), platelet count $\geq$100 $\times$ 10^9/L and treatment with COX inhibitors, platelet count 50-99 $\times$ 10^9/L and no treatment, platelet count 50-99 $\times$ 10^9/L and treatment of PDA with COX inhibitors

Variable	Unadjusted OR	95% CI	aOR	95% CI
$\geq$100 $\times$ 10^9/L platelets, no treatment	1.0		1.0	
$\geq$100 $\times$ 10^9/L platelets, treatment	1.23	0.64-2.36	0.89	0.43-1.87
50-99 $\times$ 10^9/L platelets, no treatment	3.05	1.15-8.06	3.40	1.13-10.29
50-99 $\times$ 10^9/L platelets, treatment	67.10	8.21-548.50	53.27	5.87-483.53
	P interaction = .014		*P* interaction = .022	

Multivariable analysis was adjusted for gestational age (wk), early-onset sepsis, sex, and antenatal steroids.

[95% CI 1.09-10.16] and for those with both moderately low platelet counts and COX inhibitor treatment 43 [95% CI 4.5-413].

Discussion

We report an association between a moderately low platelet count between 50 and 99 $\times$ 10^9/L, treatment of PDA with COX inhibitors and IVH in preterm infants with a gestational age of less than 32 weeks. Treatment of PDA with COX inhibitors increased the risk for bleeding in the case of moderately low platelet counts on DOL 2-7, but this was not the case in infants with a platelet count of $\geq$100 $\times$ 10^9/L. The associations remained significant when only newborn infants with severe IVH were analyzed and also when infants with early- and late-onset sepsis were excluded from the analysis.

A role for thrombocytopenia in IVH was postulated in several studies, but the results reported in the literature are controversial. One publication linked platelet counts below 100 $\times$ 10^9/L with an increased rate of IVH[7]; this was not confirmed by others.[18,19] In most studies, time-point of occurrence of thrombocytopenia was not taken into account. A study differentiating thrombocytopenia on DOL 1 versus DOL 2 in the context of risk for IVH in preterm infants was published by Dani et al[20]; they found lower platelet counts at 24-48 hours in infants with severe IVH as compared with infants without severe IVH and no difference in platelet counts measured within 24 hours of birth. Platelet counts after DOL 2 were not taken into account. It is known that the platelet nadir typically occurs after DOL 1. In patients admitted to neonatal intensive care units, about 75% of all episodes of neonatal thrombocytopenia are either present at birth or develop by 72 hours of life[12,13] with platelets falling slowly to reach a platelet nadir at DOL 4-5 of life and recovering by 7-10 days.[12,14]

We, therefore, differentiated between platelet counts on DOL 1 and platelet counts on DOL 2-7. We found that platelet counts on DOL 1 did not influence risk for IVH, but thrombocytopenia with a platelet count between 50 and 99 $\times$ 10^9/L after the first DOL until the end of the first week was associated with a 3-fold risk for IVH. This result also indicates that platelet counts after DOL 1 are a better predictor for IVH than are platelet counts obtained within the first 24 hours after birth.

However, the risk for intracerebral bleeding in preterm infants is difficult to predict.[21] Current data suggest that not only platelet counts but also factors such as platelet dysfunction and coagulation abnormalities might play an important role. Impaired platelet function in cord blood was described in studies using platelet aggregometry. These platelets were less reactive than adult platelets,[22,23] and this hyporeactivity may contribute to the propensity of preterm infants to IVH.[24,25] In 2 studies, the period of hyporeactivity was within the first 10 days of life,[8,9] but Strauss et al concluded that the period of time after birth with lower reactivity of platelets is uncertain.[26]

It is well known that COX inhibitors cause an incomplete and intermittent inhibition of prostaglandin synthesis and, thus, altered platelet function. This effect was described for adult[27] as well as newborn platelets.[28,29] However, the effect on primary hemostasis was small.[30] Our study found no effect on cerebral bleeding risk in patients with $\geq$100 $\times$ 10^9/L platelets, but the combination of moderate thrombocytopenia and COX inhibitor treatment on DOL 2-7 amplified the risk for IVH. These findings indicate that a decreased platelet count potentiates the risk for bleeding in the presence of COX inhibitors. Lack of an association between COX inhibitor treatment and IVH in the absence of moderate thrombopenia should be interpreted with caution because the study was not adequately sized to detect associations of moderate strength (80% power to detect an OR of 2.49 at an α = 0.05 level).

Another risk factor for IVH in our study was early-onset sepsis. Sepsis is often accompanied by low platelet counts and abnormalities in coagulation. Therefore, we separately calculated bleeding risk in patients without sepsis, who had moderately low thrombocytes and were treated with COX inhibitors. The increased cerebral bleeding risk in patients with moderately low thrombocytes and COX inhibitor treatment remained significant (data not shown).

In conclusion, in preterm infants with moderate thrombocytopenia, benefits of treatment of PDA with COX inhibitors have to be carefully balanced against potential risks due to significantly increased risk of cerebral bleeding. To assess the risk for cerebral bleeding in preterm infants with thrombocytopenia and COX inhibitor treatment, a blood cell count should be obtained after the first DOL. ■

Submitted for publication Jul 18, 2012; last revision received Oct 4, 2012; accepted Dec 11, 2012.

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