JPPT | Letter to the Editor

Do Postnatal Corticosteroids Negatively Impact the Neurodevelopmental Outcomes of Extremely Preterm Infants?

To the Editor—The study by David et al[1] assessed the impact of postnatal corticosteroids (PNC), used to treat hypotension or respiratory conditions, on neurodevelopmental outcomes at 20 months corrected age. The study concluded that prolonged, repeated exposure to dexamethasone (DEX) with or without hydrocortisone (HC) was associated with adverse cognitive, language, and motor outcomes at 20 months corrected age.[1]

The diagnosis and grading of bronchopulmonary dysplasia (BPD) are not defined. The authors state that the use of PNC was based on individual physician preferences. Did these factors lead to practice variation in the use of PNC? Why was HC used as the first-line drug to prevent BPD as it is not effective in significantly decreasing the risk of BPD.[2]

The infants who received PNC, compared with those who did not, were significantly more immature, with lower birthweight, and with more morbidities (BPD, retinopathy of prematurity, necrotizing enterocolitis, and home oxygen (see Table 1 in David et al.[1]). Why did the authors not match the subjects based on gestational age, birthweight, and severity of respiratory disease?

The initiation of DEX was at an average of 51.8 ± 28.7 days of life. Is this not beyond the postnatal window when PNC is useful to prevent BPD?[2] Infants who were treated with PNC had significantly higher rates of BPD compared with infants who were not treated with PNC (HC 83%, DEX ± HC 92% vs no PNC 43%; see Table 1 in David et al.[1]). Thus, in this study, PNC did not decrease BPD, and infants with BPD are at increased risk of neurodevelopmental impairment (NDI),[3] especially those who require protracted ventilatory support.[4] Thus, is it not likely that the DEX ± HC group consisted of infants with severe BPD, inherently placing them at higher baseline risk for adverse neurodevelopmental outcomes? Without adjusting for BPD severity or incorporating it as a mediator or moderator variable, the attribution of poorer outcomes solely to PNC exposure may be misleading.

Should the authors not follow the TRIPOD guidelines outlined by the EQUATOR Network,[5] which are the standard for transparent reporting of prediction model development and validation? For example, the multivariable model in their published Table 4[1] lacks model performance measures, which are essential for evaluating the validity of predictive models. The stability of the model estimate is uncertain given the small sample size and the number of covariates that were included. Furthermore, unmeasured confounders, such as genetic predispositions,[6] socioeconomic status,[7] and intraventricular hemorrhage Grades 1 to 2,[8] may also influence neurodevelopmental outcomes but are not accounted for in the analysis. In addition, is it not better to evaluate infants for diagnosing significant developmental delay using Bayley III at 21 to 24 months instead of at 18 to 20 months?[9]

The study by Melan et al[10] is a retrospective, single-center cohort study like the study by David et al,[1] but used betamethasone or HC to prevent BPD and found that there was an increased risk of NDI in the PNC-treated infants compared with those who were not (62.7% vs 38.1%, p = 0.0020). However, when the investigators did a multivariable analysis, the results showed that the risk factors for NDI were male sex (p = 0.027) and severe neonatal morbidity (p = 0.007) and not PNC.[10] Onland et al[11] found that higher cumulative doses of DEX administered after the first week of life decreased the risk of BPD without increased risk of NDI and that DEX started between 7 and 14 days decreased the risk of adverse Mental Development Index. Raghuveer et al[2] found that a medium cumulative dose (2–3 mg/kg) of DEX, administered for 14 days or more, significantly reduced BPD without increasing the risk of NDI. These studies contradict the conclusions of the David et al study.[1]

Caitlynn B. Bohanon Franco, MPH (c); Rosey E. Zackula, MA; and Talkad S. Raghuveer, MD

Article Information

Affiliations. Department of Population Health (CBBF), Office of Research (REZ), Department of Pediatrics (TSR), University of Kansas School of Medicine Wichita, Wichita, KS.

Correspondence. Talkad S. Raghuveer, MD; raghuveer.talkad3@gmail.com

Disclosure. The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria. All authors attest to meeting the four criteria recommended by the ICMJE for authorship of this manuscript.

References

1. David J, Foschi C, Greene MM, et al. Neurodevelopmental outcome at 20 months corrected age in extremely preterm infants after exposure to dexamethasone and hydrocortisone in the NICU. *J Pediatr Pharmacol Ther*. 2025;30(1):84–92.
2. Raghuveer TS, Zackula RE, Lakhotia R, Binder SA. Systemic steroids and bronchopulmonary dysplasia: a systematic review and meta-analysis. *J Perinatol*. 2024;44(2):223–234.
3. Schmidt B, Asztalos EV, Roberts RS, et al. Impact of bronchopulmonary dysplasia, brain injury, and severe retinopathy of prematurity on the outcome of extremely low-birth weight infants at 18 months: results from the trial of Indomethacin prophylaxis in preterms. *JAMA*. 2002;289(9):1124–1129.
4. Walsh MC, Morris BH, Wrage LA, et al. Extremely low birth weight neonates with protracted ventilation: mortality and 18-month neurodevelopmental outcomes. *J Pediatr*. 2005;146:798–804.
5. Moons, KGM, Altman DG, Reitsma JB, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. *Ann Intern Med* 2015;162(1):W1–73.
6. Srivastava S, Lewis SA, Cohen JS, et al. Molecular diagnostic yield of exome sequencing and chromosomal microarray in cerebral palsy: a systematic review and meta-analysis. *JAMA Neurol*. 2022;79:1287–1295.
7. Benavente-Fernandez I, Siddiqi A, Miller SP. Socioeconomic status and brain injury in children born preterm: modifying neurodevelopmental outcome. *Pediatr Res*. 2020;87:391–398.
8. Rees P, Callan C, Chadda KR, et al. Preterm brain injury and neurodevelopmental outcomes: a meta-analysis. *Pediatrics*. 2022;150(6):e2022057442.
9. Garfinkle J, Khairy M, Simard M-N, et al. Corrected age at bayley assessment and developmental delay in extreme preterms. *Pediatrics*. 2024;153(2):e2023063654
10. Melan N, Pradat P, Godbert I, et al. Neurodevelopment at 24 months corrected age in extremely preterm infants treated with dexamethasone alternatives during the late postnatal period: a cohort study. *Eur J Pediatr*. 2024;184:677–687.
11. Onland W, Offringa M, De Jaegere AP, van Kaam AH. Finding the optimal postnatal dexamethasone regimen for preterm infants at risk of bronchopulmonary dysplasia: a systematic review of placebo-controlled trials. *Pediatrics* 2009;123:367–377.

AUTHOR RESPONSE: Thank you to Franco, Zackula, and Raghuveer for their thoughtful response to our article entitled, "Neurodevelopmental outcome at 20 months corrected age in extremely preterm infants after exposure to dexamethasone and hydrocortisone in the NICU."[1] We agree that the group subjected to dexamethasone was a "sicker" cohort, with lower gestational age, lower birthweight, and higher neonatal morbidities. As stated in our discussion, it is possible that the negative neurodevelopmental outcomes observed relate to these potential neonatal confounders or exposures. Regarding the timing of Bayley developmental testing, earlier testing may under-identify developmental delays; thus, it remains concerning that poorer outcomes were observed in this earlier follow-up period.[2] Similar to studies suggesting an increased risk of cerebral palsy with dexamethasone therapy,[3–5] providers during our study years were using higher doses of dexamethasone and longer durations of treatment as was historically traditional. More recently, there is growing evidence to suggest that a shorter course and lower doses of dexamethasone may lead to more favorable outcomes.[6] Since this time, our unit has similarly adopted the initial corticosteroid selection of dexamethasone with shorter courses and lower doses in treating early evolving bronchopulmonary dysplasia (BPD) (>7 days of age, <28 days of age).

With regard to the timing of treatment initiation, the subjects receiving dexamethasone were often treated for late-evolving BPD (>1-month postnatal age, <36-weeks postmenstrual age), contributing to the later age at initiation. Later courses of postnatal corticosteroids (PNC) are used to treat late-evolving BPD,[7] but current literature is limited with regard to guidance on treatment for this age group. Data from the National Institutes of Health's Prematurity and Respiratory Outcomes Program demonstrate that dexamethasone is primarily used in this population.[8] A single-center, retrospective study comparing dexamethasone, hydrocortisone, and methylprednisolone administration with the initial mean postnatal age of PNC administration of 27 days suggested that dexamethasone most effectively facilitates extubation[9]; however, lower doses and the duration of dexamethasone were again used in this study population. Data in treating late-evolving BPD remain limited, and we believe more studies are needed to appreciate the appropriate corticosteroid course for these infants. Given that dexamethasone, particularly at high doses and prolonged durations, may be harmful to the developing brain, we caution clinicians to weigh its benefits versus risks and use judicious management with regard to its dose, duration, and timing, especially in higher-risk patients with contracted or repeat courses of PNC.

Jieun David, MD

Article Information

Affiliations. Department of Pediatrics, Rush University Medical Center, Chicago, IL.

Correspondence. Jieun David, MD; jdavid2@northshore.org

Disclosure. The author declares no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria. The author attests to meeting the four criteria recommended by the ICMJE for authorship of this manuscript.

Submitted. May 16, 2025

Accepted. May 16, 2025

References

1. David J, Foschi C, Greene MM, Click K, Hunsinger B, Patra K. Neurodevelopmental outcome at 20 months corrected age in extremely preterm infants after exposure to dexamethasone and hydrocortisone in the NICU. *J Pediatr Pharmacol Ther*. 2025;30(1):84–92.
2. Garfinkle J, Khairy M, Simard MN, et al.; Canadian Neonatal Network and Canadian Neonatal Follow-Up Network Investigators. Corrected age at Bayley assessment and developmental delay in extreme preterms. *Pediatrics*. 2024;153(2):e2023063654.
3. O'Shea TM, Kothadia JM, Klinepeter KL, et al. Randomized placebo-controlled trial of a 42-day tapering course of dexamethasone to reduce the duration of ventilator dependency in very low birth weight infants: outcome of study participants at 1-year adjusted age. *Pediatrics*. 1999;104(1 Pt 1):15–21.
4. O'Shea TM, Washburn LK, Nixon PA, Goldstein DJ. Follow-up of a randomized, placebo-controlled trial of dexamethasone to decrease the duration of ventilator dependency in very low birth weight infants: neurodevelopmental outcomes at 4 to 11 years of age. *Pediatrics*. 2007;120(3):594–602.
5. Onland W, De Jaegere AP, Offringa M, van Kaam AH. Effects of higher versus lower dexamethasone doses on pulmonary and neurodevelopmental sequelae in preterm infants at risk for chronic lung disease: a meta-analysis. *Pediatrics*. 2008 Jul;122(1):92–101.
6. Doyle LW, Cheong JL, Ehrenkranz RA, Halliday HL. Late (> 7 days) systemic postnatal corticosteroids for prevention of bronchopulmonary dysplasia in preterm infants. *Cochrane Database Syst Rev*. 2017;10(10):CD001145.
7. Htun ZT, Schulz EV, Desai RK, et al. Postnatal steroid management in preterm infants with evolving bronchopulmonary dysplasia. *J Perinatol*. 2021;41(8): 1783–1796.
8. Greenberg JM, Poindexter BB, Shaw PA, et al. Respiratory medication use in extremely premature (<29 weeks) infants during initial NICU hospitalization: results from the prematurity and respiratory outcomes program. *Pediatr Pulmonol*. 2020;55(2):360–368.
9. Nath S, Reynolds AM, Lakshminrusimha S, et al. Retrospective analysis of short-term respiratory outcomes of three different steroids used in clinical practice in intubated preterm infants. *Am J Perinatol*. 2020;37(14): 1425–1431.