Postnatal Steroid Use for Bronchopulmonary Dysplasia

MA NeoQIC Respiratory Collaborative Webinar
February 22nd, 2021

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Where the world comes for answers

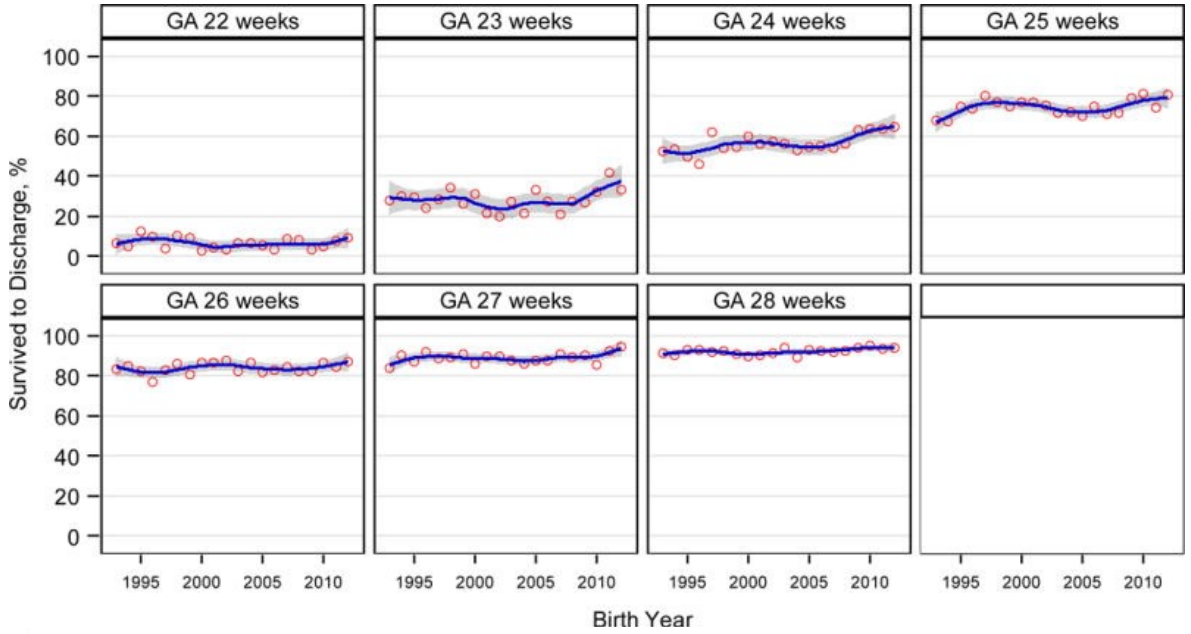
Boston Children's

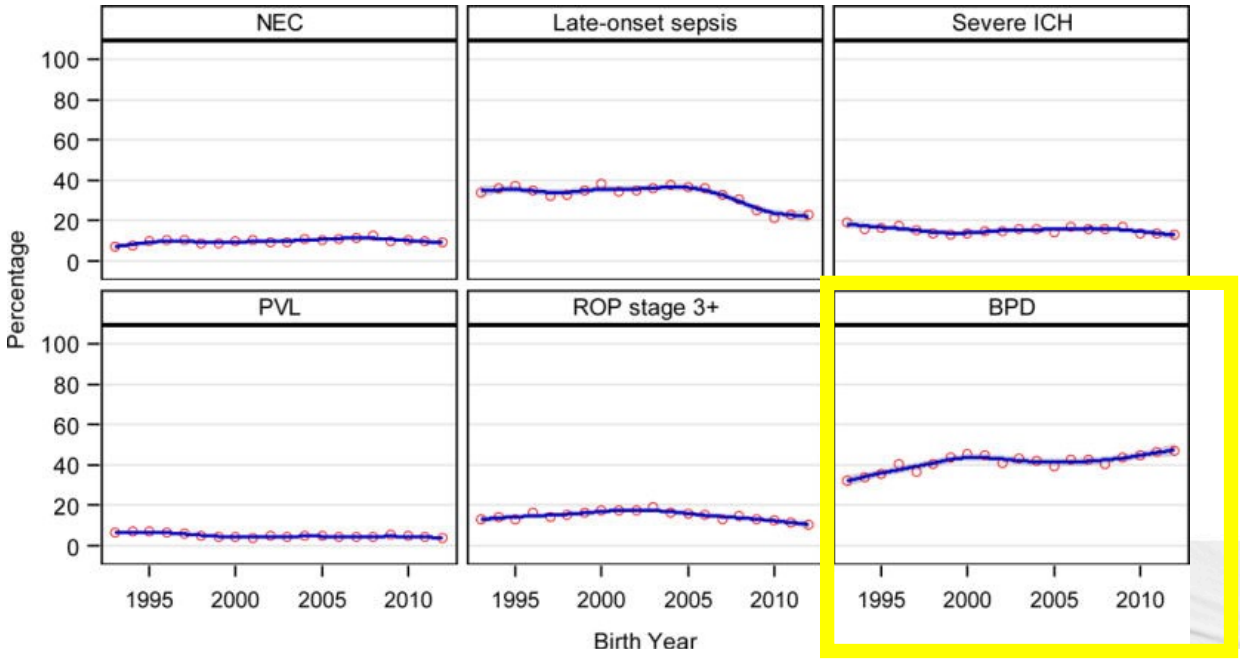
Outline

- BPD and Steroid Review
- Early Steroids
- Steroids for Prevention of BPD
- Rescue Steroids for BPD

Bronchopulmonary Dysplasia

- Major morbidity of extremely preterm infants
- Alveolar simplification, thickened alveolar septae, dysmorphic vascular growth
- BPD associated with life-long respiratory and neurodevelopmental morbidity
- While survival has increased and other morbidities stable or decreased - Rates of BPD have increased





Stoll, B, et al, JAMA, 2015.

Post-natal steroids for BPD

- **Main Mechanism: Suppression of inflammation**
- Other mechanisms: Reduction in capillary leak and reduction in pulmonary edema, Enhanced surfactant production

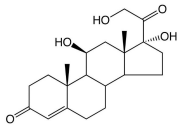
Benefit to Risk Ratio ?

Population, subpopulation ?

Timing ?

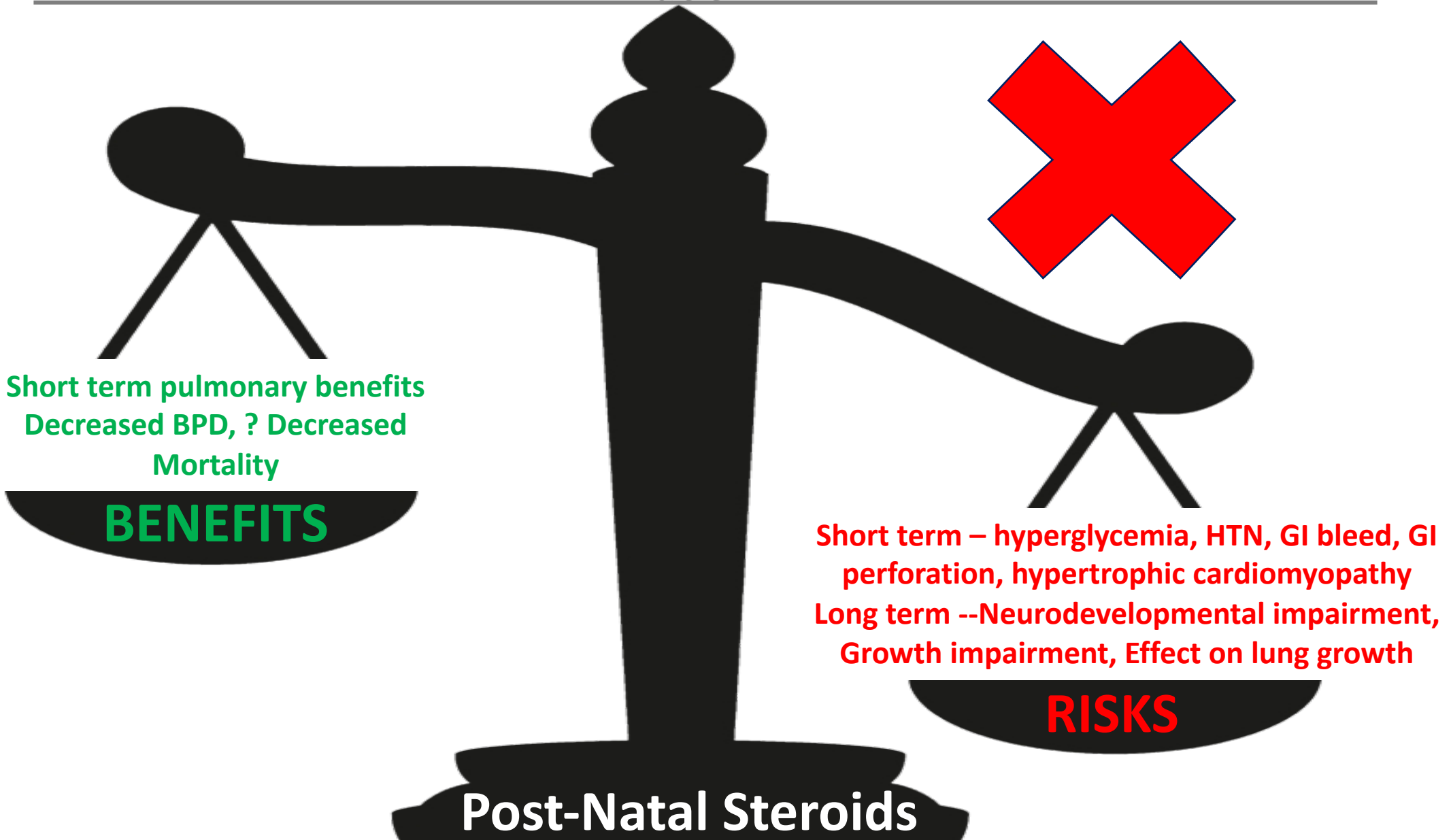
Dosing ?

Administration method ?



Steroid Preparation Option ?

Balance of potential benefits vs risks DOES NOT SUPPORT ROUTINE use

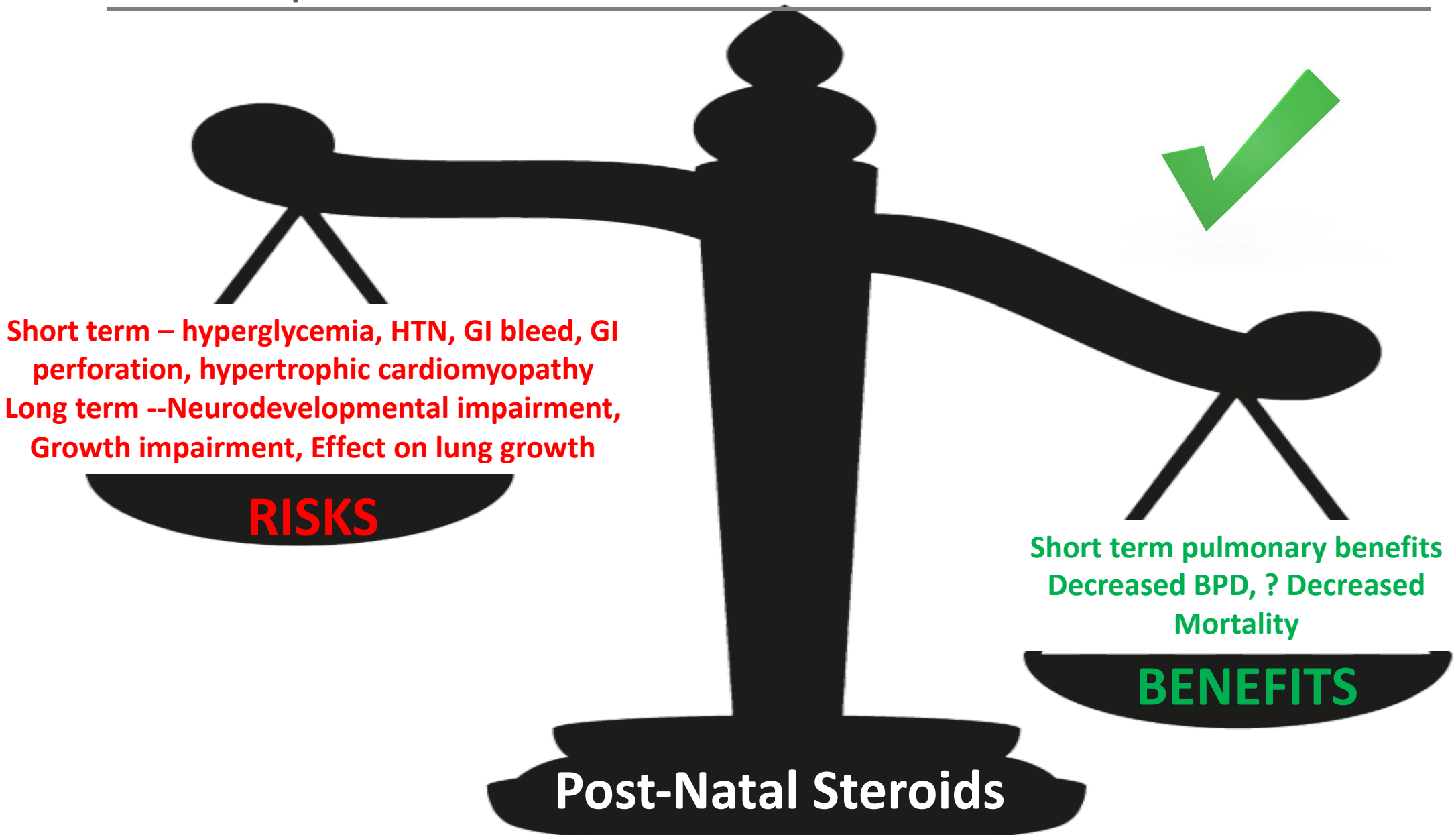


No “one size fits all” approach with post-natal steroids

- **Based on several Cochrane Reviews/Metanalysis**
  - Postnatal corticosteroid therapy **not be used routinely** in preterm infants at risk for BPD (2010 policy by AAP Committee on the Fetus and Newborn and Canadian Paediatric Society)
  - Neurodevelopmental impairment risks not acceptable when broadly applied to all preterm infants

References:
- Doyle L, et al. Early (<8 days) systemic postnatal corticosteroids for prevention of bronchopulmonary dysplasia in preterm infants, Cochrane Database Systemic Review 2017
- Dolye L, et al. Late (>7 days) systemic postnatal corticosteroids for the prevention of bronchopulmonary dysplasia in preterm infants, Cochrane Database Systemic Review 2017

Is there a specific subpopulation and timing where the balance of potential Benefits vs Risks shift to favorable?



Timing of Post-Natal Steroids

Very Early	Early	Rescue Steroids
Day 0-7	Day 14-30	~ PMA 36 weeks

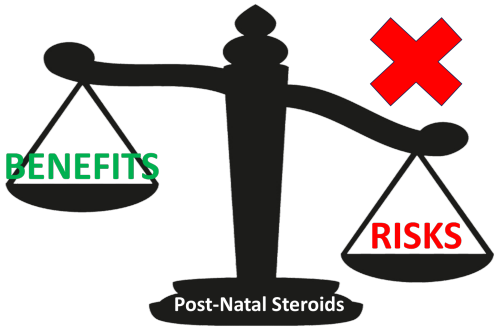
A 6 day old, former 24w5d, AGA infant remains intubated since birth and on high ventilatory settings for your unit and 50% oxygen. The infant is on full feeds; has no IVH; echo shows a small restrictive PDA.

Would you use steroids now for prevention of BPD?

Timing of Post-Natal Steroids

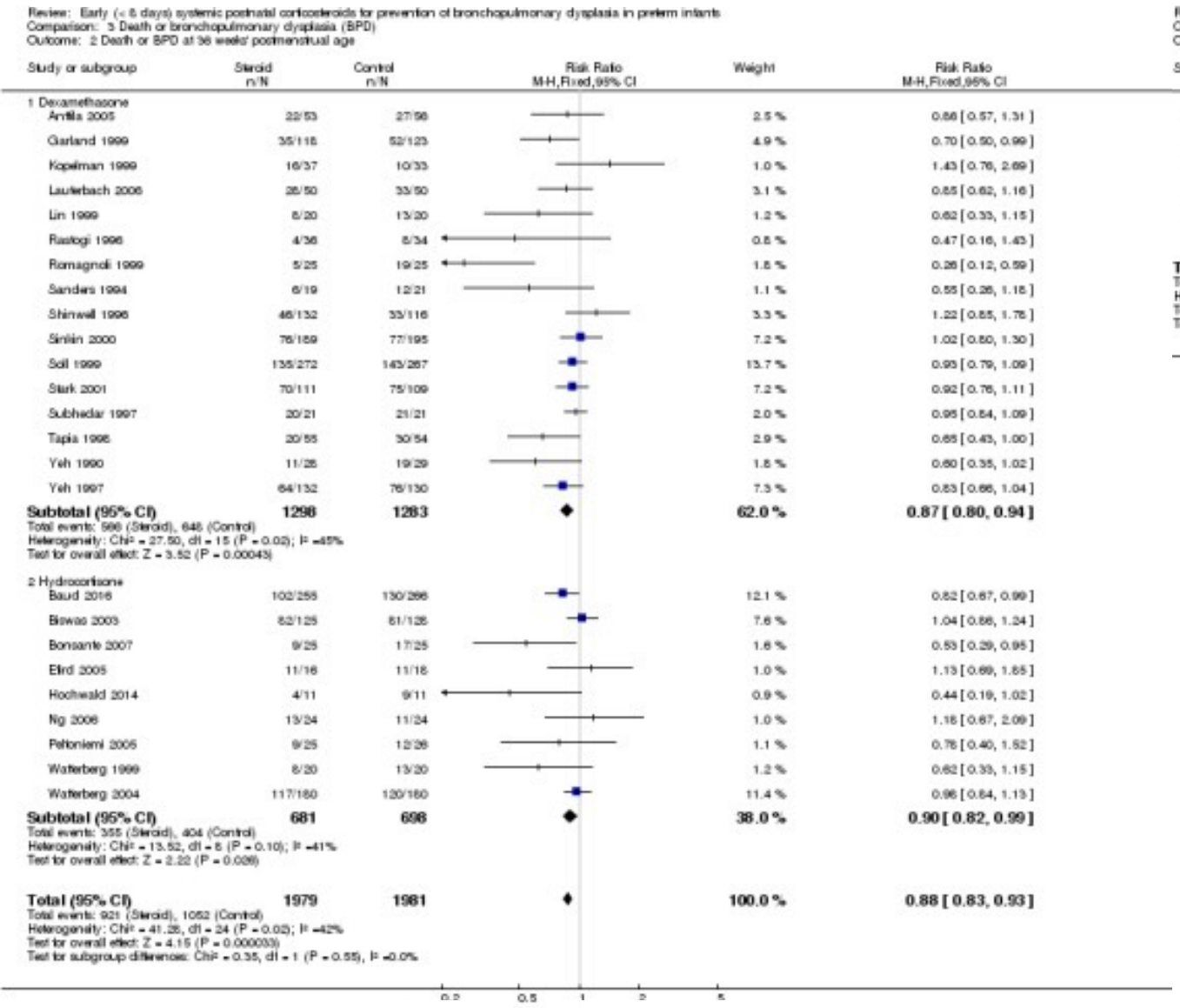
Very Early

Day 0-7



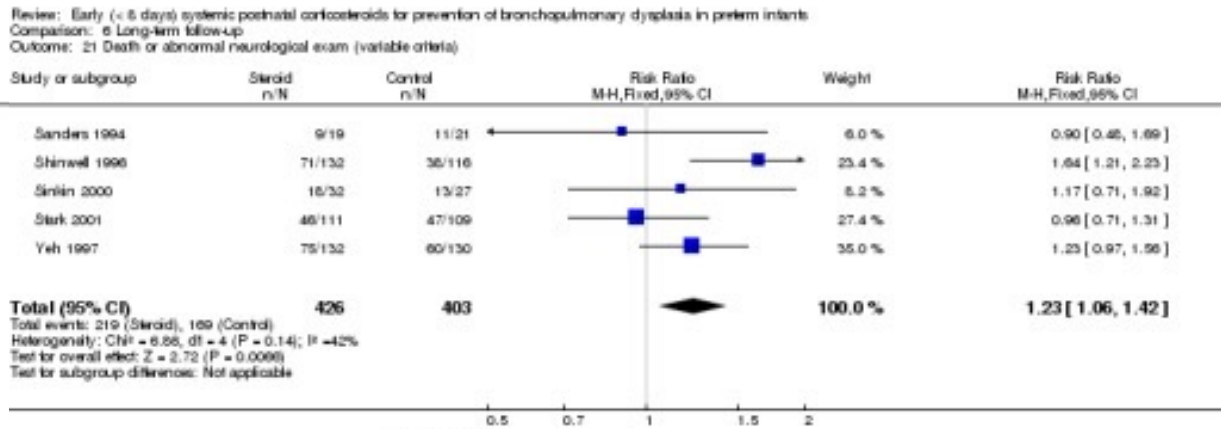
- Very Early corticosteroid therapy (0-7 days) compared with placebo:
  - Respiratory benefits: Earlier extubation; Decreased incidence of BPD both at 28 days and 36 weeks PMA
  - Risks: Increased BP, GI bleed, bowel perf, hyperglycemia, and Increased risk of CP and abnormal neurologic examination at long-term follow-up
  - No differences in mortality or in the proportion of survivors discharged home on oxygen
- In general, at BCH we do **not** recommend administering early corticosteroids therapy (infants < 7 days of age), as this approach would unnecessarily expose a significant number of preterm infants who will not develop BPD to potential adverse effects.

DEATH OR BPD at 36 weeks PMA



Favors steroid Favors control

DEATH OR ABNORMAL NEUROLOGICAL EXAM at Long-term followup



Favors steroid Favors control

Doyle L, et al. Cochrane Database Systemic Review, 2017

A 16 day old, former 24w5d, AGA infant remains intubated on conventional ventilation with 50% oxygen. The infant is on full feeds, has no IVH, and PDA was treated and is closed; the infant is on caffeine.

Would you use steroids now for prevention of BPD?

A 32 day old, former 24w5d, AGA infant on conventional ventilation on 30% oxygen. She has no IVH, a PDA was treated and is closed; the infant is on caffeine and has not been previously treated with steroids.

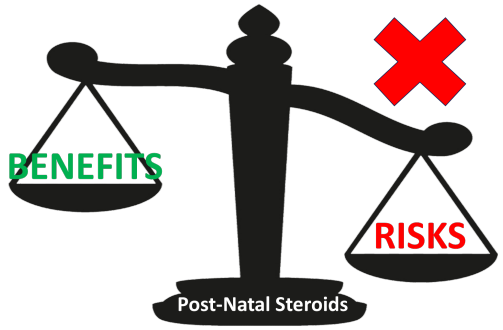
Would you use steroids now for prevention of BPD?

Timing of Post-Natal Steroids

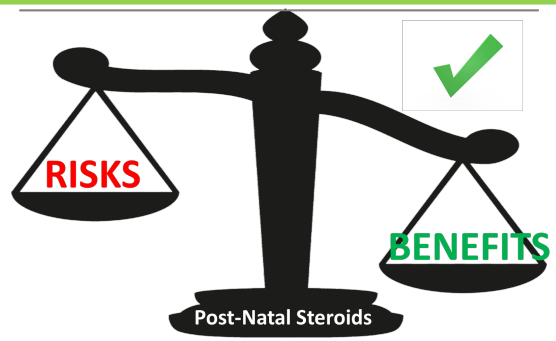
Early

> 7 days

- > 7 days of age in evolving lung disease (those on oxygen, on ventilator, or both)
- Increased survival at 28 days but not at time of discharge
- Lower rates of extubation failure
- Lower rates of BPD at 28 days and 36 weeks PMA
- Lower rates of home oxygen supplementation at discharge
- Trends towards increased CP or abnormal neurologic examination



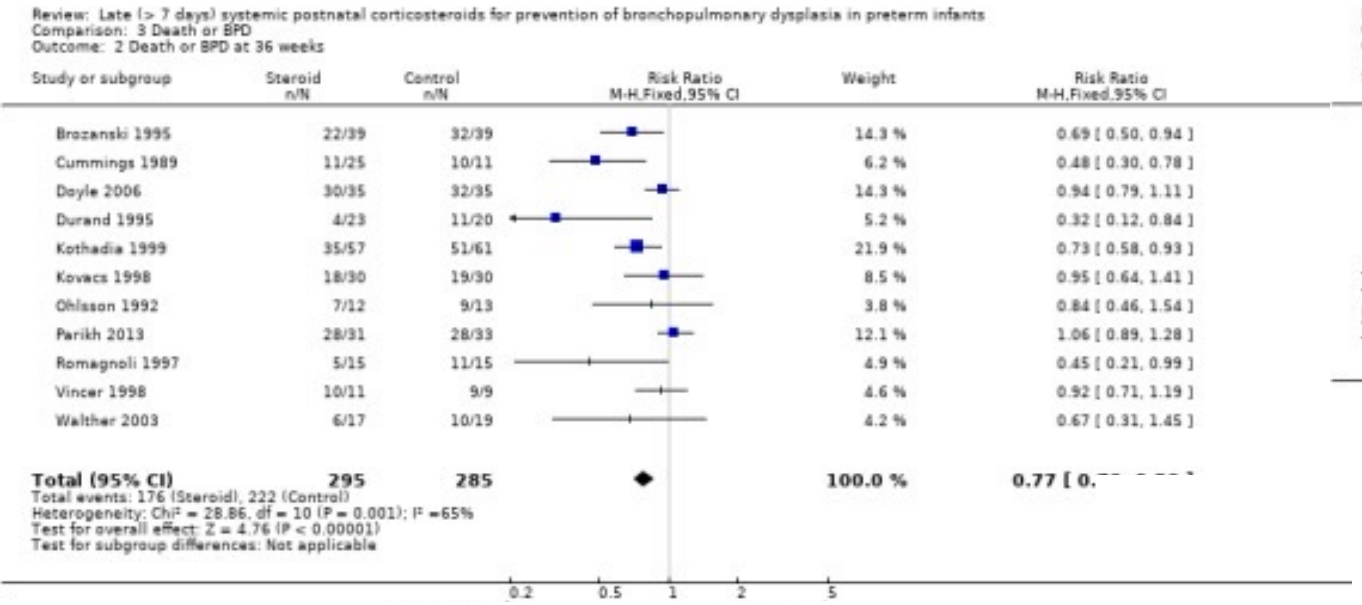
For all premature infants



For a subpopulation at highest risk of BPD

Doyle L, et al. Cochrane Database Systemic Review, 2017

DEATH OR BPD at 36 weeks PMA



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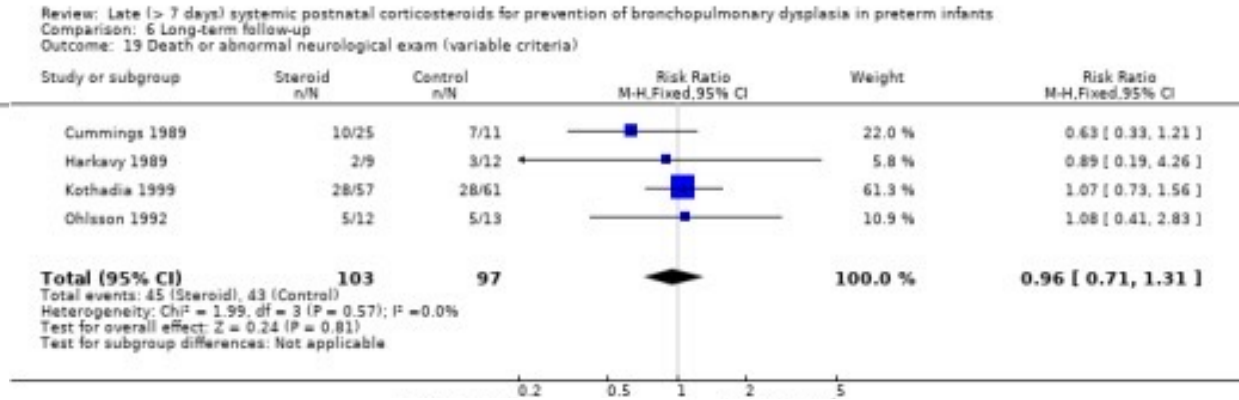
DEATH OR ABNORMAL NEUROLOGICAL EXAM at Long-term followup



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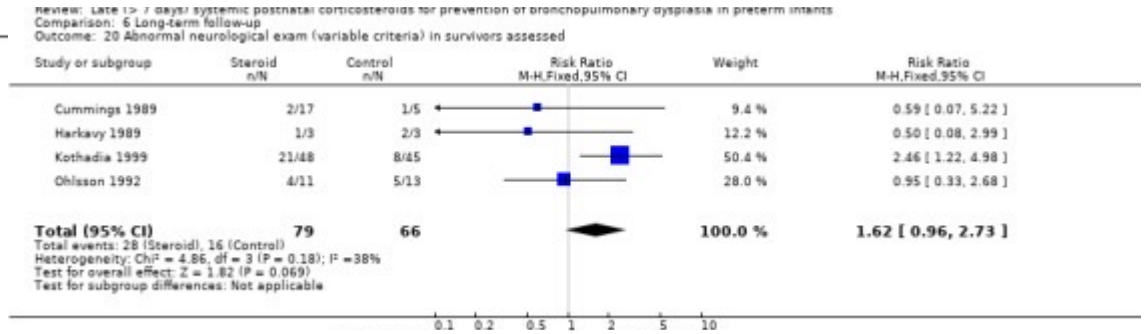
ABNORMAL NEUROLOGICAL EXAM at Long-term followup



Favors steroid Favors control

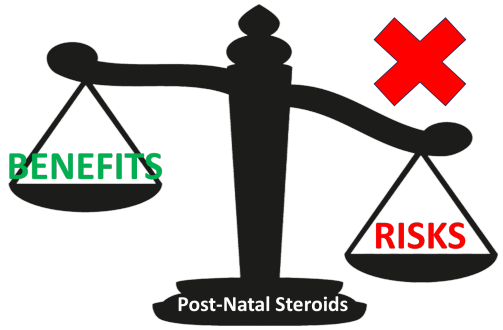
Doyle L, et al. Cochrane Database Systemic Review, 2017

Effect Modification by risk for BPD

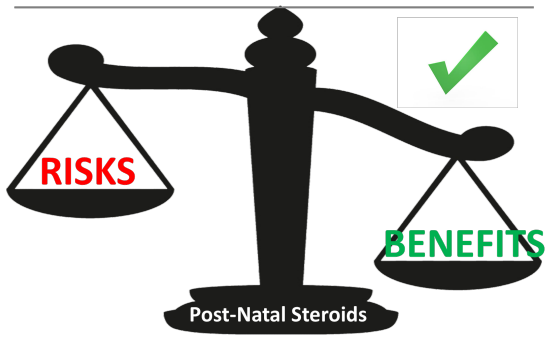
Early

Day 14-30

- Risk vs. Benefit still does not support treatment of all premature infants
- Can risk of BPD shift balance towards benefit?
- If you narrow to a subpopulation at highest risk for BPD what is correct way to choose population and timing?
  - Infants still intubated at 2-4 weeks of age?
  - Use of NICHD BPD risk calculator?



For all premature infants

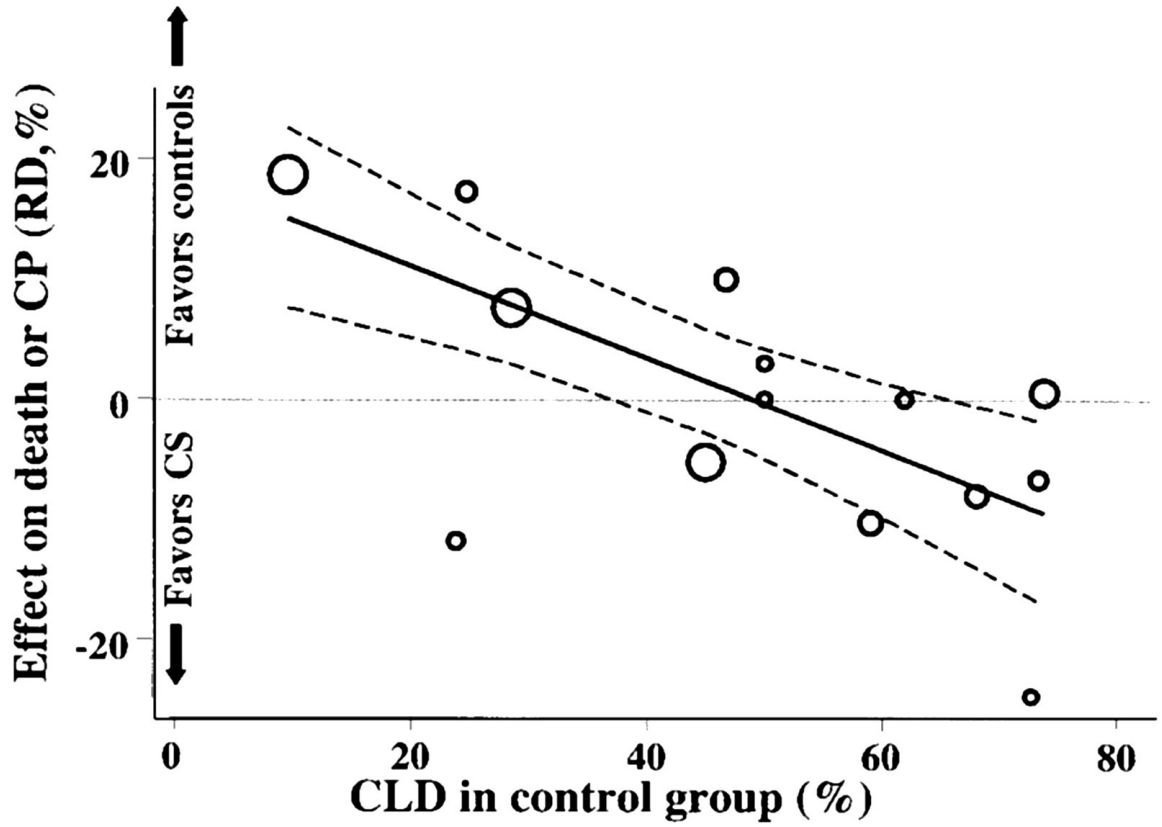


For a subpopulation at highest risk of BPD

Subpopulations – What about babies at very high risk of BPD?

- ? Effect modification by risk for BPD
- 20 RCTs, >1700 infants
- In a meta-regression analysis treatment with corticosteroids:
  - Reduced chance of death or CP for infants with > 65% risk of BPD
  - Increased chance of death or CP for infants with < 35% risk of BPD

- In a trial of 118 infants who were ventilator dependent at 15 and 25 days of age, survival to 1 year greater in the dexamethasone-treated infants vs. placebo (88 versus 74%)



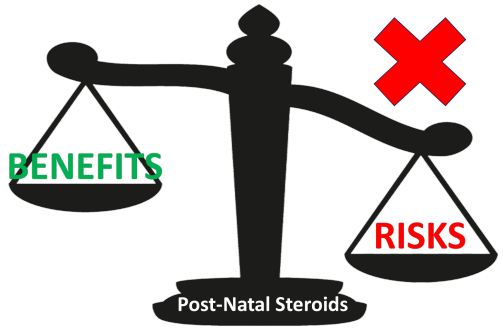
Doyle L, et al. Pediatrics, 2005.

Which steroid preparation?

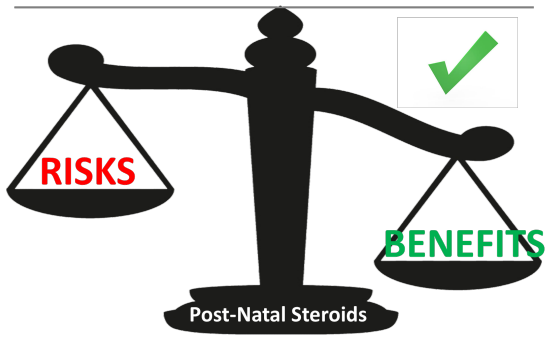
Early

Day 14-30

- Which preparation?
- Dexamethasone → benefit of low-dose dexamethasone for older infants who are ventilator dependent may outweigh risks
- Hydrocortisone → data limited and conflicted. May have decreased neurodevelopmental effects but also unclear efficacy.



For all premature infants



For a subpopulation at highest risk of BPD

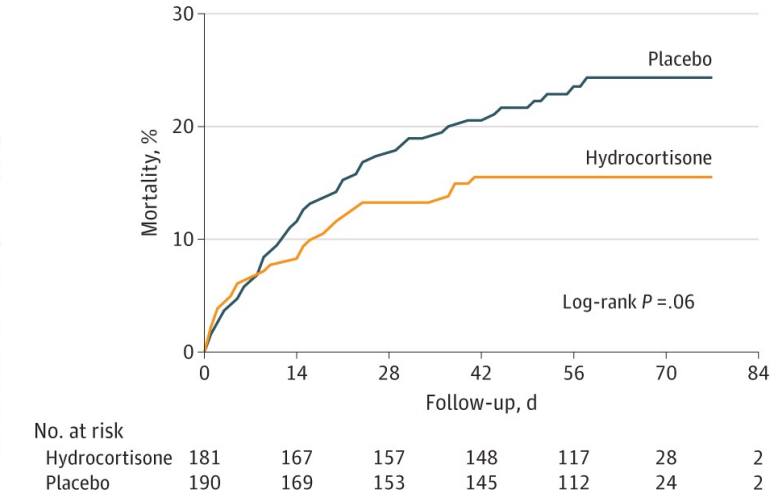
Day 14-30 Post-Natal Steroids

- ? Hydrocortisone have a lower risk than dexamethasone for long-term neurologic sequelae
- ? Efficacy of hydrocortisone for reducing BPD are limited and conflicting
- Onland, et al – hydrocortisone at day 7-14 in high risk infants → showed no difference in BPD or combined BPD or death
- ? Exploratory analysis of decreased mortality at 36 weeks but not at discharge

Does dual mineralcorticoid and glucocorticoid activity lead to less brain toxicity but also less potency to decrease pulmonary inflammation?

Table 2. Effect of Study Treatment on Primary Outcome and Secondary Outcomes From Randomization to Initial Hospital Discharge Using Intention-to-Treat Analysis

Outcomes	No./Total (%)		Difference, % (95% CI)[a]	Odds Ratio or Sub-Hazard Ratio (95% CI)[b]	*P* Value
	Hydrocortisone	Placebo			
Primary Outcome					
Death or bronchopulmonary dysplasia at 36 wk postmenstrual age[c]	128/181 (70.7)	140/190 (73.7)			
Crude analysis			−3.0 (−12.0 to 6.1)	0.86 (0.55-1.36)	
Adjusted analysis[d]			−3.6 (−12.7 to 5.4)	0.87 (0.54-1.38)	.54
Components of Primary Outcome					
Death at 36 wk postmenstrual age	28/181 (15.5)	45/190 (23.7)	−8.2 (−16.2 to −0.1)	0.59 (0.35-0.995)[e]	.048
Bronchopulmonary dysplasia at 36 wk postmenstrual age	100/181 (55.2)	95/190 (50.0)	5.2 (−4.9 to 15.2)	1.24 (0.82-1.86)[e]	.31

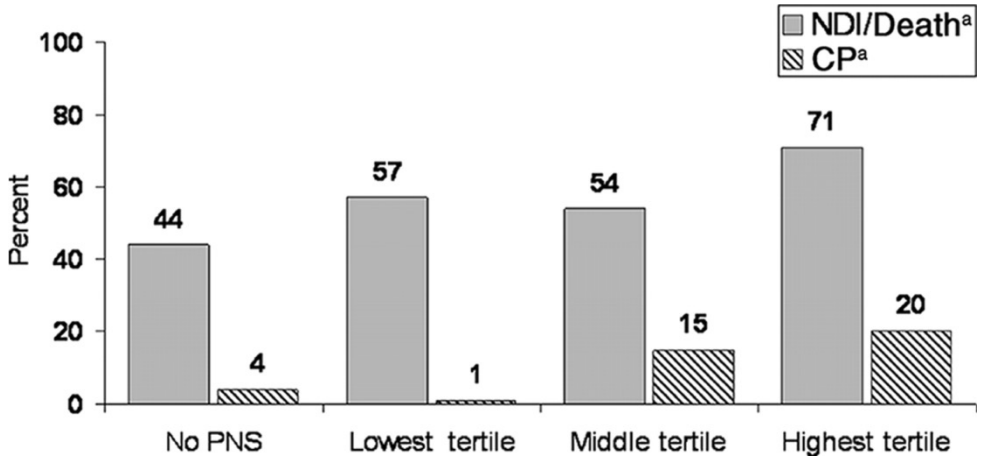


Onland, et al, JAMA, 2019
Doyle L, et al. Pediatrics, 2005

Dosing and duration of post-natal steroids

Lower is better, Shorter course is better

- Increased risk of neurologic impairment with higher doses of corticosteroid therapy or longer duration of therapy
  - Multicenter prospective cohort study: For infants exposed to postnatal dexamethasone an increase of 1 mg/kg in dexamethasone dose was associated with a two-point reduction in the Bayley MDI score, and a 40% increase in risk for CP at 18 to 22 months corrected age
  - In the EPICure study (a large prospective cohort study of preterm infants born <26 weeks gestation), increasing duration of postnatal steroid treatment was associated with poor motor outcomes



Wilson-Costello, et al. Pediatrics, 2009.
Wood, et al. et al. Arch Dis Child Fetal Neonatal Ed, 2005.

Balance of Efficacy and Safety:
Our approach to post-natal steroids for BPD Prevention

- No routine use postnatal systemic corticosteroids to prevent BPD for all extremely preterm infants
- Timing/Subpopulation: Consider systemic corticosteroids to preterm infants at a postnatal age of 14-21 days who remain ventilator-dependent and have a risk of moderate or severe risk of BPD on the NICHD BPD calculator of > 60%
- Steroid type: Low-dose dexamethasone.
- Reassess within 3 days of start for response
- Joint decision-making with family and clinical team

Boston Children's Hospital
Clinical Pathways

Date of Last Update: 9/21/2020
Date of Last CPAC Review:
Care Venue: Critical Care

Bronchopulmonary Dysplasia (BPD) Prevention, Steroids

[A]Avoid concurrent use of steroids and NSAIDs due to increased risk of spontaneous intestinal perforation

[B]High risk for BPD:
- Infant intubated (if recently re-intubated, consider excluding patient if respiratory failure due to other causes (i.e. sepsis))
  AND
- Infant's risk of BPD or Death > 60% (death or severe/moderate BPD combined) using the BPD Calculator

[C]Response to steroid treatment indicated by decreased ventilator support, decreased oxygen support, or extubation

[D]Steroids used for prevention of BPD may help:
- To reduce inflammation
- Promote extubation from ventilator
- To reduce additional barotrauma
- Attempt to intervene prior to fibrosis

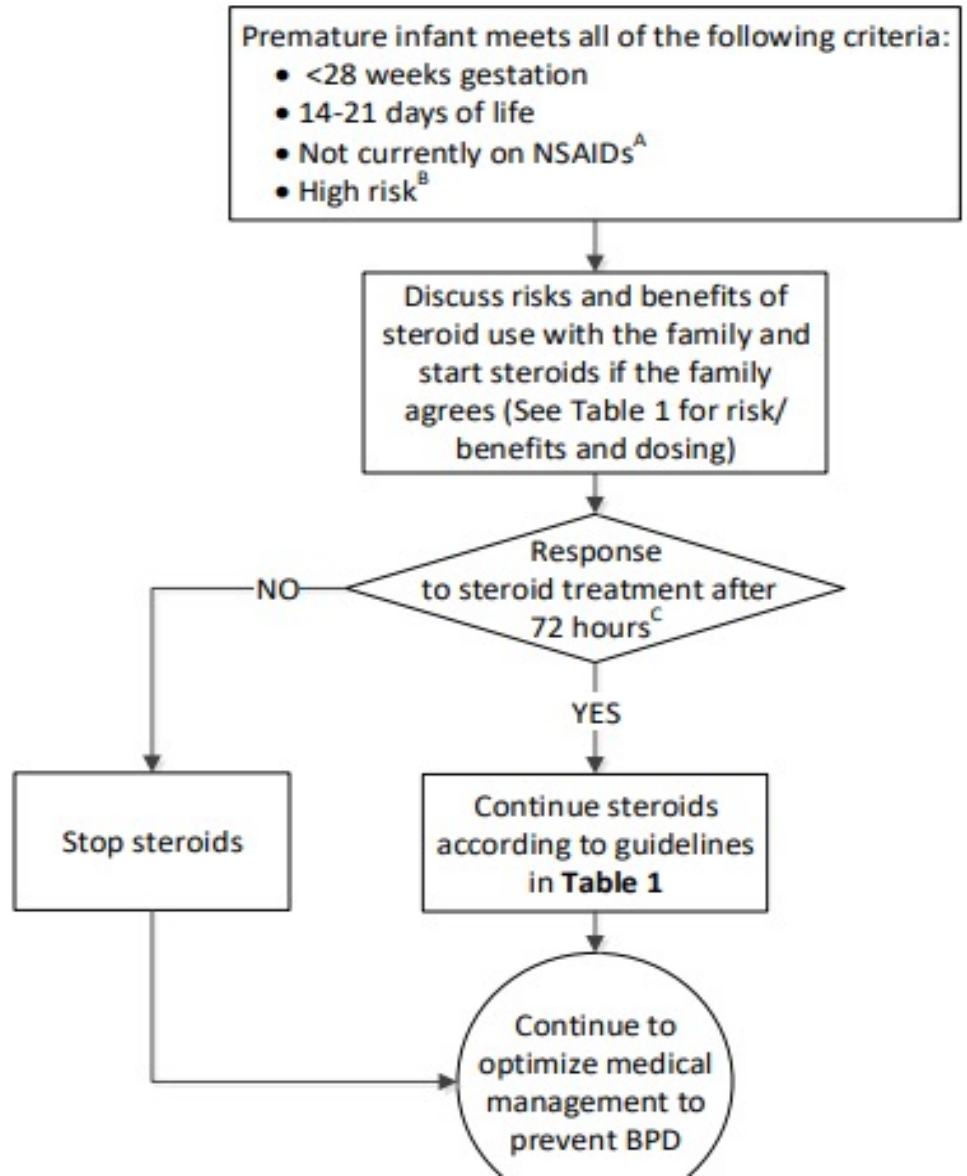


Table 1: Steroid Medication Choice[D]

- Current evidence supports use of low dose dexamethasone (DART protocol[1]) in high risk[B] neonates[2,3]
- Goal to reach anti-inflammatory plasma concentration
- Methylprednisone is an alternative steroid choice for rescue treatment for severe BPD, no clear evidence for use for prevention of BPD.
- Hydrocortisone with mixed data related to efficacy for prevention of BPD[2, 3]
- Consider use of acid-suppressing medications during steroid administration

Steroid	Course Length	Dosing (use NICU steroid powerplan)	Benefits	Risks	Properties
Dexamethasone (enteral/IV)	10 days	• **Day 1-3:** 0.15 mg/kg/dose q24 hours • **Day 4-6:** 0.1 mg/kg/dose q24 hours • **Day 7-8:** 0.05 mg/kg/dose q24 hours • **Day 9-10:** 0.02 mg/kg/dose q24 hours	• Most widely studied • Decreased rates of BPD and improvement in mortality	• Hyperglycemia, hypertension, hypertrophic cardiomyopathy, poor weight gain and CP risk	• Only Glucocorticoid activity, no Mineralcorticoid activity • Duration of action 36-72 hours

[1]Doyle LW, Davis PG, Morley CJ,McPhee A,Carlin JB *; DART Study Investigators. Low-dose dexamethasone facilitates extubation among chronically ventilator-dependent infants: a multicenter, international, randomized, controlled trial. Pediatrics. 2006;117(1):75–83*

[2]Onland W, Cools F, Kroon A, et al. *Effect of Hydrocortisone Therapy Initiated 7 to 14 Days After Birth on Mortality or Bronchopulmonary Dysplasia Among Very Preterm Infants Receiving Mechanical Ventilation: A Randomized Clinical Trial. JAMA. 2019 Jan 29; 321(4):354-363.*

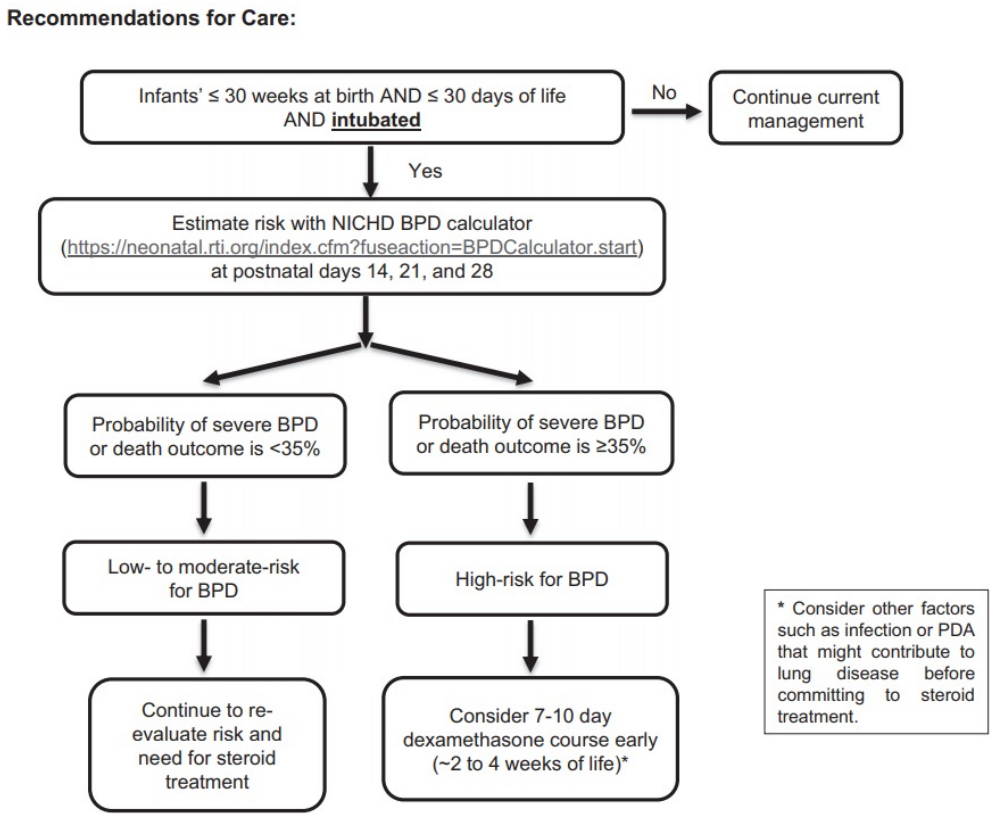
[3] Stark AR, Eichenwald E. *Prevention of bronchopulmonary dysplasia: Postnatal use of corticosteroids.* https://www.uptodate.com/contents/prevention-of-bronchopulmonary-dysplasia-postnatal-use-of-corticosteroids, accessed 05/06/20.

Journal of Perinatology
https://doi.org/10.1038/s41372-020-00862-1

QUALITY IMPROVEMENT ARTICLE

Using quality improvement to implement consensus guidelines for postnatal steroid treatment of preterm infants with developing bronchopulmonary dysplasia

Taylor P. Hansen[1] · Alexandra Oschman[2] · Eugenia K. Pallotto[1,3] · Rebecca Palmer[1] · Darian Younger[1] · Alain Cuna[1,3]



A former 24w5d AGA infant is at 36wk PMA on CPAP and 40% oxygen. The infant is fed by NJ, has no IVH, a PDA was treated and is closed; the infant is on caffeine and Lasix, and has not been previously treated with steroids.

Would you use steroids now?

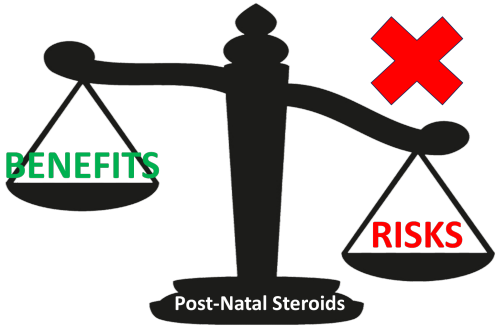
Timing of Post-Natal Steroids

Rescue Steroids

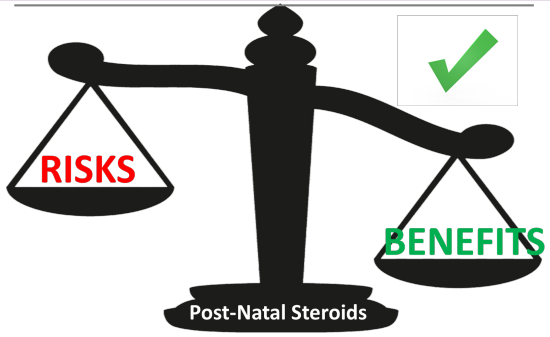
~ PMA 36 weeks

- **The risk benefit calculation is changed for infants with established BPD**
- BPD is a disease of alveolar simplification and fibrosis
- Steroids treat ongoing inflammation (infection, aspiration)…
- …but may hamper further lung growth which is the best treatment for BPD

- Which steroid?
- What course?
- What criteria?



For infants who benefit from ongoing respiratory support



For a infants with extremely severe disease (high risk of mortality or who tracheostomy is not an acceptable option)

Which steroid?

Prednisolone or methylprednisolone frequently used as “rescue”

- Wealth of experience with prednisolone from other pediatric respiratory (and non-respiratory diseases)
- Dexamethasone has much higher potency (but usually dosed accordingly)
  - Dexamethasone 25 times more potent than HC
  - Prednisolone 4-5 times more potent than HC
- Dexamethasone longer half life than prednisolone
- Metabolism of dexamethasone products in CSF may alter brain membrane lipid content

- Studies from childhood acute lymphoblastic leukemia literature comparing high doses of prednisolone and dexamethasone show mixed results, which some suggesting greater neurological long-term safety with prednisolone

Waber, D et al. Cognitive sequalae in children treated for acute lymphoblastic leukemia with dexamethasone or prednisolone. Journal of Pediatric Hematology/Oncology 2000.

Late / Rescue use of Corticosteroids

Few studies address this issue…

For infants with mod-severe BPD still on O2 at 36 weeks (especially those with shorter duration of mechanical ventilation, low PCO2)…steroids work reasonably well to wean off respiratory support

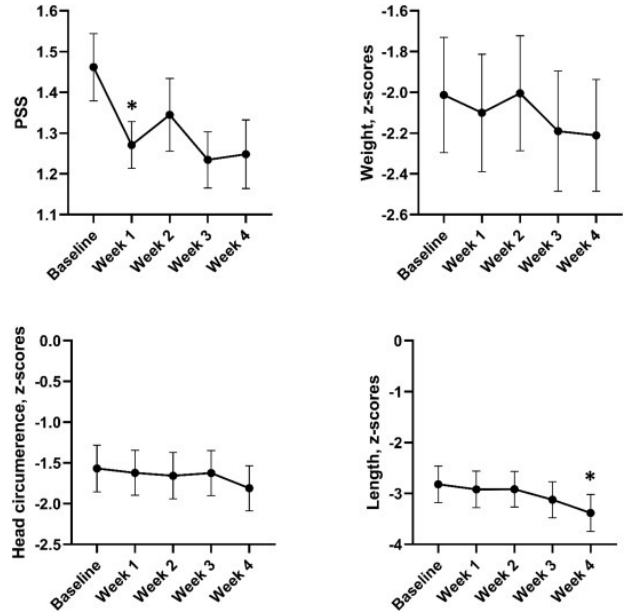
- 385 infants on O2 at 36 weeks PMA, 131 infants received oral prednisolone at mean PMA 38 weeks
  - 131 infants received oral pred – higher rates of previous dexamethasone, inhaled steroids; longer duration of MV and LOS; more likely to be discharged on O2 (37 vs 14%)
  - Prednisolone 1mg/kg BID x 5d, then 1mg/kg daily x 3d, then 1mg/kg every other day x 3 doses
- **82/131 (63%) infants who received oral prednisolone 'responded' to therapy – discharge off O2**
  - No improvement in response to multiple courses
  - Responders: less likely to be on ICS, shorter duration of MV (13d vs 28d), lower PCO2 (50 vs 59), lower bicarb (28 vs 30), lower baseline Pulmonary Acuity Score
    - *PCO2 < 48.5 had maximal predictive ability to wean off O2*
- ***However… this is not an RCT and they may have weaned off anyway***

Bhandari A, et al. Pediatrics 2008.

Late / Rescue use of Corticosteroids

What about kids with more severe disease?

- ***Prolonged steroid courses may 'stabilize' infant but rarely offer additional benefit, come with side effects***
  - 43 infants with severe BPD who received prolonged steroids (>30 days), typically 7-10 days of dexamethasone followed by 30 day prednisolone taper
    - 2mg/kg/d → 1mg/kg/d → 0.5mg/kg/d → 0.5mg/kg QOD weekly weans
  - Improved pulmonary severity score after one week of therapy by 0.2, improvement in FiO2 (0.54 to 0.42)
    - No change in resp support
  - Also... a decrease in linear growth (decrease in z-score by 0.6), 30% osteopenia, 16% HTN, 14% sepsis



Linafelter A., et al. Early Human Dev 2019

Before initiating treatment with steroids, what type of communication do you have with the infant's parents?

Long term effects

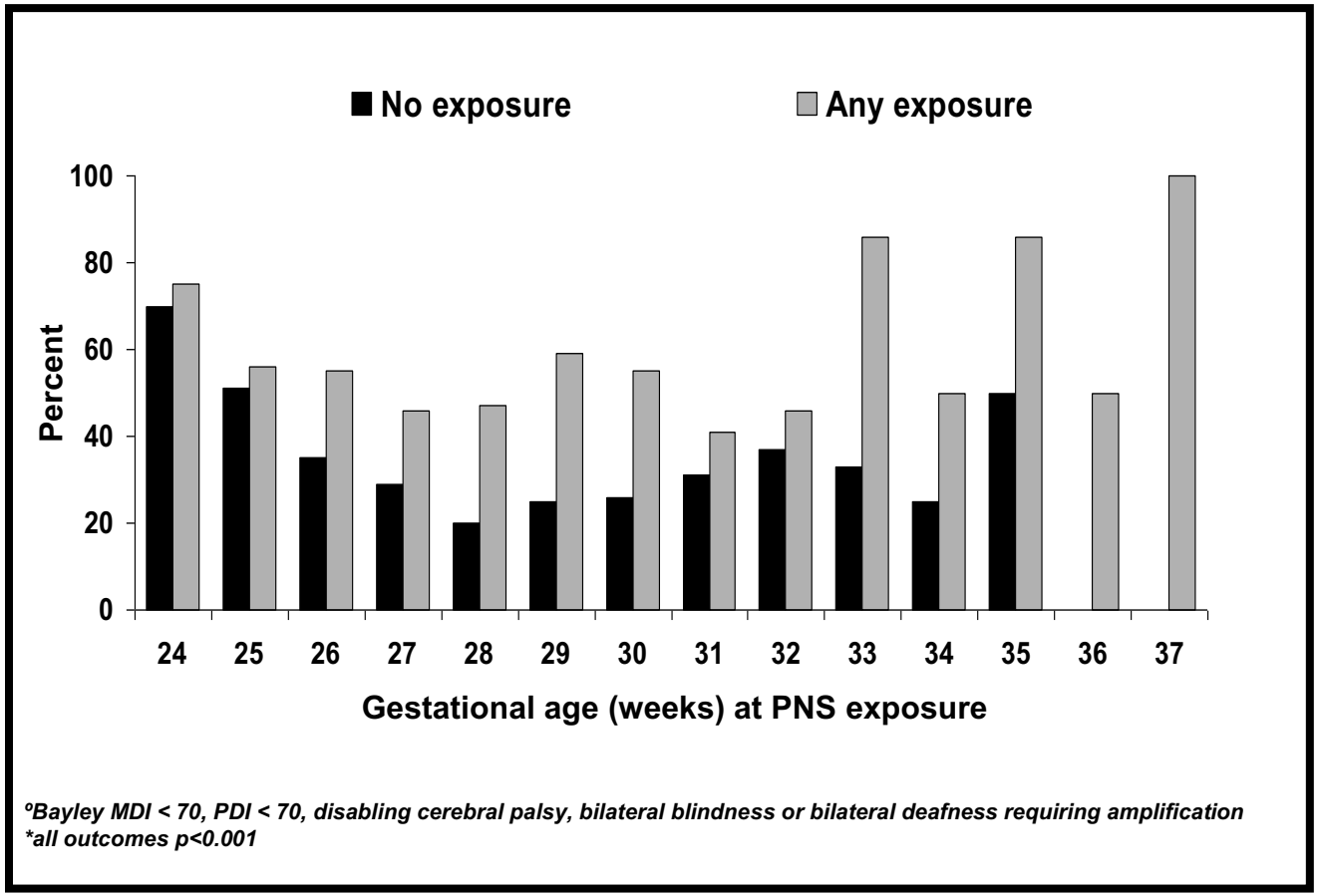
Potential concerns

- Neurodevelopmental impairment
- Compromised lung growth
- Osteopenia
- Linear growth
- Hypertension
- Cardiac remodeling (including outflow tract obstruction)
- Adrenal insufficiency

Harris C et al., PLoS One 2018

Long term effects

Neurodevelopmental Impairment Rates by Postmenstrual Age at PNS Exposure



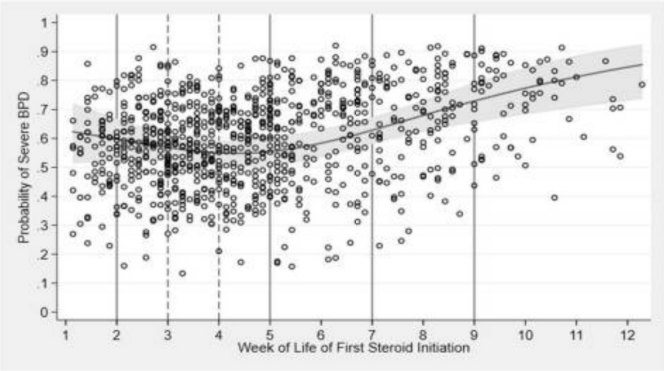
ºBayley MDI < 70, PDI < 70, disabling cerebral palsy, bilateral blindness or bilateral deafness requiring amplification
**all outcomes p<0.001*

Harmon et al., J Perinatology 2020

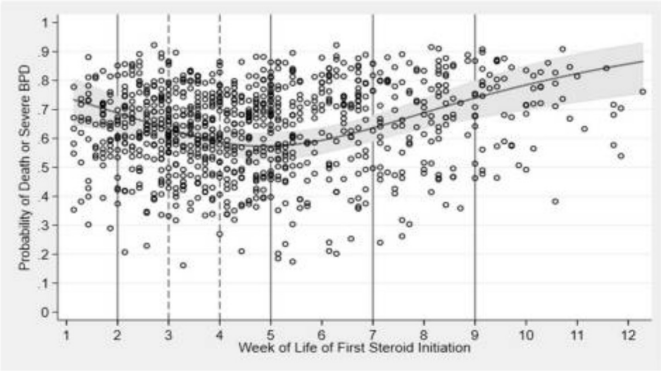
Long term effects

Neurodevelopmental Outcomes based on age of steroid initiation (NRN)

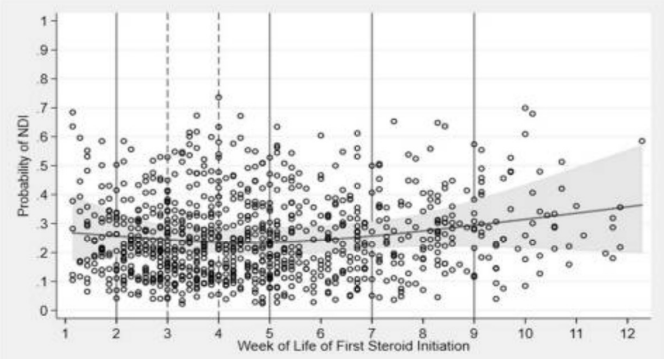
A. Severe BPD among survivors to 36 weeks PMA



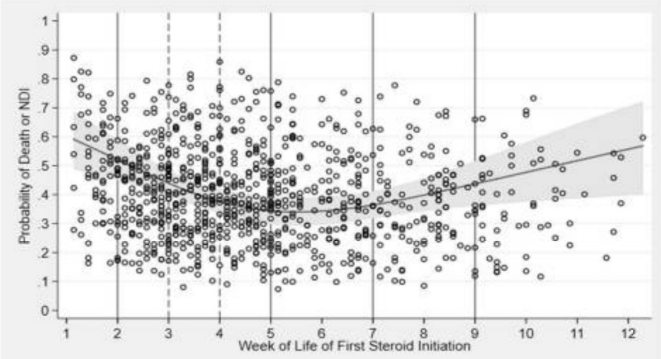
B. Death prior to 36 weeks PMA or severe BPD



C. NDI among survivors at follow-up



D. Death prior to follow-up or NDI



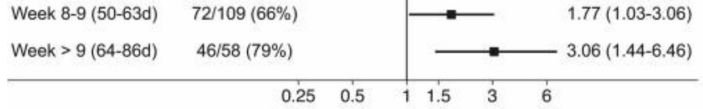
Harmon et al., J Perinatology 2020

Long term effects

Neurodevelopmental Outcomes based on age of steroid initiation (NRN)

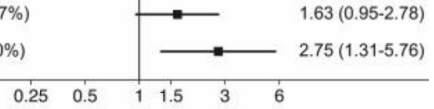
A: Severe BPD among survivors to 36 weeks PMA

Age at Steroid Initiation	Unadjusted Outcome Rates n/N (%)	Adjusted OR 95% CI	Adjusted OR 95% CI
Week 2 (8-14d)	34/58 (59%)		1.15 (0.60-2.19)
Week 3 (15-21d)	84/132 (64%)		1.43 (0.87-2.34)
Week 4 (22-28d)	88/165 (53%)		Reference
Week 5 (29-35d)	83/148 (56%)		1.13 (0.70-1.81)
Week 6-7 (36-49d)	104/181 (57%)		1.14 (0.72-1.81)
Week 8-9 (50-63d)	72/109 (66%)		1.77 (1.03-3.06)
Week > 9 (64-86d)	46/58 (79%)		3.06 (1.44-6.46)



B: Death prior to 36 weeks PMA or severe BPD

Age at Steroid Initiation	Unadjusted Outcome Rates n/N (%)	Adjusted OR 95% CI	Adjusted OR 95% CI
Week 2 (8-14d)	54/78 (69%)		1.68 (0.92-3.07)
Week 3 (15-21d)	115/163 (71%)		1.68 (1.04-2.70)
Week 4 (22-28d)	99/176 (56%)		Reference
Week 5 (29-35d)	95/160 (59%)		1.19 (0.75-1.88)
Week 6-7 (36-49d)	111/188 (59%)		1.09 (0.70-1.72)
Week 8-9 (50-63d)	76/113 (67%)		1.63 (0.95-2.78)
Week > 9 (64-86d)	47/59 (80%)		2.75 (1.31-5.76)



C: NDI among survivors to follow-up

Age at Steroid Initiation	Unadjusted Outcome Rates n/N (%)	Adjusted OR 95% CI	Adjusted OR 95% CI
Week 2 (8-14d)	15/41 (37%)		1.63 (0.72-3.70)
Week 3 (15-21d)	20/104 (19%)		0.88 (0.44-1.74)
Week 4 (22-28d)	29/131 (22%)		Reference
Week 5 (29-35d)	26/117 (22%)		1.18 (0.62-2.26)
Week 6-7 (36-49d)	38/126 (30%)		1.89 (1.02-3.51)
Week 8-9 (50-63d)	25/91 (27%)		1.71 (0.86-3.40)
Week > 9 (64-86d)	9/39 (23%)		1.22 (0.48-3.10)

D: Death prior to follow-up or NDI

Age at Steroid Initiation	Unadjusted Outcome Rates n/N (%)	Adjusted OR 95% CI	Adjusted OR 95% CI
Week 2 (8-14d)	43/69 (62%)		2.64 (1.39-4.99)
Week 3 (15-21d)	63/147 (43%)		1.42 (0.86-2.33)
Week 4 (22-28d)	58/160 (36%)		Reference
Week 5 (29-35d)	48/139 (35%)		1.02 (0.61-1.70)
Week 6-7 (36-49d)	65/153 (42%)		1.44 (0.88-2.36)
Week 8-9 (50-63d)	37/103 (36%)		1.20 (0.68-2.12)
Week > 9 (64-86d)	21/51 (41%)		1.38 (0.69-2.78)

Harmon et al., J Perinatology 2020

Long term effects

Concerns for Lung Development / Growth

- Analysis of RCT data from UK Oscillation Study
  - 179 infants with lung function measured at 11-14 years
    - 50 received dexamethasone postnatally
  - Lower FEV1, FVC, FEV1/FVC ratio, FEF 25-75 (obstruction)
  - Higher Residual volume (air trapping…like COPD)
  - Dose response to number of doses of corticosteroid
- Analysis of BCH Preterm Lung Registry data
  - Postnatal steroid exposure associated with **lower growth in FVC (less catch up)** after controlling for neonatal characteristics

Harris C et al., PLoS One 2018

Long term effects

Adrenal insufficiency

- Very little data on this, but we are finding many infants with long-term or repeated steroid exposure have secondary adrenal insufficiency even after NICU discharge
- Early hydrocortisone trials were designed on the principle of prophylaxis against relative adrenal insufficiency in early preterm infants
- Normal cortisol levels not well defined in preterm population

- BPD Clinic QI initiative
  - AM Cortisol level in infants exposed to multiple courses of steroids, within 30 days of NICU discharge, or prolonged (>3 week) taper
  - If < 10 µg/dL, refer to endocrine for ACTH axis testing and prescribe emergency steroids

BCH Guideline for Rescue Corticosteroids

The use of systemic steroids should be reserved for **exceptional clinical circumstances** (i.e. when an infant is on maximal ventilatory support at high risk for mortality), or when the child has **Severe BPD and alternative treatment choices** (tracheotomy, transfer to rehabilitation facility) **are less acceptable** than the potential side effect profile of steroids.

Definition of severe BPD:

1. Approaching EDC and unable to wean off of vent and therefore considering tracheotomy.
2. Past EDC and unable to wean off of NCO2 > 1L/min flow and therefore unable to discharge home.

Regardless of whether indicated for prevention or rescue therapy, if steroids are used, the following are recommended:

1. Parents should be fully informed about the known short- and long-term risks and agree to treatment with corticosteroids. While a formal consent is not required, a note documenting the discussion should be written in the patient's chart.
2. Other medical management should already be optimized.
3. If a patient does not show a response, the use of steroids should be discontinued after 72 hours.

Inhaled Steroids

Role in prevention and treatment of BPD

- **Early administration** of inhaled corticosteroids has not been shown to reduce rates of BPD (on their own)
  - May have lower risk of composite BPD + death
  - However, other studies have suggested slight increase in mortality (RR 1.4 adjusted for GA)
  - No suggested benefit when given after 7 days of life

Shah et al, Cochrane 2017
Onland et al, Cochrane 2017
Bassler et al, NEJM 2018

- **Intratracheal administration of budesonide + surfactant** may improve BPD+death (RR 0.6), lung inflammation (lower interleukin levels) without increasing mortality
  - No increase in NDI at 18-24 mo
  - Budesonide has extremely high glucocorticoid receptor affinity (~15 times that of prednisolone)

Yeh et al, AJRCCM 2016
Zheng et al, Pedi Pulm 2019

- **Use in established BPD** – frequently used, very little evidence
  - Two small underpowered RCTs
  - Two cross-over RCTs, reporting slight improvements in symptoms and FEV1

Yuskel et al, Thorax 1992

Summary

Postnatal Steroids to Prevent or Treat BPD

- Steroids treat inflammation, which is thought to play a key role in pathogenesis of BPD
- Evidence DOES NOT support ROUTINE use in prevention or treatment
- There may be a role for steroids in infants >14d who are at highest risk of developing BPD
- Despite the fact that steroids for BPD prevention is well studied, because of heterogenous results, differences in design, the optimal type and course of steroid remains unclear, though lower dosing is probably better
- Rescue steroids for treatment of established BPD is poorly studied; may have a role in improving oxygenation but best reserved for specific cases
- Multiple side effects need to be considered including neurodevelopmental outcomes, lung development, growth, and adrenal insufficiency; families should be informed about these risks