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Hemasree Kandraju
University of Toronto

Jaideep Kanungo
The University of British Columbia

Kyong Soon Lee
University of Toronto

Sibasis Daspal
University of Saskatchewan, College of Medicine

Mohammad Amin Adie
Windsor Regional Hospital

See next page for additional authors

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Authors

Hemasree Kandraju, Jaideep Kanungo, Kyong Soon Lee, Sibasis Daspal, Mohammad Amin Adie, Jon Dorling, Xiang Y. Ye, Shoo K. Lee, Prakesh S. Shah, Marc Beltempo, Joseph Ting, Zenon Cieslak, Rebecca Sherlock, Ayman Abou Mehrem, Jennifer Toye, Khalid Aziz, Carlos Fajardo, Jaya Bodani, Lannae Strueby, Mary Seshia, Deepak Louis, Ruben Alvaro, Amit Mukerji, Orlando Da Silva, Eugene Ng, Brigitte Lemyre, Thierry Daboval, Faiza Khurshid, and Ermelinda Pelausa

Association of Co-Exposure of Antenatal Steroid and Prophylactic Indomethacin with Spontaneous Intestinal Perforation

Hemasree Kandraju, MD[1], Jaideep Kanungo, MD[2], Kyong-Soon Lee, MD[1,3], Sibasis Daspal, MD[4], Mohammad Amin Adie, MD[5], Jon Dorling, MBChB, MD[6], Xiang Y. Ye, MSc[7], Shoo K. Lee, MBBS, FRCPC, PhD[1,7,8], and Prakesh S. Shah, MD, MSc[1,7,8], on behalf of the Canadian Neonatal Network (CNN), and Canadian Preterm Birth Network (CPTBN) Investigators*

Objective To evaluate the association of a combined exposure to antenatal steroids and prophylactic indomethacin with the outcome of spontaneous intestinal perforation (SIP) among neonates born at <26 weeks of gestation or <750 g birth weight.

Study design We conducted a retrospective study of preterm infants admitted to Canadian Neonatal Network units between 2010 and 2018. Infants were classified into 2 groups based on receipt of antenatal steroids; the latter subgrouped as recent (≤7 days before birth) or latent (>7 days before birth) exposures. The co-exposure was prophylactic indomethacin. The primary outcome was SIP. Multivariable logistic regression analysis was used to calculate aORs.

Results Among 4720 eligible infants, 4121 (87%) received antenatal steroids and 1045 (22.1%) received prophylactic indomethacin. Among infants exposed to antenatal steroids, those who received prophylactic indomethacin had higher odds of SIP (aOR 1.61, 95% CI 1.14-2.28) compared with no prophylactic indomethacin. Subgroup analyses revealed recent antenatal steroids exposure with prophylactic indomethacin had higher odds of SIP (aOR 1.67, 95% CI 1.15-2.43), but latent antenatal steroids exposure with prophylactic indomethacin did not (aOR 1.24, 95% CI 0.48-3.21), compared with the respective groups with no prophylactic indomethacin. Among those not exposed to antenatal steroids, mortality was lower among those who received prophylactic indomethacin (aOR 0.45, 95% CI 0.28-0.73) compared with no prophylactic indomethacin.

Conclusions In preterm neonates of <26 weeks of gestation or birth weight <750 g, co-exposure of antenatal steroids and prophylactic indomethacin was associated with SIP, especially if antenatal steroids was received within 7 days before birth. Among those unexposed to antenatal steroids, prophylactic indomethacin was associated with lower odds of mortality. *(J Pediatr 2021;235:34-41).*

Antenatal steroids are a standard of care for preterm infants to reduce mortality and intraventricular hemorrhage (IVH).[1] Postnatal prophylactic indomethacin has been shown to reduce severe IVH (grades 3 or 4) and patent ductus arteriosus (PDA) in preterm and extremely low birth weight neonates in both randomized trials and observational studies.[2-4] However, several exposures, including postnatal glucocorticoids and indomethacin, have been associated with spontaneous intestinal perforation (SIP). Indomethacin decreases blood flow to the intestine and may result in direct mucosal injury amplified by its enterohepatic circulation.[5,6] Some studies found that indomethacin use early in the postnatal period was associated with SIP[7-10]; however, a randomized controlled trial of indomethacin prophylaxis did not show higher rates of gastrointestinal complications linked to its use.[4] There is also conflicting evidence regarding the associations between prophylactic indomethacin and SIP when used alone or with early feeding.[11] Although

CNN	Canadian Neonatal Network
IVH	Intraventricular hemorrhage
PDA	Patent ductus arteriosus
NICU	Neonatal intensive care unit
SIP	Spontaneous intestinal perforation

several neonatal intensive care units (NICUs) have continued the practice of administering prophylactic indomethacin to preterm or extremely low birth weight neonates to reduce the risk of IVH,[12] the potential benefits of prophylactic indomethacin in preventing severe IVH may be countered by higher odds of SIP. Both SIP[13,14] and severe IVH are associated with significant morbidity, mortality, and neurodevelopmental impairment. The incidence of SIP is reported to be approximately 5% in infants <1000 g,[15] and the incidence of severe IVH is reported to be 10%-16% in extremely preterm infants.[16-18]

Experimental studies reveal that postnatal glucocorticoids alter ileal tissue growth in the neonate, resulting in mucosal hyperplasia and concomitant submucosal thinning and potentially explaining the relationship with SIP.[19,20] A secondary analyses from a recent trial revealed that higher cortisol levels after birth were associated with higher odds of SIP in infants who received postnatal hydrocortisone.[21] Exposure to antenatal steroids and prophylactic indomethacin was postulated to be associated with SIP.[22] A previous study did not find an association between antenatal steroids and SIP, whether alone or in combination with prophylactic indomethacin,[23] but it lacked data on the timing of antenatal

steroids. A case-control trial[24] found the risk for SIP was higher when antenatal betamethasone was given closer to delivery.

Considering the inconclusive state of the evidence regarding competing risks and benefits of antenatal steroids and prophylactic indomethacin for SIP and other important outcomes, our objective was to evaluate the association between antenatal steroids and prophylactic indomethacin co-exposure and the outcome of SIP among neonates of <26 weeks of gestation or <750 g birth weight, and to consider the influence of antenatal steroids exposure timing.

Methods

We conducted a retrospective cohort study including preterm infants of gestational age of <26 weeks or birth weight <750 g admitted to NICUs participating in the Canadian Neonatal Network (CNN) between January 2010 and December 2018. We excluded infants who had major congenital anomalies, those who received palliative care at admission, and those who received postnatal steroids within 14 days of birth. We also excluded infants with missing data
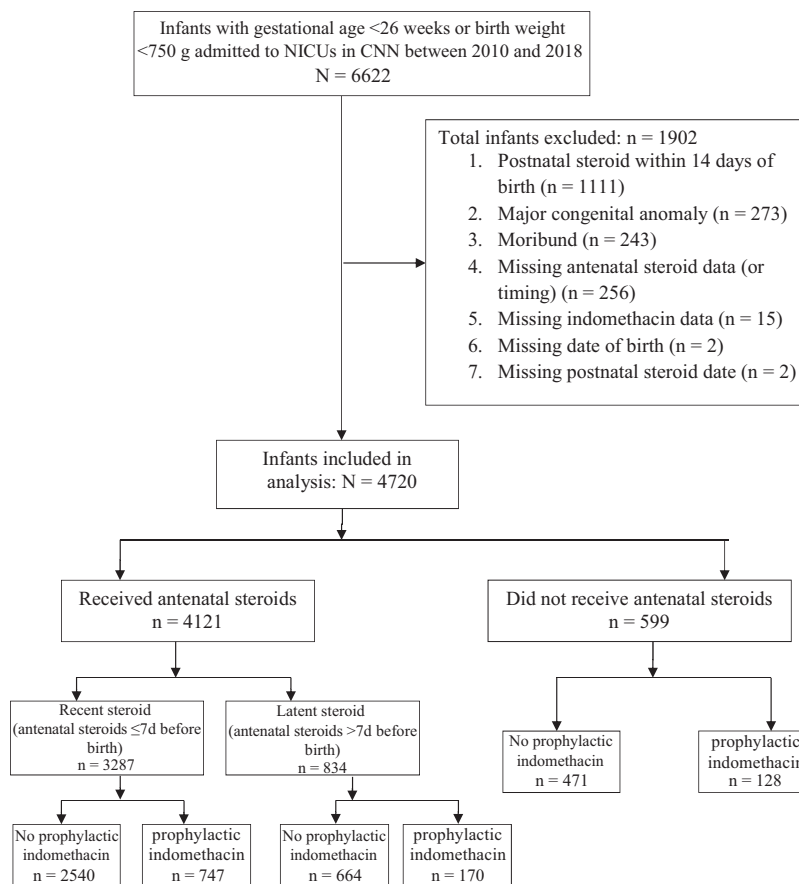

Figure. Study population.

on date of birth, timing of antenatal steroids, indomethacin use, and timing of postnatal steroid (**Figure**).

Co-exposures

We hypothesized that the timing of exposure to antenatal steroids may affect the risk of SIP, with exposure more proximate to birth having the higher risk. To explore this hypothesis, we first divided eligible infants into 2 groups: no antenatal steroids and antenatal steroids. Based on the timing of antenatal steroids, the latter group was subdivided into a "recent" steroid group (complete or partial course of antenatal steroids ≤7 days before birth) and a "latent" steroid group (complete or partial course of antenatal steroids >7 days before birth). All groups were further divided into 2 subgroups based on co-exposure to prophylactic indomethacin or not. The antenatal steroid used by centers in Canada is betamethasone 12 mg (combination of betamethasone phosphate 6 mg and betamethasone acetate 6 mg). Complete course of antenatal steroids was defined as 2 doses of 12 mg of betamethasone given 24 hours apart, and partial course was defined as receipt of only 1 dose of betamethasone. Prophylactic indomethacin was defined as the use of indomethacin within the first 24 hours after birth for prevention of IVH and not for treatment of symptomatic PDA. The dosage of prophylactic indomethacin was 0.1 mg/kg/dose given intravenously at 24-hour intervals for 3 doses.

Outcomes

Our primary outcome was occurrence of SIP, defined as radiologic finding of intestinal perforation with absence of radiological features of intestinal ischemia, such as fixed dilated bowel loops or pneumatosis intestinalis; or intraoperative surgical report; or histopathologic confirmation of perforation located in the ileum and on the antimesenteric border.[25] Our secondary outcomes were severe IVH, defined as IVH with ventricular dilatation or parenchymal hemorrhage; and mortality before discharge. Treatment for PDA was evaluated as a post-hoc outcome after the results of the primary analyses were available.

Definitions

Gestational age was defined as the best estimate based on the date of in vitro fertilization, early ultrasound, last menstrual period, obstetric estimate, or pediatric estimate, in that hierarchical order. Small for gestational age was defined as birth weight less than the 10th percentile for gestational age and sex.[26] Treated PDA was defined as therapeutic treatment with indomethacin, ibuprofen, acetaminophen, or surgical ligation for closure of PDA.

Data Collection

Data were collected from patient charts at the individual sites following procedures outlined in the CNN Abstractor's Manual.[27] The data were entered electronically and transmitted to the central coordinating center at Mount Sinai Hospital, Toronto. The CNN database has been shown to have high reliability and internal consistency.[28] Data on maternal and infant characteristics, the timing of antenatal steroids, prophylactic indomethacin (usage within the first 24 hours after birth), and other predisposing factors were retrieved from the database for analysis. Ethical approval for this study was obtained from the Research Ethics Board at Mount Sinai Hospital and the Executive Committee of the CNN.

Statistical Analyses

The study population was summarized descriptively. Maternal and infant characteristics were compared between prophylactic indomethacin exposure groups (prophylactic indomethacin and no prophylactic indomethacin) for each antenatal steroids group (none, any, recent, or latent) using the χ^2 test for categorical variables and the Student t test or Wilcoxon rank-sum test, as appropriate, for continuous variables. To examine the associations between outcomes and exposures, the outcomes were compared between the prophylactic indomethacin exposure groups for each antenatal steroids group using the χ^2 test. Multivariable logistic regression models were further applied to determine the effects of the exposures on the primary and secondary outcomes for each exposure group, adjusted for potential confounders. For a post-hoc analysis evaluating the association between prophylactic indomethacin and treatment for PDA, we applied similar methods to those described above. Data management and all statistical analyses were performed using SAS 9.4 (SAS Institute Inc). A 2-sided P value of <.05 was considered statistically significant.

Results

During the study period, a total of 6622 infants were admitted to CNN NICUs, of whom 1902 were excluded based on the exclusion criteria (**Figure**). The remaining 4720 infants (71% of total) were included in the analysis and, of these, 4121 (87%) received antenatal steroids and 1045 (22.1%) received prophylactic indomethacin. **Table I** presents comparisons of maternal and infant characteristics between different exposure groups. Infants who received prophylactic indomethacin were born at younger gestational age and had lower birth weights than those who did not receive prophylactic indomethacin. The percentage of small for gestational age was less in infants who received prophylactic indomethacin in all the steroid groups. The history of receipt of antenatal magnesium sulfate was higher in infants who were exposed to antenatal steroids and prophylactic indomethacin compared with those who were not exposed to antenatal steroids. **Table II** reports results from univariate comparisons of outcomes within each antenatal steroids group between infants who received prophylactic indomethacin and those who received no prophylactic indomethacin.

Table III shows results from adjusted analyses comparing the prophylactic indomethacin vs the no prophylactic

Table I. Maternal and infant baseline characteristics

Characteristics	No steroid		Any steroid		Recent steroid (antenatal steroids ≤7d before birth)		Latent steroid (antenatal steroids >7d before birth)	
	No prophylactic indomethacin (n = 471)	Prophylactic indomethacin (n = 128)	No prophylactic indomethacin (n = 3204)	Prophylactic indomethacin (n = 917)	No prophylactic indomethacin (n = 2540)	Prophylactic indomethacin (n = 747)	No prophylactic indomethacin (n = 664)	Prophylactic indomethacin (n = 170)
Maternal hypertension, % (n/N)	7.9 (35/440)	4.8 (6/125)	21.1 (667/3157)	14.9 (136/908)*	21.9 (548/2499)	15.3 (113/738)*	18.1 (119/658)	13.5 (23/170)
Maternal diabetes, % (n/N)	5.1 (22/430)	5.0 (6/119)	7.4 (228/3078)	6.9 (63/901)	7.0 (171/2434)	6.3 (46/734)	8.9 (57/644)	10.2 (17/167)
Magnesium sulfate, % (n/N)	12.8 (56/438)	14.1 (18/128)	58.4 (1805/3092)	69.7 (626/898)*	59.6 (1460/2449)	70.5 (514/729)*	53.6 (345/643)	66.3 (112/169)*
Gestational age, median (IQR), wk	25 (23, 25)	24 (23, 25)*	25 (24, 26)	24 (24, 25)*	25 (24, 25)	24 (24, 25)*	25 (25, 26)	25 (24, 25)*
Birth weight, mean (SD), g	715 (198)	675 (124)*	711 (136)	668 (120)*	705 (131)	683 (121)*	733 (152)	709 (116)
Male, % (n/N)	52.6 (247/470)	42.9 (55/128)	49.4 (1582/3200)	49.9 (456/913)	48.8 (1239/2537)	49.9 (371/744)	51.7 (343/663)	50.3 (85/169)
Apgar <7 at 5 min, % (n/N)	64.4 (282/438)	74.8 (86/115)*	49.8 (1589/3189)	48.4 (440/909)	51.6 (1304/2528)	49.4 (365/739)	43.1 (285/661)	44.1 (75/170)
Singleton, % (n/N)	77.9 (367/471)	75 (96/128)	77.1 (2471/3204)	73.4 (673/917)*	78.9 (2006/2540)	74.8 (559/747)*	70.0 (465/664)	67.1 (114/170)
SGA, % (n/N)	14.9 (70/470)	5.5 (7/128)*	25.1 (803/3203)	12.4 (113/915)*	23.8 (605/2539)	11.7 (87/745)*	29.8 (198/664)	15.3 (26/170)*
SNAP-II score >20, % (n/N)	45.8 (196/428)	56.4 (71/126)*	39.9 (1252/3135)	41.8 (380/909)	39.9 (991/2481)	42.1 (312/741)	39.9 (261/654)	40.5 (68/168)
Cesarean delivery, % (n/N)	40.8 (192/471)	38.3 (49/128)	61.9 (1979/3199)	52.4 (480/916)	60.6 (1538/2537)	50.7 (378/746)*	66.6 (441/662)	60 (102/170)
Inotropes within 3 d, % (n/N)	23.8 (112/471)	28.9 (37/128)	15.0 (482/3204)	12.5 (115/917)	14.4 (365/2540)	12.7 (95/747)	17.6 (117/664)	11.8 (20/170)
PPROM >1 wk, % (n/N)	2.1 (9/426)	0.8 (1/121)	8.8 (276/3128)	9.2 (83/905)	5.5 (136/2478)	5.9 (43/735)	21.5 (140/650)	23.5 (40/170)

PPROM, preterm pre-labor rupture of membranes; SGA, small for gestational age; SNAP, score for neonatal acute physiology.
*P <.05 for comparison between no prophylactic indomethacin and prophylactic indomethacin groups.

indomethacin group within each antenatal steroids exposure group. The odds of SIP were higher for infants who received any antenatal steroids and prophylactic indomethacin, and especially for those who received recent antenatal steroids and prophylactic indomethacin, compared with those in the respective antenatal steroids groups who did not receive prophylactic indomethacin. There were no differences in the odds of severe IVH or mortality before discharge for prophylactic indomethacin vs no prophylactic indomethacin in any antenatal steroids group. Among infants who did not receive antenatal steroids, the odds of mortality were lower in those exposed to prophylactic indomethacin. In the latent antenatal steroids group, there were no differences in the odds of SIP, severe IVH, or mortality according to prophylactic indomethacin exposure.

In post-hoc analyses, we evaluated whether prophylactic indomethacin was associated with treatment for PDA. Results are shown in Tables II and III. Prophylactic indomethacin administration was associated with lower rates and lower odds of treated PDA among infants who received recent or latent antenatal steroids, but not for those who did not receive antenatal steroids.

Discussion

In this large, population-based study, the overall incidence of SIP was 4.2% among neonates of <26 weeks of gestational age or <750 g birth weight. Infants exposed to antenatal steroids at any time before birth and co-exposed to prophylactic indomethacin had higher odds of SIP than those who did not receive prophylactic indomethacin, especially if antenatal steroid was received within 7 days before birth. Infants not exposed to antenatal steroids and exposed to prophylactic indomethacin had lower odds of mortality than those who did not receive prophylactic indomethacin. Infants exposed to antenatal steroids had no differences in the odds of severe IVH or mortality whether or not they received prophylactic indomethacin and infants exposed to antenatal steroids more than 7 days before birth had no differences in the odds of SIP, severe IVH, or mortality whether or not they received prophylactic indomethacin.

The relationship of antenatal steroids and prophylactic indomethacin has been explored previously. Using a national dataset, Attridge et al conducted a case-control study of infants with isolated bowel perforation matched with controls and observed that infants in the SIP group had higher rates of exposure to indomethacin alone and co-exposure of antenatal steroids and indomethacin.[23] However, the authors identified that the combination of antenatal steroids with indomethacin was not associated with increased SIP when compared with indomethacin alone. The timing of antenatal steroids was not available, and they did not differentiate between the use of indomethacin for prophylaxis or treatment of PDA. Arnautovic et al[24]

Table II. Univariate analyses of outcome rates

Outcomes	No steroid			Any steroid			Recent steroid (antenatal steroids ≤7d before birth)			Latent steroid (antenatal steroids >7d before birth)		
	No prophylactic indomethacin (471)	Prophylactic indomethacin (128)	P value	No prophylactic indomethacin (3204)	Prophylactic indomethacin (917)	P value	No prophylactic indomethacin (2540)	Prophylactic indomethacin (747)	P	No prophylactic indomethacin (664)	Prophylactic indomethacin (170)	P value
SIP, % (n/N)	5 (23/460)	4 (5/128)	.61	4 (116/3176)	6 (55/913)	**<.01**	4 (96/2516)	7 (49/743)	**<.01**	3.0 (20/660)	3.5 (6/170)	.74
Severe IVH, % (n/N)	30 (117/392)	29 (34/119)	.79	15 (462/3035)	18 (157/895)	.09	16 (371/2398)	18 (129/726)	.14	14.3 (91/637)	16.6 (28/169)	.46
Mortality, % (n/N)	43 (204/471)	32 (41/128)	**.02**	19 (606/3204)	18 (169/917)	.74	20 (510/2540)	20 (147/747)	.81	14.5 (96/664)	12.9 (22/170)	.61
Treated PDA % (n/N)	46 (200/432)	45 (55/122)	.81	50 (1585/3144)	44 (398/902)	**.001**	51 (1273/2489)	46 (338/733)	**.02**	48 (312/655)	36 (60/169)	**<.01**

Bold text indicates statistically significant differences in the outcome.

studied 57 infants with SIP and matched them with 114 infants without SIP born at <29 weeks of gestational age. Almost all infants in both groups received prophylactic indomethacin, 43% of SIP cases and 36% of controls were exposed to maternal indomethacin, and 87% of cases and 94% of controls were exposed to prenatal steroids (P = .16). However, the authors reported that, among infants with SIP, the odds of SIP increased by 1% for each 1-hour decrease in the interval between the last dose of betamethasone and birth. Wadhawan et al[10] reported a higher risk of SIP with indomethacin used for PDA, but not with prophylactic indomethacin. Contrary to our results, they reported that exposure to antenatal steroids was associated with lower odds of SIP. In that study, the co-exposure of antenatal steroids and prophylactic indomethacin was not examined and the timing of antenatal steroids was not reported. The Trial of Prophylactic Indomethacin in Preterm investigators[29] conducted a post-hoc analysis to evaluate whether antenatal steroids exposure modified the effects of prophylactic indomethacin on death or neurodevelopmental impairment, PDA, and severe IVH. They reported that antenatal steroids exposure was not associated with statistically significant heterogeneity for neonatal outcomes or longer-term effects of prophylactic indomethacin. Thus, evidence supporting or refuting this association between co-exposure to antenatal steroids and prophylactic indomethacin with SIP has been tenuous and needs exploration in a larger database or a randomized trial.

Our observation of higher SIP with antenatal steroids, especially when antenatal steroids was administered within 7 days before birth, followed by postnatal exposure to prophylactic indomethacin, may be explained by the theory that the initial insult to the gut from exposure to antenatal steroids is compounded by the effects of indomethacin. In animal studies, it was observed that, the loss of nitric oxide synthase (NOS) in the intestinal smooth muscle via combined inhibition of the neuronal NOS by steroids and endothelial NOS by indomethacin leads to disturbed intestinal motility and increases vulnerability of the intestine to perforation.[30-32] Extensive work on the pharmacokinetics and pharmacodynamics of antenatal steroids containing betamethasone[33] identified that the betamethasone acetate component of the combination, widely used in developed countries, is released very slowly in circulation, especially when given intramuscularly, leading to prolonged maternal and fetal levels for at least 4-6 days. This may explain co-exposure having a pronounced effect when exposure to antenatal steroid was recent. Kajantie et al[34] found glucocorticoid bioavailability was elevated in neonates born within 12 hours after a dose of antenatal steroids, and that this response gradually disappeared over 3 days afterward. This observed duration of action of antenatal steroids lends support to our observation of higher SIP risk when antenatal steroids exposure was more recent, as there may be inadequate time for the intestinal mucosa to recover. In a secondary analysis of a recent multicenter randomized controlled trial including infants <28 weeks of gestational age at birth, Renolleau et al[21]

Table III. Comparisons of outcome rates between prophylactic indomethacin and no prophylactic indomethacin groups

Outcomes	No steroid Unadjusted OR (95% CI)	No steroid aOR* (95% CI)	Any steroid Unadjusted OR (95% CI)	Any steroid aOR* (95% CI)	Recent steroid (antenatal steroids ≤7d before birth) Unadjusted OR (95% CI)	Recent steroid (antenatal steroids ≤7d before birth) aOR* (95% CI)	Latent steroid (antenatal steroids >7d before birth) Unadjusted OR (95% CI)	Latent steroid (antenatal steroids >7d before birth) aOR* (95% CI)
SIP	0.77 (0.29, 2.07)	0.69 (0.25, 1.88)	**1.69 (1.22, 2.35)**	**1.61 (1.14, 2.28)**	**1.78 (1.25, 2.54)**	**1.67 (1.15, 2.43)**	1.17 (0.46, 2.96)	1.24 (0.48, 3.21)
Severe IVH	0.94 (0.60, 1.48)	0.79 (0.49, 1.27)	1.19 (0.97, 1.45)	1.10 (0.89, 1.35)	1.18 (0.95, 1.47)	1.11 (0.89, 1.40)	1.19 (0.75, 1.89)	1.04 (0.65, 1.67)
Mortality	**0.62 (0.41, 0.93)**	**0.45 (0.28, 0.73)**	0.97 (0.80, 1.17)	0.89 (0.73, 1.09)	0.98 (0.80, 1.20)	0.89 (0.72, 1.10)	0.88 (0.54, 1.45)	0.89 (0.53, 1.47)
Treated PDA	0.95 (0.64, 1.43)	0.85 (0.56, 1.30)	**0.78 (0.67, 0.90)**	**0.66 (0.56, 0.77)**	**0.82 (0.69, 0.96)**	**0.70 (0.59, 0.84)**	**0.61 (0.43, 0.86)**	**0.48 (0.33, 0.69)**

ORs are for comparisons of prophylactic indomethacin vs No prophylactic indomethacin within each steroid group (no steroid, any, recent, latent). No prophylactic indomethacin was the reference group.
For OR (95% CI) values, bold text indicates statistically significant difference in odds.
*ORs were adjusted for the following factors: gestational age, maternal hypertension, receipt of magnesium sulfate, cesarean delivery, small for gestational age, and singleton birth.

measured baseline serum cortisol levels within 24 hours of life, before administration of hydrocortisone or placebo. They observed that high baseline cortisol levels were significantly associated with SIP and IVH only in hydrocortisone-exposed infants. The authors proposed that high cortisol levels immediately after birth may help to identify infants at higher risk of adverse outcomes produced by hydrocortisone. These findings provide additional evidence supporting our observation of higher risk for SIP with the combined effect of recent antenatal steroids and prophylactic indomethacin, as susceptibility of the intestine was likely increased due to higher baseline cortisol levels in the recent antenatal steroids group.

Among infants not exposed to antenatal steroids, we observed less mortality with exposure to prophylactic indomethacin, which is similar to a report from Jensen et al.[35] They noted less mortality with prophylactic indomethacin in a subgroup of infants with birth weight above the 10th percentile and among those who did not undergo medical or surgical therapy for PDA. The authors postulated that their findings may be due to a protective effect of prophylactic indomethacin against mortality by decreasing symptomatic PDA. However, we found no significant difference in treated PDA, whether or not they received prophylactic indomethacin. Trial of Prophylactic Indomethacin in Preterm and other trials found that, although prophylactic indomethacin was associated with reduced incidence of significant PDA, there was no effect on mortality.[3,4,36]

Independently, antenatal steroids and prophylactic indomethacin have been shown to reduce the incidence of severe IVH in several randomized trials and observational studies.[3,4,29,36,37] An expected protective effect of the combination of antenatal steroids and prophylactic indomethacin against severe IVH (by increasing stability of the cerebral vasculature and micro vessel maturation in the germinal matrix) was not demonstrated in our study, in any of the steroid groups, either with or without prophylactic indomethacin. Our findings may be due to the inclusion of only infants with the highest risk of IVH (eg, those born at <26 weeks of gestation or <750 g birth weight), which is a different population from those examined in previous studies.

We found none of the outcomes were different in the latent steroid group with or without prophylactic indomethacin. This can be explained by assuming that antenatal steroids levels gradually dropped after the dose and, as a result, produced no effects on the outcomes. Our findings are consistent with the Cochrane review by Roberts et al,[37] who observed that IVH was not significantly reduced in those born after 7 days of antenatal corticosteroid therapy.

Key strengths of our study were the use of a population-based cohort of very high-risk neonates, and meticulous data collection. We believe this level of detail regarding the timing of antenatal steroids exposure can help develop a personalized or targeted approach to guide the use of antenatal steroids and prophylactic indomethacin. However, we also acknowledge several study limitations. First, we did not have data on maternal indomethacin, which can increase the risk of SIP.[32,38] However, indomethacin was used as a tocolytic agent in a very small proportion of our patients. Second, it is possible that some neonates in our cohort may have received postnatal indomethacin or ibuprofen to treat PDA before developing SIP. We did have data on which patients received these drugs, but not on the timing of this treatment, and so could not evaluate the relationship. Third, because the data were coded in categories rather than age in days, we did not have data on the exact timing of the receipt of antenatal steroids or prophylactic indomethacin. More granular data on antenatal steroids or prophylactic indomethacin timing could provide more precision regarding the age of exposure and should be explored in future studies. Fourth, this was a retrospective study with the inherent potential for residual confounding. Fifth, different centers participating in CNN varied in their use of prophylactic indomethacin, and this may have affected the outcomes. However, we could not fit a model including site as a random variable because many sites had zero events and the model did not converge.

Whether or not to use prophylactic indomethacin has been debated extensively in neonatal practice, and individual NICUs have taken different approaches. Some NICUs use prophylactic indomethacin when their baseline rates of severe IVH are high, or for select populations. With prophylactic indomethacin use, the literature has suggested there is a

trade-off between an increased risk of SIP and decreased risk of severe IVH. Our findings provide new evidence that infants co-exposed to antenatal steroids and prophylactic indomethacin had higher odds of SIP than those exposed to antenatal steroids alone, especially if antenatal steroids was given within the week before birth, without decrease in the odds of severe IVH or mortality. Further studies are required to determine whether our findings are replicable.

In summary, among preterm infants born at <26 weeks of gestational age or <750 g birth weight who were exposed to antenatal steroids, co-exposure with prophylactic indomethacin was associated with higher odds of SIP, especially when antenatal steroids exposure was within 7 days before birth, but not with decreases in the odds of severe IVH or mortality. We also observed lower odds of mortality among infants not exposed to antenatal steroids who received prophylactic indomethacin compared with those who did not receive prophylactic indomethacin. Although further studies will be needed to confirm or refute our current findings, the associations we identified may support the development and evaluation of an individualized approach for prophylactic indomethacin that is based on whether antenatal steroids was received and at what time. ∎

Data Statement

Data sharing statement available at www.jpeds.com.

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50 Years Ago in THE JOURNAL OF PEDIATRICS

The Importance of Negative Studies in Current Management of Pertussis in Children

Balagtas R, Nelson K, Levin S, Gotoff S. Treatment of pertussis with pertussis immune globulin. J Pediatr 1971;79:203-8.

Although pertussis vaccine was invented in 1914 and was available as a combined diphtheria–tetanus–pertussis vaccine in 1940, in early 1970 there were ongoing efforts to improve the treatment of exposed individuals who were not completely immunized. One therapy, pertussis immune globulin, was based on reports of the beneficial effect of serum or whole blood from convalescent patients. However, there were few controlled trials. In addition, due to issues of confirming a diagnosis, there were challenges in enrolling patients early in the disease course.

In 1971, Balagtas et al conducted a double-blind, randomized controlled study to assess the effectiveness of pertussis immune globulin in 74 children who had a clinical diagnosis of pertussis. The immune globulin was administered early in the paroxysmal stage. The analysis suggested that, compared with controls, the children treated with pertussis immune globulin demonstrated no difference in the course of disease. The outcomes were based on the frequency of coughing paroxysms, whooping, and vomiting and required suctioning over the next 24 days. These findings were consistent with published controlled studies at that time. This study is an example of the importance of negative studies in helping clinicians identify therapies that are not helpful for children. In this way, the study is influential in how we currently approach our management of pertussis in children who are incompletely immunized.

Today, in general, pertussis vaccination is still the best form of prevention. However, early start of a macrolide is the optimal treatment choice of active disease as well as prevention of disease in susceptible (eg, non- or incompletely immunized) exposed individuals.[1]

Koorosh Nemati, MD
Michael D. Cabana, MD, MPH
Department of Pediatrics
The Children's Hospital at Montefiore and the Albert Einstein College of Medicine
Bronx, New York

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APPENDIX

List of Additional Members of the CNN Site Investigators and Affiliations

Marc Beltempo, MD, (Associate Director, Canadian Neonatal Network and Site Investigator), Montreal Children's Hospital at McGill University Health Center, Montréal, Québec; Joseph Ting, MD, British Columbia Women's Hospital, Vancouver, British Columbia; Zenon Cieslak, MD, Royal Columbian Hospital, New Westminster, British Columbia; Rebecca Sherlock, MD, Surrey Memorial Hospital, Surrey, British Columbia; Ayman Abou Mehrem, MD, Foothills Medical Center, Calgary, Alberta; Jennifer Toye, MD, and Khalid Aziz, MBBS, Royal Alexandra Hospital, Edmonton, Alberta; Carlos Fajardo, MD, Alberta Children's Hospital, Calgary, Alberta; Jaya Bodani, MD, Regina General Hospital, Regina, Saskatchewan; Lannae Strueby, MD, Royal University Hospital, Saskatoon, Saskatchewan; Mary Seshia, MBChB, and Deepak Louis, MD, Winnipeg Health Sciences Center, Winnipeg, Manitoba; Ruben Alvaro, MD, St. Boniface General Hospital, Winnipeg, Manitoba; Amit Mukerji, MD, Hamilton Health Sciences Center, Hamilton, Ontario; Orlando Da Silva, MD, MSc, London Health Sciences Center, London, Ontario; Eugene Ng, MD, Sunnybrook Health Sciences Center, Toronto, Ontario; Brigitte Lemyre, MD, The Ottawa Hospital, Ottawa, Ontario; Thierry Daboval, MD, Children's Hospital of Eastern Ontario, Ottawa, Ontario; Faiza Khurshid, MD, Kingston General Hospital, Kingston, Ontario; Ermelinda Pelausa, MD, Jewish General Hospital, Montréal, Québec; Keith Barrington, MBChB, Anie Lapoint, MD, and Guillaume Ethier, NNP, Hôpital Sainte-Justine, Montréal, Québec; Christine Drolet, MD, and Bruno Piedboeuf, MD, Center Hospitalier Universitaire de Québec, Sainte Foy, Québec; Martine Claveau, MSc, LLM, NNP, Montreal Children's Hospital at McGill University Health Center, Montréal, Québec; Marie St-Hilaire, MD, Hôpital Maisonneuve-Rosemont, Montréal, Québec; Valerie Bertelle, MD, and Edith Masse, MD, Center Hospitalier Universitaire de Sherbrooke, Sherbrooke, Québec; Roderick Canning, MD, Moncton Hospital, Moncton, New Brunswick; Hala Makary, MD, Dr. Everett Chalmers Hospital, Fredericton, New Brunswick; Cecil Ojah, MBBS, and Luis Monterrosa, MD, Saint John Regional Hospital, Saint John, New Brunswick; Julie Emberley, MD, Janeway Children's Health and Rehabilitation Center, St. John's, Newfoundland; Jehier Afifi, MB BCh, MSc, IWK Health Center, Halifax, Nova Scotia; Andrzej Kajetanowicz, MD, Cape Breton Regional Hospital, Sydney, Nova Scotia.

Canadian Preterm Birth Network Site Investigators and Affiliations

Wendy Whittle, MD, Mount Sinai Hospital, Toronto, Ontario; Michelle Morais, MD, Hamilton Health Sciences Center, Hamilton, Ontario; Leanne Dahlgren, MD, Children's and Women's Health Center of BC, Vancouver, British Columbia; Darine El-Chaar, MD, Children's Hospital of Eastern Ontario, Ottawa, Ontario; Katherine Theriault, MD, Center Hospitalier Universitaire de Quebec, Sainte Foy, Québec; Annie Ouellet, MD, Center Hospitalier Universitaire de Sherbrooke, Sherbrooke, Québec; Kimberly Butt, MD, Dr. Everett Chalmers Hospital, Fredericton, New Brunswick; Stephen Wood, MD, Foothills Medical Center, Calgary, Alberta; Amy Metcalfe, PhD, Foothills Medical Center, University of Calgary, Calgary, Alberta; Candace O'Quinn, MD, Foothills Medical Center, University of Calgary, Calgary, Alberta; Christy Pylypjuk, MD, Health Sciences Center, Winnipeg, Manitoba; Isabelle Boucoiran, MSc, MD, Hôpital Sainte-Justine, Montréal, Québec; Catherine Taillefer, MD, Hôpital Sainte-Justine, Montréal, Québec; Joan Crane, MD, Janeway Children's Health and Rehabilitation Center, St. John's, Newfoundland; Haim Abenhaim, MD, Jewish General Hospital, Montréal, Québec; Graeme Smith, MD, Kingston General Hospital, Kingston, Ontario; Karen Wou, MDCM, McGill University Health Center, Montréal, Québec; Sue Chandra, MD, Royal Alexandra Hospital/Stollery Children's Hospital, Edmonton, Alberta; Jagdeep Ubhi, MD, Royal Columbian Hospital, New Westminster, British Columbia; George Carson, MD, Regina General Hospital, Regina, Saskatchewan; Michael Helewa, MD, St. Boniface General Hospital, Winnipeg, Manitoba; Ariadna Grigoriu, MD, The Moncton Hospital, Moncton, New Brunswick; Rob Gratton, MD, McGill University Health Center, Montréal, Québec; James Andrews, MD, Saint John Regional Hospital, St. John, New Brunswick; Nir Melamed, MD, Sunnybrook Health Sciences Center, Toronto, Ontario; Jason Burrows, MD, Surrey Memorial Hospital, Surrey, British Columbia; Fatima Taboun, MD, Windsor Regional Hospital, Windsor, Ontario; Lara Wesson, MD, Royal University Hospital, Saskatoon, Saskatchewan; Erin MacLellan, MD, Cape Breton Regional Hospital, Mira Road, Nova Scotia; Hayley Boss, MD, Victoria General Hospital, Victoria, British Columbia; Vicky Allen, MD, IWK Health Center, Halifax, Nova Scotia.