www.jpeds.com • THE JOURNAL OF PEDIATRICS

Effect of Prophylaxis for Early Adrenal Insufficiency Using Low-Dose Hydrocortisone in Very Preterm Infants: An Individual Patient Data Meta-Analysis

Michele L. Shaffer, PhD[1], Olivier Baud, MD, PhD[2,3,4], Thierry Lacaze-Masmonteil, MD, PhD[5,6], Outi M. Peltoniemi, MD, PhD[7,8], Francesco Bonsante, MD[9], and Kristi L. Watterberg, MD[10]

Objective To assess the effect of prophylaxis for early adrenal insufficiency using low-dose hydrocortisone on survival without bronchopulmonary dysplasia (BPD) in very preterm infants using an individual patient data meta-analysis.

Study design All existing randomized controlled trials testing the efficacy of the prophylaxis of early adrenal insufficiency using low-dose hydrocortisone on survival without BPD were considered for inclusion when data were available. The primary outcome was the binary variable survival without BPD at 36 weeks of postmenstrual age.

Results Among 5 eligible studies, 4 randomized controlled trials had individual patient data available (96% of participants identified; n = 982). Early low-dose hydrocortisone treatment for 10-15 days was associated with a significant increase in survival without BPD (OR, 1.45; 95% CI, 1.11-1.90; $P = .007$; $I^2 = 0\%$), as well as with decreases in medical treatment for patent ductus arteriosus (OR, 0.72; 95% CI, 0.56-0.93; $P = .01$; $I^2 = 0\%$) and death before discharge (OR, 0.70; 95% CI, 0.51-0.97; $P = .03$; $I^2 = 0\%$). The therapy was associated with an increased risk of spontaneous gastrointestinal perforation (OR, 2.50; 95% CI, 1.33-4.69; $P = .004$; $I^2 = 31.9\%$) when hydrocortisone was given in association with indomethacin exposure. The incidence of late-onset sepsis was increased in infants exposed to hydrocortisone (OR, 1.34; 95% CI, 1.02-1.75; $P = .04$; $I^2 = 0\%$), but no adverse effects were reported for either death or 2-year neurodevelopmental outcomes as assessed in an aggregate meta-analysis.

Conclusions This individual patient data meta-analysis showed that early low-dose hydrocortisone therapy is beneficial for survival without BPD in very preterm infants. *(J Pediatr 2019;207:136-42).*

See related article, p 265

Bronchopulmonary dysplasia (BPD) is a major morbidity of very preterm birth, associated with increased risk for broad array of adverse outcomes, including respiratory complications, growth failure, neurodevelopmental impairment (NDI), and death.[1] In contrast to many other morbidities of preterm infants, its incidence has not decreased over time and actually may be increasing.[2] Evidence of early lung inflammation in infants developing BPD[2-5] had led to early treatment with high doses of anti-inflammatory glucocorticoids such as dexamethasone, resulting in short-term improvement but unacceptable short-term and long-term adverse effects.[6] The use of lower doses and alternative formulations may improve the risk:benefit.[7] Jobe recently suggested that clinicians reconsider postnatal corticosteroid treatments together with continued efforts to minimize oxygen and ventilation injury in very preterm infants to decrease the incidence and severity of BPD.[8]

Data reported since 1995 have supported the hypothesis that very preterm infants who develop BPD often have relative adrenal insufficiency during the first postnatal week, suggesting that early hydrocortisone replacement could be beneficial.[4,9,10] Among 11 randomized controlled trials (RCTs) that included hydrocortisone treatment initiated before 7 postnatal days in very preterm infants,[7] 5 were designed specifically to test the efficacy of early prophylaxis of early adrenal insufficiency

BPD	Bronchopulmonary dysplasia
NDI	Neurodevelopmental impairment
PDA	Patent ductus arteriosus
PMA	Postmenstrual age
RCT	Randomized controlled trial

From the [1]Department of Statistics, University of Washington, Seattle, WA; [2]Division of Neonatology and Pediatric Intensive Care, Department of Pediatrics, University Hospitals Geneva, Geneva; [3]University of Geneva, Switzerland; [4]University Paris Diderot, Paris, France; [5]Department of Pediatrics, Cumming School of Medicine, University of Calgary; [6]Alberta Children's Hospital Research Institute, Calgary, Alberta, Canada; [7]PEDEGO Research Unit, Medical Research Center Oulu, University of Oulu; [8]Department of Pediatrics and Adolescence, Oulu University Hospital, Finland; [9]Réanimation Néonatale et Pédiatrique, Néonatologie, Centre d'Etudes Périnatales de l'Océan Indien (CEPOI, EA 7388), Centre Hospitalier Universitaire de la Réunion, Site Sud – Saint Pierre, France; and [10]Division of Neonatology, Department of Pediatrics, University of New Mexico School of Medicine, Albuquerque, NM

Supported by a research grant from the French Ministry of Health and funded by the Département de la Recherche Clinique et du Développement, Assistance Publique-Hôpitaux de Paris (AOM 06 025 and AOM 11 129). The sponsor had no role in the data analysis and reporting. The authors declare no conflicts of interest.

https://doi.org10.1016/j.jpeds.2018.10.004

to improve survival without BPD.[11-15] These trials extended hydrocortisone therapy beyond the first postnatal week and used a dose of 1-2 mg/kg/day, which has been shown to moderately but significantly increase serum cortisol concentrations in extremely preterm neonates compared with placebo.[12]

Although 2-year follow-up data have been consistently reassuring,[7,16-19] the effect of early hydrocortisone treatment on survival without BPD and potential side effects remain unclear. Therefore, we undertook an individual patient data meta-analysis of clinical trials to examine the effect of prophylaxis of early adrenal insufficiency on these outcomes.

Methods

The PRISMA-IPD checklist of items requested to report a meta-analysis of individual patient data is available at www.jpeds.com (**Supplement**). In addition, some data items are available in the statistical analysis plan (**Appendix**; available at www.jpeds.com). Two meta-analyses identified published RCTs of early hydrocortisone therapy conducted before 2017.[7,20] We also searched MEDLINE for the terms "hydrocortisone," "cortisone," "preterm infant," "randomized," and "human." The last search was done in July 2018. We did not identify any RCTs of early low-dose hydrocortisone therapy to prevent BPD other than those included in these 2 reports.

Individual Patient Data Acquisition, Data Processing, and Quality Assessment

The principal investigators of the 5 eligible trials agreed to share deidentified data to perform an individual patient data meta-analysis. Individual patient data from 1 pilot trial (n = 40) were no longer available[11]; this individual patient data meta-analysis includes all data from the remaining 4 studies (n = 982). Because an individual patient data meta-analysis can improve the ability to address confounders or covariates of interest, we were able to account for individual patient-level factors that affected outcomes, which would not have been possible with an aggregate meta-analysis based on published data without the risk of drawing potentially incorrect conclusions owing to ecological fallacy with the application of meta-regression. In addition, meta-regression often has low power to detect relationships.[21-23] Individual patient data also allowed for inclusion of data not previously reported and standardization of outcomes and exposures across studies. In addition, the cooperation of all authors of the original publications allowed for detailed data checking.

We created a common data dictionary and asked corresponding authors to identify which data elements were available, or to suggest alternative measures if data were not available. After receiving all authors' available data, we created a final data capture template to request the individual patient datasets from all authors to reduce the amount of postprocessing needed to harmonize the datasets. Any questions regarding the individual patient datasets were discussed with the authors and corrected.

The statistician created any necessary derived variables and checked the summary statistics against available published data. All data summaries by study and treatment group were shared with the corresponding authors to check for discrepancies, and any identified errors were corrected.

Outcomes and Subgroups of Interest

The primary outcome of interest was the binary variable survival without BPD at 36 weeks postmenstrual age (PMA), and the primary predictor was receipt of early low-dose hydrocortisone treatment. Adjustment variables to be included in all models were birth weight, sex, gestational age, and antenatal steroid use. Predefined subgroups of interest included sex, histologic chorioamnionitis, gestational age strata (<26 or ≥26 weeks), and indomethacin treatment.

Secondary outcomes included days of ventilation, continuous positive airway pressure, and oxygen; supplemental oxygen at discharge; and medical or surgical treatment for patent ductus arteriosus (PDA). Prespecified potential adverse outcomes included pneumothorax, spontaneous gastrointestinal perforation, necrotizing enterocolitis, severe intraventricular hemorrhage, cystic periventricular leukomalacia, severe retinopathy of prematurity, late onset sepsis (bacterial or fungal), and the effects of hydrocortisone on weight or head circumference at 36 weeks PMA and on the 2-year neurodevelopmental outcomes.

Statistical Analyses

An a priori statistical analysis plan (**Appendix**) was created to describe and prioritize the outcomes and analyses of interest, including subgroup and sensitivity analyses, before the analysis was begun. No multiple comparisons adjustments were used for subgroup analyses. We used a 1-step approach to individual patient data meta-analysis using generalizations of logistic regression models for binary outcomes and linear regression models for quantitative outcomes based on generalized linear mixed models with Kenward-Roger approximation of degrees of freedom.[24,25] Logistic regression models were summarized using ORs and associated 95% CIs. Linear regression models were summarized using mean differences and associated CIs. We attempted to account for clustering of patients within different studies by specifying a random intercept term, assuming that the baseline is drawn at random from a normal distribution. We first considered treatment a random effect, but then simplified the models to fixed treatment effects, which yielded similar findings in terms of magnitude, direction, and significance. Statistical heterogeneity was summarized as I^2 value and associated P value. I^2 values were computed using the meta package in R (R Foundation for Statistical Computing, Vienna, Austria). We also conducted a traditional aggregate random-effects meta-analysis based on available published data for comparison of long-term developmental outcomes.[16-18]

Statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, North Carolina) for the individual patient data analysis and using Stata 12.0 (StataCorp, College Station, Texas) for the aggregate meta-analysis. Findings were considered significant at P <.05.

Results

Among 11 RCTs testing hydrocortisone early after birth in neonates (**Table I**; available at www.jpeds.com), 5 were specifically designed to test the efficacy of prophylaxis of early adrenal insufficiency to improve survival without BPD.[11-15] The other 6 trials were excluded because of significant differences in study design, such as larger study group and use of hydrocortisone at higher doses[26] or for a different purpose, including refractory hemodynamic failure,[27-30] or in combination with another treatment.[26,31] The PRISMA-IPD flow diagram is depicted in the **Figure** (available at www.jpeds.com).

Although this individual patient data meta-analysis was not prospectively planned, the studies were quite similar in hypothesis, design, and primary outcome. As shown in **Table II**, patient eligibility varied slightly across the studies, as did the dose and duration of hydrocortisone therapy; however, these differences were minor and the populations were generally comparable. **Table III** presents summary statistics by study and treatment group for all patient characteristics and primary and secondary outcomes of interest.

Primary Outcome

Table IV presents the results of the individual patient data meta-analysis for the primary outcome and its components. **Table V** (available at www.jpeds.com) provides heterogeneity estimates of individual patient data meta-analysis of all outcomes unadjusted. Heterogeneity was low in most of the outcomes, with the exception of a few respiratory support items for which not all trials had data available.

Treatment with early low-dose hydrocortisone was associated with greater odds of survival without BPD at 36 weeks PMA (unadjusted OR, 1.37; 95% CI, 1.07-1.76). Findings were similar after adjustment for sex, gestational age, and antenatal steroid use (aOR, 1.45; 95% CI, 1.11-1.90; $I^2 = 0\%$). For the components of the primary outcome, receipt of hydrocortisone was associated with significantly lower odds of BPD (aOR, 0.73; 95% CI, 0.54-0.98; $I^2 = 0\%$), but not with a significant decrease in death before 36 weeks PMA (aOR, 0.76; 95% CI, 0.54-1.07; $I^2 = 0\%$). However, hydrocortisone treatment was associated with a significant decrease in death before discharge (aOR, 0.70; 95% CI, 0.51-0.97; $I^2 = 0\%$).

Secondary Outcomes

Table IV also presents the results of the individual patient data meta-analysis for all secondary outcomes. Days of ventilation, continuous positive airway pressure, and oxygen were not significantly different between the hydrocortisone and placebo groups, and BPD severity was similar in the 2 groups. There was no significant difference in exposure to oxygen at discharge. There were significantly lower odds of any medical treatment for PDA (aOR, 0.72; 95% CI, 0.56-0.93; $I^2 = 0\%$), including both indomethacin and ibuprofen; however, there was no difference in the odds of ligation.

Exposure to hydrocortisone was associated with a significant increase in spontaneous gastrointestinal perforation (aOR, 2.50; 95% CI, 1.33-4.69; $I^2 = 31.9\%$). However, in the absence of indomethacin cotreatment, hydrocortisone was not associated with a significant increase in gastrointestinal perforation (**Table VI**). Exposure to hydrocortisone also was associated with significantly increased odds of late sepsis, both bacterial and fungal (aOR, 1.34; 95% CI, 1.02-1.75; $I^2 = 0\%$). This observed difference was not associated with increased mortality or other in-hospital adverse outcomes, or with any detectable adverse effect on 2-year neurodevelopmental outcomes in the hydrocortisone-treated group. There were no significant differences between the hydrocortisone and placebo groups for any of the remaining adverse outcomes (**Table IV**) of

Table II. Characteristics of 4 included studies providing individual patient data

	Sources			
Characteristics	**Watterberg et al, 2004[12]**	**Peltoniemi et al, 2005[13]**	**Bonsante et al, 2007[14]**	**Baud et al, 2016[15]**
Country	US	Finland	Italy	France
Funding source	National Institute of Child Health and Human Development	Foundation for Pediatric Research	University of Bari	Public Hospitals of Paris
Ethics Committee review	Yes	Yes	Yes	Yes
Parental informed consent	Yes	Yes	Yes	Yes
Loss to follow-up for primary outcome, n/N (%)	3/360 (<1)	None	None	2/523 (<1)
Design	Double-blind RCT	Double-blind RCT	Double-blind RCT	Double-blind RCT
Inclusion criteria				
Gestational age, wk		$23^{0/7}$-$29^{6/7}$	$24^{0/7}$-$29^{6/7}$	$24^{0/7}$-$27^{6/7}$
Birth weight, g	500-999 g	501-1250	500-1249	
Respiratory status	Need for mechanical ventilation at study entry	Need for mechanical ventilation before 24 h of life*	Need for mechanical ventilation after rescue surfactant	
Enrolled	Between 12 and 48 h postnatal age	Before 36 h	Before 48 h	Before 24 h
Duration of exposure	1 mg/kg/d for 12 d, then 0.5 mg/kg/d for 3 d	10 d tapered from 2.0 to 0.75 mg/kg/d	1 mg/kg/d divided into 2 doses/d for 9 d, then 0.5 mg/kg/d for 3 d	1 mg/kg/d divided into 2 doses/d for 7 d, then 0.5 mg/kg/d for 3 d

If an empty cell appears under inclusion criteria, the study did not have this criterion specified.
*A subgroup of infants with birth weight of 1000-1250 g had the additional requirement of supplemental oxygen and mechanical ventilation beyond 24 h despite surfactant therapy.

Table III. Patient characteristics and outcomes of 4 included studies providing individual patient data

Source	Watterberg et al, 2004[12]		Peltoniemi et al, 2005[13]		Bonsante et al, 2007[14]		Baud et al, 2016[15]	
Characteristic	Hydrocortisone (n = 180)	Placebo (n = 180)	Hydrocortisone (n = 25)	Placebo (n = 26)	Hydrcortisone (n = 25)	Placebo (n = 25)	Hydrocortisone (n = 255)	Placebo (n = 266)
Birth weight, g, mean (SD)	730 (126)	734 (126)	888 (204)	903 (220)	840 (200)	869 (189)	867 (151)	862 (160)
Gestational age, wk, mean (SD)	25.2 (1.5)	25.3 (1.7)	26.7 (1.6)	26.9 (1.5)	26.2 (1.5)	26.3 (1.9)	26.4 (0.9)	26.4 (0.9)
Female sex, n (%)	84 (46.7)	90 (50.0)	9 (36.0)	12 (46.2)	12 (48.0)	9 (36.0)	124 (48.6)	117 (44.0)
Race, n (%)								
White	108 (60.0)	93 (51.7)	25 (100)	26 (100)	25 (100)	25 (100)	105/247 (42.5)	112/259 (43.2)
Black	65 (36.1)	70 (38.9)	0	0	0	0	101/247 (40.9)	96/259 (37.1)
Asian	3 (1.7)	12 (6.7)	0	0	0	0	8/247 (3.2)	12/259 (4.6)
Other	3 (1.7)	4 (2.2)	0	0	0	0	31/247 (12.6)	36/259 (13.9)
Unknown	1 (0.6)	1 (0.6)	0	0	0	0	2/247 (0.8)	3/259 (1.2)
Antenatal steroid use, n (%)	138 (76.7)	146 (81.1)	23 (92.0)	25 (96.2)	17 (68.0)	20 (80.0)	238 (93.3)	246 (92.8)
Rupture of membranes >24 h, n (%)	42/168 (25.0)	47/172 (27.3)	5 (20.0)	5 (19.2)			76 (29.8)	83 (31.2)
Vaginal delivery, n (%)	77 (42.8)	63 (35.0)	14 (56.0)	13 (50.0)	4 (16.0)	4 (16.0)	132/254 (52.0)	143/264 (54.2)
Histologic chorioamnionitis, n (%)	73/140 (52.1)	78/146 (53.4)	7/15 (46.7)	7/14 (50.0)	9 (36.0)	13 (52.0)	62/218 (28.4)	72/240 (30.0)
Preeclampsia, n (%)	24 (13.3)	30 (16.7)	4 (16.0)	6 (23.1)	8 (32.0)	4 (16.0)	34 (13.3)	23 (8.7)
Multiple birth, n (%)	42 (23.3)	38 (21.1)	5 (20.0)	7 (26.9)	4 (16.0)	5 (20.0)	82 (32.2)	90 (33.8)
Inborn, n (%)	152 (84.4)	165 (91.7)	25 (100)	26 (100)	25 (100)	25 (100)	255 (100)	266 (100)
Intubated at entry, n (%)	180 (100)	180 (100)	25 (100)	26 (100)	25 (100)	25 (100)	204 (80.0)	218 (82.0)
Age at entry, h, mean (SD)	31.4 (11.2)	33.1 (12.1); n = 178	27.2 (13.5); n = 24	21.5 (9.6)	13.5 (8.9)	13.3 (12.1)	15.2 (11.6); n = 253	14.4 (11.8); n = 265
Inotropic therapy at entry, n (%)	72 (40.0)	62 (34.4)	17 (68.0)	16 (61.5)	16 (84.0)	21 (84.0)	75 (29.4)	95 (35.7)
Outcomes at 36 wk PMA, n (%)								
Survival without BPD	73/179 (40.8)	67/178 (37.6)	16 (64.0)	14 (53.9)	16 (64.0)	8 (32.0)	153 (60.0)	136 (51.1)
Death	27/179 (15.1)	28/178 (15.7)	2 (8.0)	1 (3.9)	3 (12.0)	9 (36.0)	47 (18.4)	60 (22.6)
BPD	79/152 (52.0)	83/150 (55.3)	7/23 (30.4)	11/25 (44.0)	6/22 (27.3)	8/16 (50.0)	55/208 (26.4)	70/206 (34.0)
Weight, mean (SD)	2.01 (0.32); n = 150	2.03 (0.35); n = 147	2.00 (0.30); n = 22	1.95 (0.30); n = 24	1.74 (0.28); n = 21	1.81 (0.38); n = 14	2.09 (0.33); n = 197	2.11 (0.32); n = 194
Head circumference, cm, mean (SD)	31.2 (1.5); n = 147	30.9 (1.6); n = 145	31.8 (1.3); n = 22	31.2 (1.5); n = 23	30.7 (2.1); n = 17	30.7 (2.0); n = 14	30.8 (1.6); n = 160	30.8 (1.5); n = 155
Respiratory support								
Days of ventilation, median (IQR)	26 (9-50); n = 178	30 (13-46); n = 176	4 (2-17)	13 (3-40)	4 (2-21); n = 23	15 (2-27); n = 19		
Days of CPAP, median (IQR)			16 (2-28); n = 22	25 (17-32); n = 24	15 (5-27)	9 (0-20)		
Days of oxygen, median (IQR)	73 (40-102); n = 178	71 (32-95); n = 176	55 (35-91)	93 (41-162)	58 (26-72); n = 23	50 (28-76); n = 19		
Oxygen at discharge, n/N (%)	56/150 (37.3)	58/146 (39.7)	0/23	1/23 (4.4)	0/21	0/15	17/207 (8.2)	16/202 (7.9)
Open-label steroid use, n (%)	72 (40.0)	76 (42.2)	11 (44.0)	15 (57.7)	7 (28.0)	12 (48.0)	105 (41.2)	108 (40.6)
Pneumothorax, n (%)	23 (12.8)	18 (10.0)	1 (4.0)	3 (11.5)	2 (8.0)	4 (16.0)	5 (2.0)	7 (2.6)
Insulin treatment, n (%)	74 (41.1)	62 (34.4)	9 (36.0)	7 (26.9)	9 (36.0)	10 (40.0)	112 (43.9)	115 (43.2)
Treatment for PDA, n (%)								
Medical treatment (indomethacin or ibuprofen)	69 (38.3)	73 (40.6)	9 (36.0)	17 (65.4)	5 (20.0)	9 (36.0)	119 (46.7)	147 (55.3)
Any prophylactic indomethacin	127 (70.6)	123 (68.3)	4 (16.0)	8 (30.8)	0	0	0	0
Surgical ligation	26 (14.4)	21 (11.7)	5 (20.0)	7 (26.9)	0	0	37 (14.5)	55 (20.7)
Necrotizing enterocolitis, n (%)	7 (3.9)	14 (7.8)	2 (8.0)	1 (3.9)	1 (4.0)	2 (8.0)	17 (6.7)	12 (4.5)
Spontaneous gastrointestinal perforation, n/N (%)	17/178 (9.6)	4/180 (2.2)	4 (16.0)	0	1 (4.0)	0	13 (5.1)	11/(4.1)
Late-onset sepsis (bacterial/fungal), n (%)	80 (44.4)	73 (40.6)	8 (32.0)	4 (15.4)	8 (32.0)	5 (20.0)	80 (31.4)	66 (24.8)
Severe IVH (grade 3-4), n/N (%)	33/172 (19.2)	29/176 (16.5)	4 (16.0)	3 (11.5)	1 (4.0)	2 (8.0)	38 (14.9)	37 (13.9)
Cystic PVL, n/N (%)	12/142 (8.5)	10/142 (7.0)	5 (20.0)	3 (11.5)	1 (4.0)	2 (8.0)	4 (1.6)	10 (3.8)
Severe ROP, n/N (%)	41/153 (26.8)	47/150 (31.3)	1 (4.0)	1 (3.9)	4 (16.0)	4 (16.0)	4 (1.6)	2 (0.8)
Death before discharge, n (%)	31 (17.2)	32 (17.8)	2 (8.0)	3 (11.5)	4 (16.0)	10 (40.0)	48 (18.8)	67 (25.2)

CPAP, continuous positive airway pressure; *IVH*, intraventricular hemorrhage; *PVL*, periventricular leukomalacia; *ROP*, retinopathy of prematurity.
For any cell with missing data, the denominator is provided within the cell. An empty cell indicates that not of the data were not available.

Table IV. Results of individual patient data meta-analysis of all outcomes adjusted for sex, gestational age, and any antenatal steroids

Outcomes	Hydrocortisone	Placebo	OR or Mean Difference	95% CI of OR or Mean Difference	*P* Value
Survival without BPD at 36 wk PMA, n/N (%)	258/484 (53.3)	225/495 (45.5)	1.45	1.11-1.90	.007
Death before 36 wk PMA, n/N (%)	79/484 (16.3)	98/495 (19.8)	0.76	0.54-1.07	.12
BPD at 36 wk PMA, n/N (%)	147/405 (36.3)	172/397 (43.3)	0.73	0.54-0.98	.038
Death before discharge, n/N (%)	85/485 (17.5)	112/497 (22.5)	0.70	0.51-0.97	.0327
Weight at 36 wk PMA, g, mean	2036 (n = 390)	2061 (n = 379)	−24.11	−71.36 to 23.14	.32
Head circumference at 36 wk, cm, mean	31.0 (n = 346)	30.9 (n = 337)	0.19	−0.05 to 0.42	.12
Respiratory support					
Days of ventilation, mean	32.3 (n = 226)	31.7 (n = 221)	−0.63	−7.28 to 6.01	.85
Days of CPAP, mean	17.2 (n = 47)	17.7 (n = 49)	−0.12	−5.78 to 5.55	.97
Days of oxygen, mean	74.1 (n = 226)	75.2 (n = 221)	−2.17	−12.07 to 7.73	.67
Oxygen at discharge, n/N (%)	73/401 (18.2)	75/386 (19.4)	0.92	0.64-1.33	.65
Open-label steroid use, n/N (%)	195/485 (40.2)	211/497 (42.5)	0.90	0.70-1.17	.44
Pneumothorax, n/N (%)	31/485 (6.39)	32/497 (6.44)	0.98	0.58-1.64	.93
Insulin treatment, n/N (%)	204/485 (42.1)	194/497 (39.0)	1.12	0.86-1.45	.42
Medical treatment for PDA (indomethacin or ibuprofen), n/N (%)	202/485 (41.7)	246/497 (49.5)	0.72	0.56-0.93	.012
Any prophylactic indomethacin, n/N (%)	61/485 (12.6)	63/497 (12.7)	0.96	0.65-1.41	.83
Surgical ligation, n/N (%)	68/485 (14.0)	83/497 (16.7)	0.80	0.56-1.14	.21
Necrotizing enterocolitis, n/N (%)	27/485 (5.57)	29/497 (5.84)	0.95	0.55-1.63	.85
Spontaneous gastrointestinal perforation	35/483 (7.25)	15/497 (3.02)	2.50	1.33-4.69	.004
Late-onset sepsis (bacterial/fungal), n/N (%)	176/485 (36.3)	148/497 (29.8)	1.34	1.02-1.75	.0357
Severe IVH (grade 3-4), n/N (%)	76/477 (15.9)	71/493 (14.4)	1.10	0.76-1.59	.60
Cystic PVL, n/N (%)	22/447 (4.92)	25/459 (5.45)	0.89	0.49-1.60	.69
Severe ROP, n/N (%)	50/458 (10.9)	54/467 (11.6)	0.92	0.59-1.45	.72

pneumothorax, necrotizing enterocolitis, severe intraventricular hemorrhage, cystic periventricular leukomalacia, and severe retinopathy of prematurity. There also were no significant differences in weight or head circumference at 36 weeks PMA between the 2 groups.

Table VI. Subgroup analyses of primary outcome and other selected outcomes adjusted for sex, gestational age, and any antenatal steroids unless the adjustment factor is used to define the subgroup

Outcomes	OR	95% CI	*P* value
Survival to 36 wk without BPD			
Male	1.40	0.97-2.02	.074
Female	1.52	1.02-2.26	.038
Gestational age <26 wk	1.38	0.91-2.09	.13
Gestational age ≥26 wk	1.52	1.07-2.17	.020
No chorioamnionitis	1.40	0.97-2.02	.074
Chorioamnionitis	2.01	1.19-3.39	.009
Death before discharge			
Male	0.73	0.47-1.14	.17
Female	0.66	0.41-1.07	.094
Gestational age <26 wk	0.87	0.58-1.32	.53
Gestational age ≥26 wk	0.46	0.26-0.82	.008
No chorioamnionitis	0.71	0.44-1.15	.16
Chorioamnionitis	0.43	0.23-0.82	.010
Late-onset sepsis			
Male	1.41	0.96-2.05	.076
Female	1.23	0.83-1.83	.29
Gestational age <26 wk	1.60	1.08-2.37	.019
Gestational age ≥26 wk	1.14	0.78-1.65	.50
No chorioamnionitis	1.06	0.72-1.55	.77
Chorioamnionitis	1.91	1.18-3.08	.009
Spontaneous gastrointestinal perforation			
No indomethacin	1.52	0.73-3.15	.26
Indomethacin	9.37	2.02-43.49	.004

Planned Subgroup Analyses

Table VI summarizes the effect of treatment group on the primary study outcome as well as on late-onset sepsis and mortality before discharge, by subgroup of interest (sex, gestational age, histologic chorioamnionitis, and indomethacin exposure) adjusted for sex, gestational age, and any antenatal steroids unless the adjustment factor is used to define the subgroup of interest. Although individual odds ratios vary somewhat among subgroups, the effect is generally consistent for improvement in survival without BPD at 36 weeks PMA. Of particular interest is that the effect was similar for boys and girls. The outcomes for the subgroup chorioamnionitis showed that the incidence of late-onset sepsis was significantly increased (OR, 1.91; 95% CI, 1.18-3.08), but at the same time the incidence of survival without BPD was increased (OR, 2.01; 95% CI, 1.19-3.39) and mortality before discharge was decreased (OR, 0.43; 95% CI, 0.23-0.82).

The results of the individual patient data meta-analysis were compared with aggregate meta-analysis based on the published data of the four studies included. For the aggregate meta-analysis of the four studies, there was no significant difference in the odds of survival without BPD at 36 weeks PMA (OR, 1.40; 95% CI, 0.98-2.00).

Long-Term Outcomes

Because of differences in assessment tools used (the Griffiths Developmental Scale, Bayley Scale of Infant Development, and revised Brunet-Lezine Scale), only cerebral palsy (CP) and NDI were compared in 709 of 785 (90%) and 706 of 785 (90%) children at age 2 years, respectively, using aggregate meta-analysis. These analyses were performed based on the available data collected from the 4 RCTs included in the individual patient data meta-analysis (**Table VII**; available at www.jpeds.com).[16-18] Hydrocortisone therapy did not show a significant benefit; however, the direction of effect consistently favored the hydrocortisone-treated group for NDI (OR, 0.76; 95% CI, 0.52-1.12). For CP, individual study results were mixed in direction, but overall there was no significant relationship between hydrocortisone exposure and CP (OR, 0.95; 95% CI, 0.56-1.60).

Discussion

In this study, an individual patient data meta-analysis of 4 published RCTs showed that early low-dose hydrocortisone treatment in very preterm infants was associated with significantly increased survival without BPD, as well as a decreased need for PDA treatment and reduced mortality before discharge. The fifth published study of this therapy, a 40-patient pilot RCT for which data were no longer available, also showed a benefit; therefore, its omission does not affect the conclusions of our analysis.[11]

Other findings of note include a significant decrease in the incidence of treatment for PDA in infants treated with hydrocortisone. We have previously reported significantly lower cortisol concentrations in infants diagnosed with PDA, as well as in infants who subsequently develop BPD,[4,9,32] suggesting that adrenal insufficiency may be a contributing factor to the well-known association of PDA with BPD.[33] In addition, in the absence of indomethacin exposure, hydrocortisone therapy did not have an effect on the incidence of spontaneous gastrointestinal perforation. Studies in which ibuprofen was used as treatment for PDA also reported no effect of hydrocortisone therapy on perforation.[14,15,17]

Our analysis confirms an association between early low-dose hydrocortisone exposure and late-onset sepsis; nonetheless, treatment was associated with a significantly improved survival without BPD at 36 weeks PMA and survival to discharge, with no adverse effects on neurodevelopmental outcomes at 2 years.[16-19] Follow-up of a small number of children (n = 27) at age 5-7 years suggested a correlation between early hydrocortisone treatment and later neurocognitive impairment[34]; however, the 2-year outcomes of 694 children enrolled in all these studies showed no adverse neurodevelopmental effects and identified possible benefits. Longer-term follow-up of previous cohort studies also have been reassuring.[35] Children in the PREMILOC study will be assessed at age 5-7 years.[18]

Planned subgroup analyses showed that hydrocortisone appears to be similarly efficacious for both boys and girls. The direction of effect was beneficial in both gestational age strata; however, effects were more pronounced in the infants born at ≥26 weeks of gestation, consistent with the increased fragility and resistance to therapies of the most immature infants.[2] In the presence of chorioamnionitis, the incidence of late-onset sepsis was increased with hydrocortisone therapy, but a benefit was still seen in the primary outcome and in survival to discharge. Chorioamnionitis is a risk factor for late-onset sepsis[36]; treatment with hydrocortisone may affect the immune response, yet reduce inflammatory injury and thereby improve outcomes in exposed infants, because systemic inflammation has been shown to precede clinical symptoms of the early phase of BPD.[5] As always, subgroup analyses, even when preplanned, should be interpreted with caution.

Only 5 trials, including the 4 included in this analysis and that reported by Watterberg et al in 1999,[11] were specifically designed to assess the effect of early low-dose hydrocortisone as prophylaxis of early adrenal insufficiency in very preterm infants. Four other RCTs tested the effect of early hydrocortisone in hypotensive preterm infants,[27-30] including 1 trial testing hydrocortisone in association with dopamine[30] and 1 trial investigating the effect of early triiodothyronine therapy on mortality and respiratory morbidity that included low-dose hydrocortisone as an adjunct therapy.[31] Those studies found no significant benefit in survival without BPD at 36 weeks; however, the shorter treatment periods in those studies might have affected their results. We have reported lower cortisol concentrations and a decreased response to ACTH stimulation continuing beyond the first postnatal week in infants who subsequently developed BPD.[9,32,37]

Strengths of this study include access to individual patient data for 982 patients, harmonization of data and outcome definitions across studies, and very close comparability of the study populations and the therapeutic intervention. Our results differ from those of an aggregate meta-analysis of the 4 studies showing no difference in the odds of survival without BPD at 36 weeks PMA, demonstrating that an individual patient data meta-analysis can improve the ability to address important confounders at the individual patient level.

Limitations of the study include the loss of 40 patients in the original pilot study[11] and loss of accuracy regarding the time of first dose. In addition, exposure to indomethacin as a confounding variable was not balanced across all studies.

In conclusion, this individual patient data meta-analysis shows that early, low-dose hydrocortisone therapy provides significant benefits in survival without BPD, PDA closure, and survival to discharge in very preterm infants. Increases in intestinal perforation and late-onset sepsis, 2 reported adverse effects of this hydrocortisone treatment, did not appear to negate the overall benefits of hydrocortisone in this population. ■

Submitted for publication May 17, 2018; last revision received Oct 1, 2018; accepted Oct 3, 2018

Reprint requests: Olivier Baud, MD, PhD, Division of Neonatology, Department of Pediatrics, University Hospitals, Rue Willy-Donzé 6, 1205 Genève, Geneva, Switzerland. E-mail: olivier.baud@hcuge.ch

References

1. Jensen EA, Schmidt B. Epidemiology of bronchopulmonary dysplasia. Birth Defects Res A Clin Mol Teratol 2014;100:145-57.
2. Stoll BJ, Hansen NI, Bell EF, Walsh MC, Carlo WA, Shankaran S, et al. Trends in care practices, morbidity, and mortality of extremely preterm neonates, 1993-2012. JAMA 2015;314:1039-51.
3. Balany J, Bhandari V. Understanding the impact of infection, inflammation, and their persistence in the pathogenesis of bronchopulmonary dysplasia. Front Med (Lausanne) 2015;2:90.

4. Watterberg KL, Scott SM, Backstrom C, Gifford KL, Cook KL. Links between early adrenal function and respiratory outcome in preterm infants: airway inflammation and patent ductus arteriosus. Pediatrics 2000;105:320-4.
5. Leroy S, Caumette E, Waddington C, Hébert A, Brant R, Lavoie PM. A time-based analysis of inflammation in infants at risk of bronchopulmonary dysplasia. J Pediatr 2018;192:60-5.e1.
6. Doyle LW, Ehrenkranz RA, Halliday HL. Early (<8 days) postnatal corticosteroids for preventing chronic lung disease in preterm infants. Cochrane Database Syst Rev 2014;5:CD001146.
7. Doyle LW, Cheong JL, Ehrenkranz RA, Halliday HL. Early (<8 days) systemic postnatal corticosteroids for prevention of bronchopulmonary dysplasia in preterm infants. Cochrane Database Syst Rev 2017;10:CD001146.
8. Jobe AH. Mechanisms of lung injury and bronchopulmonary dysplasia. Am J Perinatol 2016;33:1076-8.
9. Watterberg KL, Scott SM. Evidence of early adrenal insufficiency in babies who develop bronchopulmonary dysplasia. Pediatrics 1995;95:120-5.
10. Huysman MW, Hokken-Koelega AC, De Ridder MA, Sauer PJ. Adrenal function in sick very preterm infants. Pediatr Res 2000;48:629-33.
11. Watterberg KL, Gerdes JS, Gifford KL, Lin HM. Prophylaxis against early adrenal insufficiency to prevent chronic lung disease in premature infants. Pediatrics 1999;104:1258-63.
12. Watterberg KL, Gerdes JS, Cole CH, Aucott SW, Thilo EH, Mammel MC, et al. Prophylaxis of early adrenal insufficiency to prevent bronchopulmonary dysplasia: a multicenter trial. Pediatrics 2004;114:1649-57.
13. Peltoniemi O, Kari MA, Heinonen K, Saarela T, Nikolajev K, Andersson S, et al. Pretreatment cortisol values may predict responses to hydrocortisone administration for the prevention of bronchopulmonary dysplasia in high-risk infants. J Pediatr 2005;146:632-7.
14. Bonsante F, Latorre G, Iacobelli S, Forziati V, Laforgia N, Esposito L, et al. Early low-dose hydrocortisone in very preterm infants: a randomized, placebo-controlled trial. Neonatology 2007;91:217-21.
15. Baud O, Maury L, Lebail F, Ramful D, El Moussawi F, Nicaise C, et al. Effect of early low-dose hydrocortisone on survival without bronchopulmonary dysplasia in extremely preterm infants (PREMILOC): a double-blind, placebo-controlled, multicentre, randomised trial. Lancet 2016;387:1827-36.
16. Watterberg KL, Shaffer ML, Mishefske MJ, Leach CL, Mammel MC, Couser RJ, et al. Growth and neurodevelopmental outcomes after early low-dose hydrocortisone treatment in extremely low birth weight infants. Pediatrics 2007;120:40-8.
17. Peltoniemi OM, Lano A, Puosi R, Yliherva A, Bonsante F, Kari MA, et al. Trial of early neonatal hydrocortisone: two-year follow-up. Neonatology 2009;95:240-7.
18. Baud O, Trousson C, Biran V, Leroy E, Mohamed D, Alberti C. Association between early low-dose hydrocortisone therapy in extremely preterm neonates and neurodevelopmental outcomes at 2 years of age. JAMA 2017;317:1329-37.
19. Baud O, Trousson C, Biran V, Leroy E, Mohamed D, Alberti C. Two-year neurodevelopmental outcomes of extremely preterm infants treated with early hydrocortisone: treatment effect according to gestational age at birth. Arch Dis Child Fetal Neonatal Ed 2018. doi: 10.1136/archdischild-2017-313756. [Epub ahead of print].
20. Doyle LW, Ehrenkranz RA, Halliday HL. Postnatal hydrocortisone for preventing or treating bronchopulmonary dysplasia in preterm infants: a systematic review. Neonatology 2010;98:111-7.
21. Lambert PC, Sutton AJ, Abrams KR, Jones DR. A comparison of summary patient-level covariates in meta-regression with individual patient data meta-analysis. J Clin Epidemiol 2002;55:86-94.
22. Berlin JA, Santanna J, Schmid CH, Szczech LA, Feldman HI. Individual patient- versus group-level data meta-regressions for the investigation of treatment effect modifiers: ecological bias rears its ugly head. Stat Med 2002;21:371-87.
23. Higgins JP, Thompson SG. Controlling the risk of spurious findings from meta-regression. Stat Med 2004;23:1663-82.
24. Kenward MG, Roger JH. Small sample inference for fixed effects from restricted maximum likelihood. Biometrics 1997;53:983-97.
25. Fitzmaurice GM, Laird NM, Ware JH. Applied longitudinal analysis. 2nd ed. Hoboken (NJ): John Wiley & Sons; 2011.
26. Baden M, Bauer CR, Colle E, Klein G, Taeusch HW Jr, Stern L. A controlled trial of hydrocortisone therapy in infants with respiratory distress syndrome. Pediatrics 1972;50:526-34.
27. Efird MM, Heerens AT, Gordon PV, Bose CL, Young DA. A randomized-controlled trial of prophylactic hydrocortisone supplementation for the prevention of hypotension in extremely low birth weight infants. J Perinatol 2005;25:119-24.
28. Ng PC, Lee CH, Bnur FL, Chan IH, Lee AW, Wong E, et al. A double-blind, randomized, controlled study of a “stress dose” of hydrocortisone for rescue treatment of refractory hypotension in preterm infants. Pediatrics 2006;117:367-75.
29. Batton BJ, Li L, Newman NS, Das A, Watterberg KL, Yoder BA, et al. Feasibility study of early blood pressure management in extremely preterm infants. J Pediatr 2012;161:65-9.e1.
30. Hochwald O, Palegra G, Osiovich H. Adding hydrocortisone as first line of inotropic treatment for hypotension in very low birth weight infants. Indian J Pediatr 2014;81:808-10.
31. Biswas S, Buffery J, Enoch H, Bland M, Markiewicz M, Walters D. Pulmonary effects of triiodothyronine (T3) and hydrocortisone (HC) supplementation in preterm infants less than 30 weeks gestation: results of the THORN trial: Thyroid Hormone Replacement in Neonates. Pediatr Res 2003;53:48-56.
32. Watterberg KL, Gerdes JS, Cook KL. Impaired glucocorticoid synthesis in premature infants developing chronic lung disease. Pediatr Res 2001;50:190-5.
33. 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.
34. Peltoniemi OM, Lano A, Yliherva A, Kari MA, Hallman M; Neonatal Hydrocortisone Working Group. Randomised trial of early neonatal hydrocortisone demonstrates potential undesired effects on neurodevelopment at preschool age. Acta Paediatr 2016;105:159-64.
35. Rademaker KJ, de Vries WB. Long-term effects of neonatal hydrocortisone treatment for chronic lung disease on the developing brain and heart. Semin Fetal Neonatal Med 2009;14:171-7.
36. Gowda H, Norton R, White A, Kandasamy Y. Late-onset neonatal sepsis: a 10-year review from North Queensland, Australia. Pediatr Infect Dis J 2017;36:883-8.
37. Watterberg KL, Shaffer ML, Garland JS, Thilo EH, Mammel MC, Couser RJ, et al. Effect of dose on response to adrenocorticotropin in extremely low birth weight infants. J Clin Endocrinol Metab 2005;90:6380-5.

Appendix

Brief Statistical Analysis Plan for Hydrocortisone Meta-Analysis

Overview. Five RCTs that tested low-dose hydrocortisone during the first postnatal days with the primary outcome of improving survival without BPD have been completed and published. Individual patient data are no longer available for the first trial of 40 patients. We will conduct an individual patient data meta-analysis of the remaining 4 trials. Although this individual patient data meta-analysis was not prospectively planned, the studies are quite similar in hypothesis, design, and primary outcome. Patient eligibility varies slightly across the studies, as do the dose and duration of hydrocortisone therapy; however, these differences are minor, and the populations generally overlap.

Data Analysis. Descriptive data will be presented for each study when available, and overall, including the variables shown in Appendix Table I. We will take a 1-step approach to individual patient data meta-analysis using generalizations of logistic regression models for binary outcomes and linear regression models for quantitative outcomes based on generalized linear mixed models with Kenward-Rogers approximation of degrees of freedom. We will account for clustering of patients within different studies by specifying a random intercept term, assuming that the baseline is drawn at random from a normal distribution. We will consider treatment a random effect and adjustment factors random effects. We will assume different residual variances for each study because patient eligibility varies slightly from study to study, as well as dose and duration of hydrocortisone therapy. Simplifications of modeling assumptions, such as fixed effects in place of random effects and a common residual variance, will be considered if models fail to converge.

The primary outcome of interest is the binary variable survival without BPD at 36 weeks, and the primary predictor is receipt of hydrocortisone treatment. Primary and secondary outcomes of interest are summarized in Appendix Table II. Adjustment variables included in all models are birth weight, sex, gestational age, antenatal steroids, and age at first dose.

Similar subgroup analyses will be conducted for the following groups: boys/girls, histologic chorioamnionitis, gestational age strata, and receipt of indomethacin.

References

1. Bonsante F, Latorre G, Iacobelli S, Forziati V, Laforgia N, Esposito L, et al. Early low-dose hydrocortisone in very preterm infants: a randomized, placebo-controlled trial. Neonatology 2007;91:217-21.
2. Peltoniemi O, Kari MA, Heinonen K, Saarela T, Nikolajev K, Andersson S, et al. Pretreatment cortisol values may predict responses to hydrocortisone administration for the prevention of bronchopulmonary dysplasia in high-risk infants. J Pediatr 2005;146:632-7.
3. Watterberg KL, Gerdes JS, Cole CH, Aucott SW, Thilo EH, Mammel MC, et al. Prophylaxis of early adrenal insufficiency to prevent bronchopulmonary dysplasia: a multicenter trial. Pediatrics 2004;114:1649-57.
4. Baud O, Maury L, Lebail F, Ramful D, El Moussawi F, Nicaise C, et al. Effect of early low-dose hydrocortisone on survival without bronchopulmonary dysplasia in extremely preterm infants (PREMILOC): a double-blind, placebo-controlled, multicentre, randomised trial. Lancet 2016;387:1827-36.

Appendix Table I. Descriptive variables to be summarized overall and by study

Variable	Availability				Scale
	Bonsante et al, 2007[1]	Peltoneimi et al, 2005[2]	Watterberg et al, 2004[3]	Baud et al, 2016[4]	
Birth weight	Y	Y	Y	Y	Quantitative (g)
Gestational age	Y	Y	Y	Y	Quantitative (wk)
Sex	Y	Y	Y	Y	Binary
Apgar 1-min score	Y	Y	Y	N	Quantitative
Apgar 5-min score	Y	Y	Y	Y	Quantitative
Race/ethnicity	Y	All white	Y	Y	Categorical: 1, white; 2, black; 3, Asian; 4, other; 9, unknown
Antenatal steroids	Y (any/full)	Y (any/full/partial)	Y (detailed)	Y	Binary (any vs none)
Rupture of membranes	N	>24 h Y/N	Y (h)	Y (>24 h)	Binary (>24 h Y/N)
Vaginal/Cesarean delivery	Y	Y	Y	Y	Binary
Chorioamnionitis	Y (histologic)	Y (histologic)/Y (clinical)	Y (histologic detailed, clinical)	Y (histologic/ clinical)	Binary (histologic Y/N); binary (clinical Y/N)
Preeclampsia	Y	Y	Y	Y	Binary
Multiple birth	Y (individual random)	Y (individual random)	Y (twin, random together)	Y (how random?)	Binary (Y/N)
Inborn/outborn	Y (all inborn)	Y (all inborn)	Y	Y (inborn)	Binary
Intubated at entry	Y (all)	Y (all)	Y (all)	Y (both)	Binary
Age at entry	Y (at first dose)	Y (at first dose)	Y (at first dose)	Y (at first dose)	Quantitative, h
CRIB score	Y	N	Y	N	Quantitative
Blood pressure					
Daily	N	Y	Y	Y	Daily systolic
Inotropic therapy at study entry	Y	Y	Y	Y	Binary (any Y/N)

CRIB, Clinical Risk Index for Babies.

Appendix Table II. Primary and secondary outcomes

	Availability				
Outcomes	Bonsante et al, 2007[1]	Peltoneimi et al, 2005[2]	Watterberg et al, 2004[3]	Baud et al, 2016[4]	Scale
Survival without BPD	Y (clinical)	Y (clinical)	Y (clinical, physiological)	Y (physiological)	Binary (Y/N clinical and Y/N physiological)
Severity at 36 wk	FiO_2 >30%/vent; Home on O_2	FiO_2/CPAP/vent	FiO_2/MAP/vent/CPAP	FiO_2/MAP/vent/CPAP	Categorical (moderate, O_2 <30% at 36 wk; severe, >30% or any positive pressure)
Days of ventilation/CPAP/oxygen	Y/Y/Y	Y/Y/Y	Y/N/Y	N/N/N	Quantitative
Oxygen at discharge	Y	Y	Y	N	Binary
Pneumothorax/pulmonary interstitial emphysema	Y/N	Y/N	Y/Y	Y/N	Binary/binary
PDA treatment	Y	Y (indomethacin/ibuprofen/ligation/other)	Y (indomethacin/ligation/other)	Y (ilbuprofen/ligation)	Binary (any treatment Y/N)
Insulin treatment	Y	Y	Y	Y	Binary
Necrotizing enterocolitis	Y	Y	Y (stage)	Y	Binary
Gastrointestinal perforation/indomethacin	Y/Y	Y/Y	Y/Y	Y (ibuprofen)	Binary/binary
Late-onset sepsis (bacterial or fungal)	Y	Y	Y	Y	Binary/binary
IVH grade 3-4/PVL	Y/Y	Y/Y	Y/Y	Y severe/Y	Binary (severe Y/N)/binary
ROP grade	Y	Y	Y	Y (severe)	Binary (severe Y/N)
Death before discharge	Y	Y	Y	Y	Binary
36 wk weight and head circumference	Y *z*-scores	Y actual values	Y actual values; length not available	Y actual values	*z*-scores
Open-label steroid use/type of steroid use	Y (dex BPD hydrocortisone-BP)	Y (+ inhaled)	Y (dex all)	Y (Y, inhaled)	Binary (use Y/N); binary (inhaled Y/N); binary (systemic Y/N)
Any indomethacin exposure	Inbuprofen prophylaxis for PDA	Indomethacin Rx	Prenatal or subsequent indomethacin Rx	Ibuprofen	Any exposure (Y/N)

CPAP, continuous positive airway pressure; *IVH*, intraventricular hemorrhage; *MAP*, mean airway pressure; *PVL*, periventricular leukomalacia; *ROP*, retinopathy of prematurity.

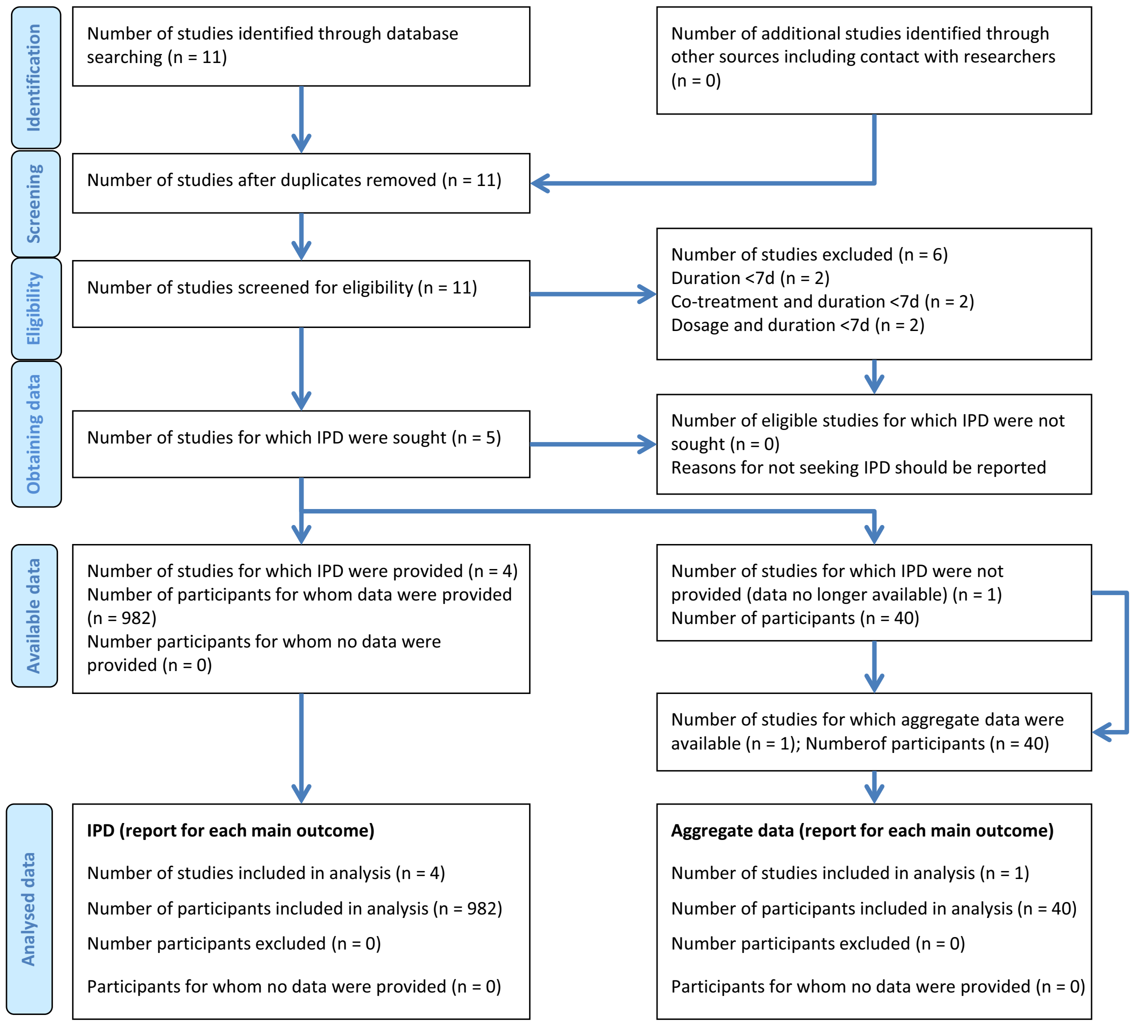

Figure. PRISMA-IPD flow diagram.

Table I. RCTs using early hydrocortisone in preterm neonates and selection of studies in individual patient sata meta-analysis

Study: Authors	Year	Dosage	Cotreatment	Exposure	Population	Number of Patients	Included in Individual Patient Data	Excluded in Individual Patient Data	Reason for Exclusion
Baden et al[26]	1972	15 mg/kg	No	12 h	26-36 wk with respiratory distress syndrome	44		X	Dosage; duration <7 d
Watterberg et al[11]	1999	0.5-1 mg/kg/d	No	12 d	500-999 g, ventilated	40		X	Data not available
Watterberg et al[12]	2004	0.5-1 mg/kg/d	No	12 d	500-999 g, ventilated	360	X		Data not available
Biswas et al[31]	2003	0.5-1 mg/kg/d	Yes (triiodothyronine)	5 d	<30 wk, ventilated	253		X	Cotreatment, duration <7 d
Efird et al[27]	2005	0.3-1 mg/kg/d	No	5 d	24-28 wk and <1000 g, with hypotension	34		X	Duration <7 d
Peltoniemi et al[13]	2005	0.75-2 mg/kg/d	No	10 d	<31 wk or <1251 g, ventilated	51	X		
Ng et al[28]	2006	1 mg/kg/8 h	No	5 d	<1500 g, refractory hypotension	48		X	Dosage; duration <7 d
Bonsante et al[14]	2007	0.5-1 mg/kg/d	No	12 d	24-30 wk or <1250 g, ventilated	50	X		
Batton et al[29]	2012	0.5-1 mg/kg/12 h	Yes (dopamine)	3.5 d	23-26 wk with hypotension	10		X	Cotreatment; duration <7 d
Hochwald et al[30]	2014	0.5-2 mg/kg/6 h	No	48 h	<31 wk or <1251 g, hypotension	22		X	Duration <7 d
Baud et al[15]	2016	0.5-1 mg/kg/d	No	10 d	24-28 wk, all but severe intrauterine growth retardation	523	X		

Table V. Heterogeneity estimates of individual patient data meta-analysis of all outcomes unadjusted

Outcomes	Heterogeneity: I^2, %	Heterogeneity: P Value
Survival without BPD at 36 wk PMA	0	.298
Death before 36 wk PMA	0	.310
BPD at 36 wk PMA	0	.621
Death before discharge	0	.397
Weight at 36 wk PMA, g	0	.853
Head circumference at 36 wk, cm	0	.463
Respiratory support		
Days of ventilation	0	.464
Days of CPAP	67.9	.078
Days of oxygen	54.0	.114
Oxygen at discharge	0	.949
Open-label steroid use	0	.433
Pneumothorax	0	.459
Insulin treatment	0	.722
Medical treatment for PDA (either indomethacin or ibuprofen)	0	.261
Any prophylactic indomethacin	0	.191
Surgical ligation	13.7	.218
Necrotizing enterocolitis	19.6	.238
Spontaneous gastrointestinal perforation	31.9	.322
Late sepsis (bacterial/fungal)	0	.662
Severe IVH (grade 3-4)	0	.887
Cystic PVL	0	.338
Severe ROP	0	.759

Aggregate meta-analysis: CP: $I^2 = 0\%$, $P = .726$ NDI: $I^2 = 0\%$, $P = .897$; BPD: $I^2 = 30.9\%$, $P = .227$.

Table VII. Characteristics of the studies in the long-term outcomes meta-analysis

Characteristics	Watterberg et al, 2007[16]		Peltoniemi et al, 2009[17]		Bonsante et al, 2007 follow-up study as reported in Peltoniemi et al, 2009[17]		Baud et al, 2017[18]	
Treatment group	Hydrocortisone	Placebo	Hydrocortisone	Placebo	Hydrocortisone	Placebo	Hydrocortisone	Placebo
Survivors at follow-up, n	146	145	23	23	20	14	207	199
Lost to follow-up, n (%)	20 (13.7)	19 (13.1)	0	1 (4.35)	0	0	13 (6.28)	14 (7.04)
Age at follow-up, yr	2		2		2		2	
Type of assessment used	BSID-II		BSID-II and Griffiths Developmental Scale		BSID-II		Revised Brunet- Lezine Scale and standardized neurologic exam	
Cutoff score defining severe NDI	DQ <70		MDI or DQ <70		DQ <70		DQ <70	
CP,* n/N (%)	16/126 (12.7)	18/126 (14.3)	2/23 (8.70)	0/22 (0)	2/19 (10.5)	2/14 (14.3)	12/194 (6.19)	10/185 (5.41)
NDI, n/N (%)	48/123 (39.0)	55/125 (44.0)	5/23 (21.7)	5/22 (22.7)	4/20 (20.0)	3/14 (21.4)	14/194 (7.22)	21/185 (11.4)

BSID, Bayley Scale of Infant Development; *DQ*, developmental quotient; *MDI*, mental developmental index.
*All levels of CP.