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Stopping the Swinging Pendulum of Postnatal Corticosteroid Use

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In this issue of *The Journal*, Stark et al¹ remind us of an unsolved dilemma in neonatal medicine: Does the use of postnatal corticosteroids to treat or prevent broncho-pulmonary dysplasia (BPD) convey more benefit than harm? The neonatal community's answer to this question has swung like a pendulum violently from side to side: At one extreme, large doses of “prophylactic” steroids were given early in life to very low birthweight infants at varying risk of developing BPD and its sequelae. At the other extreme, physicians virtually stopped using postnatal corticosteroids, even for the indication of weaning a chronically ventilator-dependent preterm infant off respiratory support. Since learning from history may free us from repeating it, we will first place the report by Stark et al¹ in historical perspective.

By 1989, after increasing recognition that BPD was an inflammatory disease, steroid therapy was a logical treatment option. Early randomized trials culminated in wide clinical adoption of dexamethasone to facilitate weaning from mechanical ventilation.^{2–4} For those practicing neonatology in that era, there was a palpable excitement: we finally had a “cure” for BPD. Though largely corrected nowadays, few investigators of common neonatal therapies examined long-term safety at that time.^{5–8} The obvious short-term benefits of steroid therapy induced the first methodological error made by our collective community: viewing the outcome of successful extubation as adequate to introduce a powerful drug into widespread use.

On this ground, 2 practice creeps occurred—of timing and of dosing. The famous “Cummings’ regimen” started steroids during the third week of life.⁹ Neonatologists argued that if later was good, then earlier must be better. The apparent benefit of Cummings’ “industrial” dosing (8.86 mg/kg over 42 days) was escalated to a regimen beginning before 12 hours of life with a total dosage of 6.16 mg/kg of dexamethasone over 28 days, with dramatic benefit in early extubation.¹⁰ However, Yeh et al¹¹ later examined survivors at 18 months and found an excess of cerebral palsy (CP) in children exposed to such early, high-dose corticosteroids. Shortly afterward, the trial of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Neonatal Research Network

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(NRN), testing early low-dose dexamethasone (0.89 mg/kg over 10 days and started within 12 hours), was halted early after the Data and Safety Monitoring Board identified excess gastrointestinal perforations in the dexamethasone arm.¹² Soon thereafter, Halliday and Ehrenkranz¹³ summarized 21 trials of early steroids in the Cochrane Reviews on this therapy and pointed out: “The benefits of early postnatal corticosteroid treatment (<96 hours) may not outweigh the known or potential adverse effects of this treatment.” Even more uncertainty existed about later steroid use.^{14,15}

Subsequent comparisons suggested that premature infants exposed to postnatal dexamethasone (mean duration of therapy 28 ± 22 days, median dose 0.25 mg/kg/d) had smaller brain volumes on magnetic resonance imaging than those who had not received steroids.¹⁶ However, observations that BPD itself has deleterious effects on the growing neonatal brain were also beginning to accumulate.^{17,18} A second collective error was made: neonatologists assumed that steroids would lead to an increased rate of CP, regardless of the timing, dosing regimen, and target population.¹⁹

By 2002, collective concern about a possible casual link between steroids and CP culminated in a virtual embargo on postnatal corticosteroids from the joint policy statement of the American Academy of Pediatrics (AAP) and the Canadian Pediatric Society.^{20,21} Steroid use for very low birth-weight infants at risk of or with BPD was limited to “exceptional clinical circumstances.” This was coupled with a call for further study of short- and long-term outcomes of postnatal steroid exposure, but this sage message was mostly lost.²¹ We had committed a third collective error: creating an inimical climate that ultimately prevented rather than enabled the conduct and completion (Dexamethasone: A Randomized Trial (DART) was already ongoing) of the necessary clinical trials.

Rare voices called for a more measured approach.²²⁻²⁴ However, many neonatologists stopped using steroids virtually completely.²⁵ The international DART trial had been designed to evaluate low-dose (0.89 mg/kg over 10 days) steroids for infants unable to be extubated by 3 weeks of age and planned to assess developmental outcomes at 18-24 months.^{24,26} Unfortunately, the trial ground to a halt as clinicians rapidly lost equipoise. Doyle et al^{26,27} could only reiterate benefits of the early-stopped DART trial in achieving extubation with dexamethasone but were not powered to comment meaningfully on developmental outcomes. A year later, the Watterberg et al²⁸ trial of early (started within 12-48 hours of birth) hydrocortisone for prevention of BPD was also stopped early for excess gastrointestinal perforations in the steroid arm. This series of events—early stopped trials and embargos on further use of steroids—was both challenged and defended.^{29,30}

The next milestone was the innovative meta-regression by Doyle et al,³¹ which gave us a unifying interpretation of the underlying issues. The **Figure** plots net benefit or net harm (death or CP at 2 years) against baseline BPD event rate (in control groups of infants) in randomized trials then published. An excess risk associated with steroid use when there is a low control group event rate of BPD shifts to a net benefit when started at a higher event rate. Thus, if an infant is only 1 day old but likely to be extubated easily, potential risk outweighs benefit. However, for infants still intubated at 2 weeks, risk:benefit favors

steroids. Updated Cochrane reviews and NICHD network data confirm this interpretation.³²⁻³⁴

With this background, what can we learn from the study by Stark et al? The group from the NICHD Neonatal NRN reports the 18- to 22-month developmental outcomes of children enrolled during 1998-1999 in the early stopped trial of early dexamethasone to prevent death or BPD in extremely low birth weight infants.^{1,28} Although dexamethasone started in the first 24 hours of life failed to reduce the primary outcome of death or BPD, in this small population it also did not cause a measurable change in adverse long-term outcomes.

The sole statistically significant difference in developmental outcomes in the report by Stark et al is a higher rate of abnormal neurologic examination in participants who were randomized to placebo and later treated with open-label corticosteroids (conducted in the pre-AAP statement era), compared with those in the placebo group who were never exposed to steroids. This contamination testifies to clinicians' convictions about steroids. Although this finding could be interpreted as a signal for harm, an alternate explanation is equally likely. High rates of contamination with open-label steroids in the study preclude unbiased comparisons of groups of patients with and without steroid exposure. The subgroup analysis of the placebo group is essentially a cohort study that suffers from significant confounding by indication, without the benefit of randomization. Looking again at the Doyle et al meta-regression, one wonders: Did the placebo/open-label steroid group have a higher baseline risk for BPD and, consequently, a higher baseline risk for abnormal neurologic outcomes³¹?

Although researchers struggled to conduct the appropriate trials, clinicians at the bedside voted with their feet. Lacking other definitive therapies, we continued using steroids, though far less frequently.^{35,36} In 2006, Walsh et al²⁵ examined the NRN and Vermont Oxford Network datasets and reported a declining trend in the use of dexamethasone, presumably in response to the 2002 AAP/Canadian Pediatric Society statement. However, 8% of very low birthweight infants were still treated with postnatal corticosteroids. In 2013, Soll et al³⁷ reported that this 8% rate has remained unchanged and that the smallest infants continue to receive steroids at the highest rates. Studies such as that by Stark et al¹ in *The Journal* this month reassure us that steroids do not universally lead to adverse neurodevelopment, even when given early.

However, we continue to grapple with uncertainty about which infants with BPD are at greatest risk of a poor neuro-developmental outcome and may benefit from corticosteroids and about which infants stand to suffer risk without benefit. There is only one way to stop the pendulum rationally: large, well-designed, placebo-controlled clinical trials. Given all the existing data, most would now agree that early postnatal corticosteroids are harmful and should not be further tested. Rather, we should consider trials for infants unable to be extubated by 14-21 days, who are at significant risk of harm from BPD. Such trials must be large enough to measure the impact of steroids on both pulmonary outcomes and important long-term developmental outcomes. We eagerly anticipate the next installment in this story: the ongoing NRN trial of hydrocortisone for preterm infants with established ventilator dependency, which is appropriately powered for 22- to 26-month developmental outcomes, along with the STOP-BPD trial in the Netherlands and Belgium

(www.neonatologystudies.nl/stopbpd) and, similarly, the French PREMILOC study (<http://clinicaltrials.gov/show/NCT00623740>). Two of these are recruiting infants with established ventilator dependency and are appropriately powered to measure both incidence of BPD at 36 weeks corrected age and developmental outcomes at 2 years. The combined results of these trials may assist the clinician regarding when and what corticosteroid may improve respiratory outcomes (benefit) without risk of adverse neurologic outcomes.

Glossary

AAP	American Academy of Pediatrics
BPD	Bronchopulmonary dysplasia
CP	Cerebral palsy
DART	Dexamethasone: A Randomized Trial
NICHD	<i>Eunice Kennedy Shriver</i> National Institute of Child Health and Human Development
NRN	Neonatal Research Network

References

1. Stark AR, Carlo WA, Vohr BR, Papile LA, Saha S, Bauer CR, et al. Death or neurodevelopmental impairment at 18 to 22 months in a randomized trial of early dexamethasone to prevent death or chronic lung disease in extremely low birth weight infants. *J Pediatr*. 2014; 164:34–9. [PubMed: 23992673]
2. Avery GB, Fletcher AB, Kaplan M, Brudno DS. Controlled trial of dexamethasone in respirator-dependent infants with bronchopulmonary dysplasia. *Pediatrics*. 1985; 75:106–11. [PubMed: 3880879]
3. 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. [PubMed: 4561296]
4. Mammel MC, Green TP, Johnson DE, Thompson TR. Controlled trial of dexamethasone therapy in infants with bronchopulmonary dysplasia. *Lancet*. 1983; 1:1356–8. [PubMed: 6134136]
5. Zhang B, Schmidt B. Do we measure the right end points? A systematic review of primary outcomes in recent neonatal randomized clinical trials. *J Pediatr*. 2001; 138:76–80. [PubMed: 11148516]
6. Tarnow-Mordi W, Mitra A. Postnatal dexamethasone in preterm infants is potentially lifesaving, but follow up studies are urgently needed. *BMJ*. 1999; 319:1385–6. [PubMed: 10574836]
7. Bhuta T, Ohlsson A. Systematic review and meta-analysis of early post-natal dexamethasone for prevention of chronic lung disease. *Arch Dis Child Fetal Neonatal Ed*. 1998; 79:F26–33. [PubMed: 9797621]
8. Schmidt B, Davis P, Moddemann D, Ohlsson A, Roberts RS, Saigal S, et al. Long-term effects of indomethacin prophylaxis in extremely-low-birth-weight infants. *N Engl J Med*. 2001; 344:1966–72. [PubMed: 11430325]
9. Cummings JJ, D'Eugenio DB, Gross SJ. A controlled trial of dexamethasone in preterm infants at high risk for bronchopulmonary dysplasia. *N Engl J Med*. 1989; 320:1505–10. [PubMed: 2657423]
10. Yeh TF, Lin YJ, Hsieh WS, Lin HC, Lin CH, Chen JY, et al. Early post-natal dexamethasone therapy for the prevention of chronic lung disease in preterm infants with respiratory distress syndrome: a multicenter clinical trial. *Pediatrics*. 1997; 100:E3. [PubMed: 9310536]
11. Yeh TF, Lin YJ, Huang CC, Chen YJ, Lin CH, Lin HC, et al. Early dexamethasone therapy in preterm infants: a follow-up study. *Pediatrics*. 1998; 101:E7. [PubMed: 9565440]

12. Stark AR, Carlo WA, Tyson JE, Papile LA, Wright LL, Shankaran S, et al. Adverse effects of early dexamethasone in extremely-low-birth-weight infants. National Institute of Child Health and Human Development Neonatal Research Network. *N Engl J Med*. 2001; 344:95–101. [PubMed: 11150359]
13. Halliday HL, Ehrenkranz RA. Early postnatal (<96 hours) corticosteroids for preventing chronic lung disease in preterm infants. *Cochrane Database Syst Rev*. 2000;CD001146. [PubMed: 10796252]
14. Halliday HL, Ehrenkranz RA, Doyle LW. Delayed (>3 weeks) postnatal corticosteroids for chronic lung disease in preterm infants. *Cochrane Database Syst Rev*. 2003;CD001145. [PubMed: 12535401]
15. Halliday HL, Ehrenkranz RA, Doyle LW. Moderately early (7-14 days) postnatal corticosteroids for preventing chronic lung disease in preterm infants. *Cochrane Database Syst Rev*. 2003;CD001144. [PubMed: 12535400]
16. Murphy BP, Inder TE, Huppi PS, Warfield S, Zientara GP, Kikinis R, et al. Impaired cerebral cortical gray matter growth after treatment with dexamethasone for neonatal chronic lung disease. *Pediatrics*. 2001; 107:217–21. [PubMed: 11158449]
17. Schmidt B, Asztalos EV, Roberts RS, Robertson CM, Sauve RS, Whitfield MF. Impact of bronchopulmonary dysplasia, brain injury, and severe retinopathy on the outcome of extremely low-birth-weight infants at 18 months: results from the trial of indomethacin prophylaxis in preterms. *JAMA*. 2003; 289:1124–9. [PubMed: 12622582]
18. Walsh MC, Morris BH, Wragge LA, Vohr BR, Poole WK, Tyson JE, et al. Extremely low birthweight neonates with protracted ventilation: mortality and 18-month neurodevelopmental outcomes. *J Pediatr*. 2005; 146:798–804. [PubMed: 15973322]
19. Kirpalani H, Whyte R. Truths, associations, and hypotheses. *J Pediatr*. 2011; 159:359–61. [PubMed: 21679967]
20. Barrington KJ. Hazards of systemic steroids for ventilator-dependent preterm infants: what would a parent want? *CMAJ*. 2001; 165:33–4. [PubMed: 11468952]
21. Postnatal corticosteroids to treat or prevent chronic lung disease in pre-term infants. *Pediatrics*. 2002; 109:330–8. [PubMed: 11826218]
22. Taylor C, Shah PS, Dunn MS. Meta-analysis of postnatal steroid use challenged. *Pediatrics*. 2002; 109:716–7. author reply 716–7. [PubMed: 11927722]
23. Halliday HL. Postnatal steroids: a dilemma for the neonatologist. *Acta Paediatr*. 2001; 90:116–8. [PubMed: 11236036]
24. Doyle L, Davis P, Morley C. Effect of AAP statement regarding postnatal corticosteroids on ongoing and future randomized, controlled trials. *Pediatrics*. 2002; 110:1032–3. author reply 1032–3. [PubMed: 12415053]
25. Walsh MC, Yao Q, Horbar JD, Carpenter JH, Lee SK, Ohlsson A. Changes in the use of postnatal steroids for bronchopulmonary dysplasia in 3 large neonatal networks. *Pediatrics*. 2006; 118:e1328–35. [PubMed: 17079534]
26. Doyle LW, Davis PG, Morley CJ, McPhee A, Carlin JB. Low-dose dexamethasone facilitates extubation among chronically ventilator-dependent infants: a multicenter, international, randomized, controlled trial. *Pediatrics*. 2006; 117:75–83. [PubMed: 16396863]
27. Doyle LW, Davis PG, Morley CJ, McPhee A, Carlin JB. Outcome at 2 years of age of infants from the DART study: a multicenter, international, randomized, controlled trial of low-dose dexamethasone. *Pediatrics*. 2007; 119:716–21. [PubMed: 17403842]
28. 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. [PubMed: 15574629]
29. Roberts RS. Early closure of the Watterberg trial. *Pediatrics*. 2004; 114:1670–1. [PubMed: 15574631]
30. Gordon PV. Weighing statistical certainty against ethical, clinical, and biologic expediency: the contributions of the Watterberg trial tip the scales in the right direction. *Pediatrics*. 2005; 115:1446–7. author reply 7. [PubMed: 15867074]

31. Doyle LW, Halliday HL, Ehrenkranz RA, Davis PG, Sinclair JC. Impact of postnatal systemic corticosteroids on mortality and cerebral palsy in preterm infants: effect modification by risk for chronic lung disease. *Pediatrics*. 2005; 115:655–61. [PubMed: 15741368]
32. Halliday HL, Ehrenkranz RA, Doyle LW. Early (< 8 days) postnatal corticosteroids for preventing chronic lung disease in preterm infants. *Cochrane Database Syst Rev*. 2010:CD001146. [PubMed: 20091516]
33. Halliday HL, Ehrenkranz RA, Doyle LW. Late (>7 days) postnatal corticosteroids for chronic lung disease in preterm infants. *Cochrane Database Syst Rev*. 2009:CD001145. [PubMed: 19160189]
34. Laughon MM, Langer JC, Bose CL, Smith PB, Ambalavanan N, Kennedy KA, et al. Prediction of bronchopulmonary dysplasia by post-natal age in extremely premature infants. *Am J Respir Crit Care Med*. 2011; 183:1715–22. [PubMed: 21471086]
35. Jobe AH. Postnatal corticosteroids for preterm infants—do what we say, not what we do. *N Engl J Med*. 2004; 350:1349–51. [PubMed: 15044647]
36. Schmidt B, Roberts R, Millar D, Kirpalani H. Evidence-based neonatal drug therapy for prevention of bronchopulmonary dysplasia in very-low-birth-weight infants. *Neonatology*. 2008; 93:284–7. [PubMed: 18525211]
37. Soll RF, Edwards EM, Badger GJ, Kenny MJ, Morrow KA, Buzas JS, et al. Obstetric and neonatal care practices for infants 501 to 1500 g from 2000 to 2009. *Pediatrics*. 2013; 132:222–8. [PubMed: 23858426]

Figure.

The relationship between baseline rates of chronic lung disease (CLD) in control groups of infants and the effect of corticosteroids on death or cerebral palsy (CP) in published trials of steroids for treatment or prevention of CPD. CS, corticosteroids; RD, risk difference. Reproduced with permission from *Pediatrics*, Vol. 115, Pages 655-61, © 2005 by the American Academy of Pediatrics.