The Association of Hydrocortisone Dosage on Mortality in Infants Born Extremely Premature

Veeral N. Tolia, MD[1], Timothy M. Bahr, MD[2], Monica M. Bennett, PhD[3], Gregory Martin, MD[2], Rachel G. Greenberg, MD[4], Matthew M. Laughon, MD[5], and Reese H. Clark, MD[6]

Objective To characterize common dosing strategies and to investigate the association between hydrocortisone dosage and in-hospital mortality in infants born extremely premature.

Study design We performed a retrospective review of a cohort of infants born ≤30 weeks' gestational age from 2010 to 2016 from the Pediatrix Clinical Data Warehouse who received hydrocortisone in the first 14 postnatal days. Infants were divided by initial hydrocortisone dosage (high: >2 mg/kg/d vs low: ≤2 mg/kg/d). Baseline characteristics and medication coexposures were compared and mortality was evaluated in a multivariable analysis.

Results A total of 1427 infants were included, 733 with high dosage (51%) and 694 with low dosage (49%). The groups were similar with regard to baseline characteristics. Infants in the high-dosage group had significantly more exposure to any vasopressors (89% vs 84%, $P < .001$) and greater mortality (50% vs 23%, $P < .001$) vs the low-dosage group. High dosage of hydrocortisone was associated independently with death (aOR 3.27, 95% CI 2.47-4.34, $P < .001$) in a multivariable regression analysis including propensity scoring for dosage and other covariates. When the cohort was split into quartiles by dosage, mortality was lower in the lower-dosage quartiles compared with the higher quartiles (mortality range 13%-50%).

Conclusions In this retrospective analysis of a large sample of infants born premature, increased initial hydrocortisone dosage was associated independently with increased mortality. Trials to assess the impact of hydrocortisone dosage in this population are needed. *(J Pediatr 2019;207:143-7).*

The use of hydrocortisone in neonatal intensive care units (NICUs) is increasing and has become common in hypotensive infants born extremely premature.[1] Despite this, dosing strategies are poorly defined and vary widely. Pharmacy reference texts suggest a wide dosing range of up to 3 mg/kg/d,[2,3] and clinical trials have studied low doses for the prevention of bronchopulmonary dysplasia[4-6] and varied doses for the treatment of hypotension.[7,8] To date, there are no reports that characterize current dosing practices for early hydrocortisone in infants born premature. Furthermore, no clinical trials have compared different dosing regimens to assess comparative effectiveness or differences in outcomes.

The purpose of this study was to use a large clinical dataset of infants born premature to summarize the characteristics of infants who received hydrocortisone in the first 14 days of life. Our objective was to characterize common dosing strategies and to investigate the association between hydrocortisone dosage and in-hospital mortality.

Methods

This study was a retrospective cohort review of infants treated with hydrocortisone. Data were sourced from the Pediatrix Clinical Data Warehouse. Clinical data on these neonates are recorded during their hospitalization in the NICU. Admission, discharge, and daily progress notes are generated with a proprietary computer-assisted tool, and these data are stored in an electronic database. Clinicians providing care to patients interact with the patient's data on a daily basis to generate progress notes and billing. Each day's note is stored along with medications, procedures, and diagnoses. The local data are deidentified, made compliant with the Health Insurance Portability and Accountability Act of 1996 regulations, and consolidated within the Clinical Data Warehouse, which is configured into tables that can be joined and queried for statistical analyses. The details of this data set have been described in detail elsewhere.[9,10] This dataset is approved for queries by the Western institutional review board (Olympia, Washington) and the MEDNAX research advisory committee (Sunrise, Florida).

NICU Neonatal intensive care unit

From the [1]Division of Neonatology, Department of Pediatrics, Baylor University Medical Center and Pediatrix Medical Group, Dallas, TX; [2]Department of Child Health, Banner University Medical Center and the University of Arizona College of Medicine, Phoenix, AZ; [3]Center for Clinical Effectiveness, Baylor Scott & White Health, Dallas, TX; [4]Division of Neonatology, Department of Pediatrics, Duke University and Duke Clinical Research Institute, Durham; [5]Division of Neonatology, Department of Pediatrics, The University of North Carolina at Chapel Hill, Chapel Hill, NC; and [6]The Center for Research, Education, Quality and Safety, Mednax, Inc, Sunrise, FL

The authors declare no conflicts of interest.

Portions of this study were presented at the Pediatric Academic Societies annual meeting, May 5-8, 2018, Toronto, Ontario, Canada.

https://doi.org10.1016/j.jpeds.2018.11.023

Infants were eligible for inclusion in our study if they required admission to a participating NICU, were discharged between January 1, 2010, and December 31, 2016, had a birth weight ≥400 g, and were born between 23 and 30 weeks' gestation. From all eligible infants, we identified those with early hydrocortisone exposure that included dosage, and these infants constituted the study cohort.

We collected the following independent variables: maternal age, antenatal steroid exposure, antenatal antibiotics, cesarean delivery, multiple gestation, outborn birth status, gestational age at birth, birth weight, small for gestational age status, 1- and 5-minute Apgar scores, sex, and race/ethnicity. Gestational age was determined by the admitting physician and not standardized across sites. We also collected data on therapies used during the infant's hospital stay, including use of mechanical ventilation on day 0, 1, or 2, and exposure to the following medications during the first 14 postnatal days: any surfactant, dexamethasone, indomethacin, dopamine, dobutamine, epinephrine, milrinone, and nitric oxide. Our primary outcome was death of any cause before NICU discharge.

Data on medication exposures are captured daily in the Clinical Data Warehouse for all infants. For this study, we included infants with exposure to intravenous hydrocortisone in the first 14 days after birth. Dosage data were available for a subset of sites. Data on dosages were stored in a free-text field, which was extracted from the initial day of hydrocortisone exposure and coded to determine dosage (reported in mg/kg/d), dose (in mg/kg/dose), and dosing frequency (number of doses per day). In patients with data reported in body surface area, the dosage was converted to mg/kg/d using the following formula: mg/m^2/day * body surface area/weight on day of birth.[11] We used dosage in our analysis because other measures of exposure (such as cumulative hydrocortisone exposure) would be biased by mortality.

Statistical Analyses

After preliminary analysis, the cohort was divided into 2 groups based on the median initial dosage of hydrocortisone: infants in the high-dosage group: >2 mg/kg/d and infants in the low-dosage group: ≤2 mg/kg/d. Demographic and treatment characteristics of the 2 groups were compared. Continuous variables (eg, gestational age and birth weight) were evaluated to determine whether they were parametric. Parametric data were assessed with 2-tailed *t* tests. Nonparametric continuous variables were assessed with Kruskal–Wallis one-way ANOVA. Categorical variables (eg, race and sex) were evaluated with Pearson χ^2 tests.

Logistic regression was used to calculate the unadjusted and aOR for death after excluding transfers. For the adjusted multivariable model, we first calculated the propensity score for high-dosage hydrocortisone exposure using all infant baseline and treatment characteristics including hydrocortisone start date. This propensity score was included as a covariate along with antenatal steroid exposure; multiple gestation; outborn birth status; gestational age at birth; birth weight; small for gestational age status; 5-minute Apgar score; sex; race/ethnicity; mechanical ventilation on day 0, 1, or 2; and medication coexposure (as listed previously) in the final model. Birth weight and gestational age were included as continuous variables, and the model was adjusted for random center effect. We also evaluated the effect of dosage on mortality in a model that used inverse probability weights calculated from the propensity scores, as well as a model that excluded any propensity score technique but included all other covariates.

To determine the impact of excluding transferred infants, two-sensitivity analyses were performed. First, we used multiple imputation for the primary outcome for these infants with the Markov Chain Monte Carlo technique. This logistic regression analysis was repeated with 20 imputed datasets and the pooled OR of death was calculated.[12] The second sensitivity analysis used a combined outcome of death or transfer.

Because of the wide range of recommended hydrocortisone dosage, we also performed a secondary analysis, in which we divided the cohort into approximate quartiles based on initial dosage (<1 mg/kg/d, 1-2 mg/kg/d, >2-3 mg/kg/d, and >3 mg/kg/d) and repeated the descriptive and multivariable analysis. All statistical analyses were performed using JMP 12 and SAS 9.4 (SAS Institute, Cary, North Carolina).

Results

There were 615 421 infants reported in the dataset between 2010 and 2016, of whom 68 838 (11%) met the gestational age and birth weight inclusion criteria. Of these infants, 5138 (8%) were treated with hydrocortisone within the first 14 postnatal days. Infants treated with hydrocortisone were smaller, more immature, were less likely to have received antenatal steroids, and were more likely to be treated with vasopressors and mechanical ventilation. They were more likely to have surrogate markers for severe illness such as lower Apgar scores, were more often small for gestational age, and were more often male (**Table I**; available at www.jpeds.com). From this group, we identified 1427 infants from 99 NICUs with full initial dosing data who constituted our study cohort. The infants without dosing data were similar to our study cohort (**Table II**; available at www.jpeds.com).

The median dose of initial hydrocortisone was 2 mg/kg/d (10-90th percentile = 0.4-4 mg/kg/d) and the median individual dose of hydrocortisone was 1 mg/kg/dose (10-90th percentile = 0.25-1 mg/dose). Dosage was converted from body surface area to mg/kg/d in 126 infants. Dividing the cohort by the median initial dosage, we defined 733 (51%) infants in the high-dosage group and 694 (49%) infants in the low-dosage group. The groups were similar with respect to baseline characteristics although infants in the high-dosage group were more likely to receive vasopressors and other vasoactive drugs (**Table III**).

Differences in initial hydrocortisone dosing and mortality are described in **Table IV**. Mortality was significantly greater for infants in the high-dosage group compared with infants in the low-dosage group (50% vs 23%, unadjusted OR 3.9, 95% CI 3.0-4.9, $P < .001$) after transfers were excluded. This difference persisted (aOR 3.27, 95% CI 2.47-4.34, $P < .001$) after

Table III. Infant baseline and treatment characteristics by hydrocortisone dosage group

Characteristics	Low dosage, ≤2 mg/kg/d	High dosage, >2 mg/kg/d	*P* value
n	694	733	
Maternal age, y, median (10-90th %)	28 (19-37)	27 (20-37)	.032
Antenatal steroids, n (%)	539 (78)	547 (75)	.192
Antenatal antibiotics, n (%)	371 (53)	412 (56)	.312
Cesarean delivery, n (%)	535 (77)	541 (74)	.149
Multiple gestation, n (%)	165 (24)	172 (23)	.901
Outborn, n (%)	167 (24)	159 (22)	.313
Gestational age, wk, median (10th-90th %)	25 (23-28)	25 (23-28)	.713
Birth weight, g, median (10th-90th %)	698 (550-1100)	710 (500-1040)	.387
Small for gestational age, n (%)	132 (19)	150 (20)	.668
One-minute Apgar, median (10th-90th %)	3 (1-7)	3 (1-7)	.059
Five-minute Apgar, median (10th-90th %)	6 (3-8)	6 (3-8)	.056
Male, n (%)	395 (57)	433 (59)	.420
Race/ethnicity, n (%)			.590
Asian	27 (4)	20 (3)	
Black	191 (28)	224 (31)	
Hispanic	113 (16)	115 (16)	
Other	41 (6)	41 (6)	
White	322 (46)	333 (45)	
Mechanical ventilation on day 0-2, n (%)	630 (91)	676 (92)	.787
Mechanical ventilation on hydrocortisone start day	673 (97)	722 (99)	.093
Medication use in first 14 postnatal days, n (%)			
Surfactant	630 (91)	665 (91)	.971
Dexamethasone	34 (5)	37 (5)	.904
Indomethacin	215 (31)	215 (29)	.526
Any vasopressors	580 (84)	650 (89)	.006
Dopamine	562 (81)	629 (86)	.015
Dobutamine	171 (25)	287 (39)	<.001
Epinephrine	122 (18)	242 (33)	<.001
Milrinone	14 (2)	38 (5)	.002
Nitric oxide	112 (16)	169 (23)	.001

Table IV. Hydrocortisone dosing and mortality in low-dosage and high-dosage groups

Characteristics	Low dosage	High dosage	*P* value
Dosing range	≤2 mg/kg/d	>2 mg/kg/d	
n (%)	694 (49%)	733 (51%)	
Dosage in mg/kg/d, median (10-90%)	1 (0.25-2)	3 (2.4-4.8)	<.001
Individual dose in mg/kg, median (10%-90%)	0.5 (0.1-1)	1 (1-2)	<.001
Dosing frequency, doses per day*			<.001
Infants with 1 dose/d (%)	165 (24)	2 (0)	
Infants with 2 doses/d (%)	338 (49)	70 (10)	
Infants with 3 doses/d (%)	114 (16)	488 (67)	
Infants with 4 doses/d (%)	35 (5)	119 (16)	
Age start of hydrocortisone in days, median (10%-90%)	3 (0-12)	3 (0-12)	.454
Final disposition, n (%)			
Alive	436 (63)	261 (36)	<.001
Died	160 (23)	369 (50)	<.001
Transferred	98 (14)	103 (14)	.879
Mortality excluding transfers	27%	59%	<.001
Age at death, median (10%-90%)	13 (2-63.5)	8 (1-34)	<.001

*Data on dosing frequency missing for 96 (7%) of infants.

risk adjustment for the following covariates: propensity for high-dosage hydrocortisone; antenatal steroid exposure; multiple gestation; outborn birth status; gestational age at birth; birth weight; small for gestational age status; 5-minute Apgar score; sex; race/ethnicity; mechanical ventilation on day 0, 1 or 2; and medication coexposure. We found substantively identical results in the adjusted model that used the propensity score for inverse probability weights (aOR 3.28, 95% CI 2.48-4.33, $P < .001$) as well in the adjusted model that excluded propensity scores (aOR 3.33, 95% CI 2.52-4.40, $P < .001$). In the sensitivity analyses, we found only modest changes in the point estimate when imputing the outcome for the transferred infants (aOR 2.71, 95% CI 2.05-3.58, $P < .001$) or using a combined outcome of death or transfer (aOR 3.65, 95% CI 2.07-3.38, $P < .001$).

In the secondary analysis, the cohort was divided into 4 approximate quartiles based on initial dosage. Among the 4 groups, there were significant differences with regard to sex and use of dopamine, dobutamine, epinephrine, milrinone, and inhaled nitric oxide (**Table V**; available at www.jpeds.com). As there were only modest differences in individual dose (from 0.5 mg/kg/dose to 1.2 mg/kg/dose in the first to fourth quartiles respectively, **Table VI**), the main determinant of dosage appeared to be frequency of the drug administration. Mortality increased by dosing quartile of hydrocortisone, from 15% in the infants treated with <1 mg/kg/d, to 33% in those infants given 1-2 mg/kg/d dosage, and to 51% and 50%, respectively, in the 2 groups with greatest exposure (>2-3 mg/kg/d and >3 mg/kg/d). After risk adjustment for the same covariates in the primary analysis, the odds of death were significantly greater in each 1:1 comparison of a higher dosage quartile with a lower dosage quartile except for the comparison between the 2 highest dosing groups, suggesting a dose–response relationship (**Table VII**).

Discussion

In this multicenter retrospective cohort study, we found that high initial dosage of early hydrocortisone was associated with a large difference in absolute mortality and increased odds of death. This finding persisted in the multivariable regression and secondary analyses. Our findings are especially concerning, given recent cohort studies reporting increased mortality or morbidity with hydrocortisone treatment.[13,14]

Several robust prospective trials have assessed the safety and efficacy of low-dose hydrocortisone to prevent bronchopulmonary dysplasia,[4,6] but our study has important differences in its target population and medication use. In our cohort, we suspect that hypotension was the most common indication for hydrocortisone because of the high reported coexposure of any vasopressors in our infants. In addition, >75% of the infants in our cohort were treated with larger hydrocortisone dosages than used in those prospective trials. Finally, our study period

Table VI. Hydrocortisone dosing and mortality by dosing quartiles

Characteristics	First quartile	Second quartile	Third quartile	Fourth quartile	*P* value
Dosing range	<1 mg/kg/d	1-2 mg/kg/d	>2-3 mg/kg/d	>3 mg/kg/d	
n (%)	318 (22%)	376 (26%)	387 (27%)	346 (24%)	
Median dosage in mg/kg/d (10th-90th %)	0.5 (0.2-0.9)	1.6 (1-2)	3 (2.2-3)	4 (3.1-6)	<.001
Median individual dose in mg/kg/dose (10th-90th %)	0.3 (0.1-0.5)	0.7 (0.5-1)	1 (0.8-1)	1.1 (1-2)	<.001
Dosing frequency, doses per day*					<.001
Infants with 1 dose/d (%)	130 (41)	35 (9)	0 (0)	2 (1)	
Infants with 2 doses/d (%)	129 (41)	209 (56)	44 (11)	26 (8)	
Infants with 3 doses/d (%)	45 (14)	69 (18)	319 (82)	169 (49)	
Infants with 4 doses/d (%)	8 (3)	27 (7)	13 (3)	106 (31)	
Final disposition, n (%)					
Alive	226 (71)	210 (56)	129 (33)	132 (38)	<.001
Died	48 (15)	112 (30)	197 (51)	172 (50)	<.001
Transferred	44 (14)	54 (14)	61 (16)	42 (12)	.551
Age at death, median (10%-90%)	26 (4-75)	12 (2-56)	9 (1-32)	7 (1-35)	<.001

*Data on dosing frequency missing for 96 (7%) infants.

preceded the publication of the initial PREMILOC (Early Low-Dose Hydrocortisone to Improve Survival without Bronchopulmonary Dysplasia in Extremely Preterm Infants) study results, reducing the likelihood of widespread practice of prophylactic use as described in that trial.

One small prospective study evaluated high-dose hydrocortisone for hypotension in larger infants than our cohort and reported significant short-term improvement in hypotension but also a modest, nonsignificant increase in mortality among treated infants.[7] Other cohort studies have evaluated the effects of hydrocortisone on hypotension, but our study may be less subject to confounding by treatment indication vs reports comparing infants treated with hydrocortisone with those who were not treated.[13,14]

Watterberg summarized the limited data available for hydrocortisone dosing for hypotension and suggested that a dose range of 1-2 mg/kg/d should be adequate in infants born extremely preterm.[15] She also suggested caution at higher doses, as studies have suggested that prolonged exposure to high concentrations of glucocorticoids may have adverse effects in both children[16-18] and adults.[19,20] More than one-half of our study population received an initial dosage greater than this recommendation. Importantly, we found that the primary driver of higher hydrocortisone dosage was dosing frequency. Because infants born premature have longer half-life for hydrocortisone compared with newborns born at term,[21] it is possible that the more frequent dosing we found in the infants in the high-dosage group resulted in a sustained exposure to high concentrations of the glucocorticoid, which was harmful. Hydrocortisone has many effects on the body (eg, anti-inflammation and immunosuppression), but the mechanism by which this relationship between hydrocortisone and death could be causal is unknown, and a study of observational nature cannot evaluate causality.

Table VII. Logistic regression matrix for odds of mortality comparing each dosing quartile

Quartiles	Comparison quartile		
Referent	Second quartile 1-2 mg/kg/d	Third quartile >2-3 mg/kg/d	Fourth quartile >3 mg/kg/d
First quartile	2.41 (1.54-3.78)	6.04 (3.87-9.41)	5.27 (3.38-8.24)
Second quartile		2.50 (1.72-3.63)	2.19 (1.51-3.17)
Third quartile			1.14 (0.79-1.65)*

Each cell reports the aOR (CI) of mortality (95% CI) when the referent quartile is compared with the comparison quartile.
P value for each aOR was < .001 except *, where *P* = .495.
This model was adjusted for antenatal steroid exposure; multiple gestation; outborn birth status; gestational age at birth; birth weight; small for gestational age status; 5-minute Apgar score; sex; race/ethnicity; mechanical ventilation on day 0, 1, or 2; and medication coexposures.

The most important limitation to this study is the effect of bias from confounding by treatment indication. Although both dosage groups had similar baseline demographic and treatment characteristics, it is likely that some infants were treated with higher dosing because of more severe illness and consequently were more likely to die. We attempted to account for this limitation by incorporating the propensity for dosage category in our analysis, and it is encouraging that this did not substantially change the point estimate. We used as many variables as were available to adjust for degree of illness but did not have access to other important measures (such as blood gas measurements, sepsis, and treatment with blood transfusions or bicarbonate) that, as surrogate markers for illness severity, could potentially reduce our reported associations. We also may have missed unmeasured factors related to mortality. A well-designed randomized trial could mitigate these sources of bias, but others have reported significant barriers to enrollment in prospective studies of hydrocortisone treatment.[22,23] In the absence of greater quality of evidence, neonatologists often have relied on cohort studies to identify harm from medication exposures, most notably with regard to antibiotics and antireflux medications.[24,25] Our data provide no evidence that higher dosages of hydrocortisone improve survival compared with lower dosages.

Our study has other limitations. Because of the study design, these results must be interpreted as hypothesis generating. Drug and drug dosing data in this dataset are derived from physician entries and not from pharmacy records. In addition, we did not calculate the cumulative dosage of hydrocortisone or duration of treatment, which have been reported in previous studies of hydrocortisone.[13] Cause of death is not collected in

the data set, and we are only able report short-term outcomes as we do not have post-NICU outcomes for any of the infants. Finally, as with all administrative datasets, underreporting and inaccurate reporting are possible despite prospective data entry and internal consistency checks.

In summary, we observed an association between mortality and early higher initial dosage of hydrocortisone in a large retrospective cohort of infants born premature treated in the first 14 postnatal days. Our study provides no evidence that an initial dosage of hydrocortisone of >2 mg/kg/d improves survival and suggests that this intervention could cause harm. Based on this study's findings as well as dosing recommendations by previous analysis and pharmacokinetics,[15] clinicians should avoid hydrocortisone dosing >1 mg/kg every 12 hours for infants born extremely preterm. There remains an urgent need for randomized clinical trials to determine the optimal dosing strategy for hydrocortisone in this vulnerable population. ■

Submitted for publication Jul 6, 2018; last revision received Oct 25, 2018; accepted Nov 7, 2018

Reprint requests: Veeral N. Tolia, MD, 3500 Gaston Ave, 3 Hoblitzelle, Dallas, TX 75246. E-mail: veeral.tolia@baylorhealth.edu

References

1. Rios DR, Moffett BS, Kaiser JR. Trends in pharmacotherapy for neonatal hypotension. J Pediatr 2014;165:697-701, e691.
2. Lexicomp Online. Pediatric and neonatal Lexi-drugs online. Hudson (OH): Lexi-Comp, Inc; 2013 Accessed February 26, 2018. Updated April 15, 2013.
3. Thomson Reuters Clinical Editorial Staff. Neofax 2011. Montvale (NJ): Thomson Reuters; 2011.
4. 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.
5. 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.
6. 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.
7. 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.
8. 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.
9. Spitzer AR, Ellsbury DL, Handler D, Clark RH. The Pediatrix BabySteps Data Warehouse and the Pediatrix QualitySteps improvement project system—tools for "meaningful use" in continuous quality improvement. Clin Perinatol 2010;37:49-70.
10. Bixler GM, Powers GC, Clark RH, Walker MW, Tolia VN. Changes in the diagnosis and management of patent ductus arteriosus from 2006 to 2015 in United States Neonatal Intensive Care Units. J Pediatr 2017;189:105-12.
11. Ogden SJ, Fluharty L. Calculation of drug doses. 9th ed. Maryland Heights, (MO): Mosby; 2011.
12. Schafer JL. Analysis of incomplete multivariate data. London, England: Chapman & Hall/CRC; 1997.
13. Altit G, Vigny-Pau M, Barrington K, Dorval VG, Lapointe A. Corticosteroid therapy in neonatal septic shock-do we prevent death? Am J Perinatol 2018;35:146-51.
14. Batton B, Li L, Newman NS, Das A, Watterberg KL, Yoder BA, et al. Early blood pressure, antihypotensive therapy and outcomes at 18-22 months' corrected age in extremely preterm infants. Arch Dis Child Fetal Neonatal Ed 2016;101:F201-6.
15. Watterberg KL. Hydrocortisone dosing for hypotension in newborn infants: less is more. J Pediatr 2016;174:23-6.
16. 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.
17. Sauberan JB, Reed EM, Vaucher YV, Katheria AC. Oliguria during hydrocortisone dosage wean in very low birth weight infants. Am J Perinatol 2014;31:673-6.
18. 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.
19. Sherlock M, Reulen RC, Alonso AA, Ayuk J, Clayton RN, Sheppard MC, et al. ACTH deficiency, higher doses of hydrocortisone replacement, and radiotherapy are independent predictors of mortality in patients with acromegaly. J Clin Endocrinol Metab 2009;94:4216-23.
20. Zueger T, Kirchner P, Herren C, Fischli S, Zwahlen M, Christ E, et al. Glucocorticoid replacement and mortality in patients with nonfunctioning pituitary adenoma. J Clin Endocrinol Metab 2012;97:E1938-42.
21. Vezina HE, Ng CM, Vazquez DM, Barks JD, Bhatt-Mehta V. Population pharmacokinetics of unbound hydrocortisone in critically ill neonates and infants with vasopressor-resistant hypotension. Pediatr Crit Care Med 2014;15:546-53.
22. 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.
23. Watterberg KL, Fernandez E, Walsh MC, Truog WE, Stoll BJ, Sokol GM, et al. Barriers to enrollment in a randomized controlled trial of hydrocortisone for cardiovascular insufficiency in term and late preterm newborn infants. J Perinatol 2017;37:1220-3.
24. Clark RH, Bloom BT, Spitzer AR, Gerstmann DR. Empiric use of ampicillin and cefotaxime, compared with ampicillin and gentamicin, for neonates at risk for sepsis is associated with an increased risk of neonatal death. Pediatrics 2006;117:67-74.
25. Terrin G, Passariello A, De Curtis M, Manguso F, Salvia G, Lega L, et al. Ranitidine is associated with infections, necrotizing enterocolitis, and fatal outcome in newborns. Pediatrics 2012;129:e40-5.

Table I. Comparison of baseline and treatment characteristics of infants with and without hydrocortisone exposure

Characteristics	No hydrocortisone	Hydrocortisone	*P* value
n	63 700	5138	
Maternal age, y, median (10th-90th %)	28 (20-37)	28 (19-36)	.001
Antenatal steroids, n (%)	51 365 (81)	3899 (76)	<.001
Antenatal antibiotics, n (%)	34 145 (54)	2747 (53)	.850
Cesarean delivery, n (%)	44 800 (71)	3790 (75)	<.001
Multiple gestation, n (%)	15 706 (25)	1250 (24)	.614
Outborn, n (%)	10 537 (17)	1217 (24)	<.001
Gestational age, wk, median (10th-90th %)	28 (24-30)	25 (23-28)	<.001
Birth weight, g, median (10th-90th %)	1060 (650-1510)	705 (510-1140)	<.001
Small for gestational age, n (%)	7314 (11)	1002 (20)	<.001
One-minute Apgar, median (10th-90th %)	6 (1-8)	3 (1-7)	<.001
Five-minute Apgar, median (10th-90th %)	8 (5-9)	6 (2-8)	<.001
Female, n (%)	30 017 (47)	2192 (43)	<.001
Race/ethnicity, n (%)			<.001
Asian	1866 (3)	140 (3)	
Black	17 680 (28)	1578 (31)	
Hispanic	12 103 (19)	948 (18)	
Other	4644 (7)	344 (7)	
White	27 407 (43)	2128 (41)	
Mechanical ventilation on day 0-2, n (%)	36 646 (60)	4638 (95)	<.001
Medication use in first 14 postnatal days, n (%)			
Surfactant	42 257 (66)	4608 (90)	<.001
Dexamethasone	791 (1)	215 (4)	<.001
Any vasopressors	9979 (16)	4289 (83)	<.001
Dopamine	8821 (14)	4094 (80)	<.001
Dobutamine	1301 (2)	1411 (27)	<.001
Epinephrine	1955 (3)	1357 (26)	<.001
Milrinone	148 (0.2)	171 (3)	<.001
Nitric oxide	1243 (2)	928 (18)	<.001
Discharge type, n (%)			<.001
Alive	50 686 (80)	2650 (52)	
Died	4747 (7)	1762 (34)	
Transferred	8227 (13)	721 (14)	

Table II. Comparison of baseline and treatment characteristics of the study cohort with infants that did not have hydrocortisone dosage data

	No dosing data	Study cohort	*P* value
n	3711	1427	
Maternal age, years, median (10-90th %)	28 (19-36)	27 (19-36)	.460
Antenatal Steroids, n (%)	2812 (76)	1086 (76)	.856
Antenatal antibiotics, n (%)	1965 (53)	783 (55)	.212
Cesarean section, n (%)	2719 (73)	1076 (76)	.084
Multiple gestation, n (%)	915 (25)	337 (24)	.468
Outborn, n (%)	890 (24)	326 (23)	.420
Gestational age, weeks, median (10-90th %)	25 (23-28)	25 (23-28)	.857
Birth weight, grams, median (10-90th %)	706 (510-1150)	700 (520-1120)	.515
Small for gestational age, n (%)	705 (19)	282 (20)	.547
One minute Apgar, median (10-90th %)	3 (1-7)	3 (1-7)	.294
Five minute Apgar, median (10-90th %)	6 (2-8)	6 (2-8)	.728
Female, n (%)	1601 (43)	595 (42)	.413
Race/ethnicity, n (%)			.120
Asian	93 (3)	47 (3)	
Black	1163 (31)	415 (29)	
Hispanic	719 (19)	228 (16)	
Other	264 (7)	82 (6)	
White	1472 (40)	655 (46)	
Mechanical Ventilation on Day 0-2, n (%)	3337 (90)	1306 (92)	.033
Medication use in first 14 postnatal days, n (%)			
Surfactant	3316 (89)	1295 (91)	.125
Dexamethasone	145 (4)	71 (5)	.087
Any vasopressors	3068 (83)	1230 (86)	.001
Dopamine	2911 (78)	1191 (83)	<.0001
Dobutamine	956 (26)	458 (32)	<.0001
Epinephrine	996 (27)	364 (26)	.377
Milrinone	120 (3)	52 (4)	.435
Nitric Oxide	648 (17)	281 (20)	.063
Discharge Type, n (%)			.026
Alive	1942 (52)	697 (49)	
Died	1244 (34)	529 (37)	
Transferred	522 (14)	199 (14)	

Table V. Infant baseline and medication characteristics by hydrocortisone dosage quartile

Characteristics	First quartile	Second quartile	Third quartile	Fourth quartile	*P* value
n (%)	318 (22%)	376 (26%)	387 (27%)	346 (24%)	
Maternal age, y, median (10th-90th %)	28 (19-37)	28 (20-37)	27 (19-36)	27 (20-37)	.053
Antenatal steroids, n (%)	254 (80)	285 (76)	294 (76)	253 (73)	.235
Antenatal antibiotics, n (%)	167 (53)	204 (54)	211 (55)	201 (58)	.523
Cesarean delivery, n (%)	241 (76)	294 (78)	282 (73)	259 (75)	.283
Multiple gestation, n (%)	77 (24)	88 (23)	98 (25)	74 (21)	.646
Outborn, n (%)	85 (27)	82 (22)	83 (21)	76 (22)	.251
Gestational age, wk, median (10th-90th %)	25 (23-28)	25 (23-28)	25 (23-28.2)	25 (23-28)	.119
Birth weight, g, median (10th-90th %)	717 (550-1100)	680 (500-1040)	700 (510-1150)	710 (510-1160)	.168
Small for gestational age, n (%)	60 (19)	72 (19)	77 (20)	73 (21)	.951
One-minute Apgar, median (10th-90th %)	3 (1-7)	3 (1-7)	3 (1-7)	3 (1-7)	.282
Five-minute Apgar, median (10th-90th %)	7 (3-8)	6 (3-8)	6 (2-8)	6 (2-8)	.198
Male, n (%)	203 (64)	192 (51)	237 (61)	196 (57)	.004
Race/ethnicity, n (%)					.783
Asian	14 (4)	13 (3)	11 (3)	9 (3)	
Black	83 (26)	108 (29)	118 (30)	106 (31)	
Hispanic	44 (14)	69 (18)	58 (15)	57 (16)	
Other	21 (7)	20 (5)	24 (6)	17 (5)	
White	156 (49)	166 (44)	176 (45)	157 (45)	
Mechanical ventilation on day 0-2, n (%)	277 (87)	353 (94)	360 (93)	316 (91)	.123
Mechanical ventilation on hydrocortisone start day	305 (96)	368 (98)	382 (99)	340 (98)	.095
Medication use in first 14 postnatal days, n (%)					
Surfactant	289 (91)	341 (91)	348 (90)	317 (92)	.888
Dexamethasone	14 (4)	20 (5)	24 (6)	13 (4)	.499
Indomethacin	109 (34)	106 (28)	119 (31)	96 (28)	.237
Any vasopressors	266 (84)	314 (84)	347 (90)	303 (88)	.035
Dopamine	256 (81)	306 (81)	339 (88)	290 (84)	.041
Dobutamine	78 (25)	93 (25)	153 (40)	134 (39)	<.001
Epinephrine	51 (16)	71 (19)	130 (34)	112 (32)	<.001
Milrinone	4 (1)	10 (3)	15 (4)	23 (7)	.002
Nitric oxide	53 (17)	59 (16)	97 (25)	72 (21)	.005