

Hydrocortisone

- Relative adrenal insufficiency
- Mechanisms of action:
 - Improves response to catecholamines
 - Decreases catecholamine metabolism
 - Upregulates angiotensin receptors
- Primary historical concerns:
 - Developmental outcomes
 - Combined with indomethacin
- Wide range of dosing used

Scott and Watterberg. Ped Res. 1994; Aoki, et al. Int J Environ Res Public Health. 2022. UNIVERSITY OF NEBRASKA MEDICAL CENTER | CHILDREN'S NEBRASKA

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Hydrocortisone

D: Initial Hydrocortisone Dose by Site

ELBW infants, 1 mg/kg \approx 10 mg/m²

Peebles, et al. J Perinatol. 2022. UNIVERSITY OF NEBRASKA MEDICAL CENTER | CHILDREN'S NEBRASKA

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Newborns are not just small children!

What we're actually giving

	Body Weight (kg)	Surface Area (m ²)	Ratio (cm ² /kg)
Adult	70	1.73	250
Premature infant	1.5	0.13	870
Very premature infant	0.5	0.07	1400

	Ht (cm)	Wt (kg)	BSA (m ²)	Dose (mg/m ²)
NB 27 wk	34.5	0.92	0.09	3.6 mg
TEA	47.4	2.53	0.18	7.2 mg
5 months	51	4.86	0.26	10.4 mg
10 years	140	34	1.16	34 mg

What endo thinks we're giving

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Conversions

COMMENTARIES | JANUARY 01 1959
BODY SURFACE AS A BASIS FOR DOSAGE

GILBERT S. FOMBER
 Pediatrics (1959) 23 (1): 3-5.
<https://doi.org/10.1542/pech.23.1.3>

"It becomes difficult to construct postulates relating their action to cutaneous size. Very few drugs are excreted in appreciable amounts through the skin..."

"The objection is that the use of the rule tends to endow the surface of the body with properties and functions which it may well not possess.

"Should the pediatrician bow once more to expediency or insist that each new advance in the field be based on a sound scientific foundation and acceptable theory?"

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Pubmed

Neonatal Hydrocortisone Articles Indexed in PubMed

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Hydrocortisone Dosing for Hypotension in Newborn Infants: Less Is More

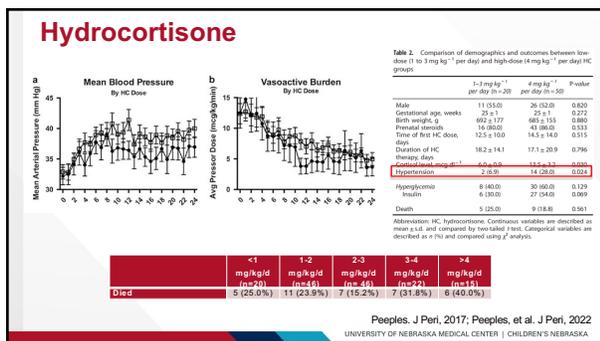
Krist L. Watterberg, MD

Less is more... unless it's coffee

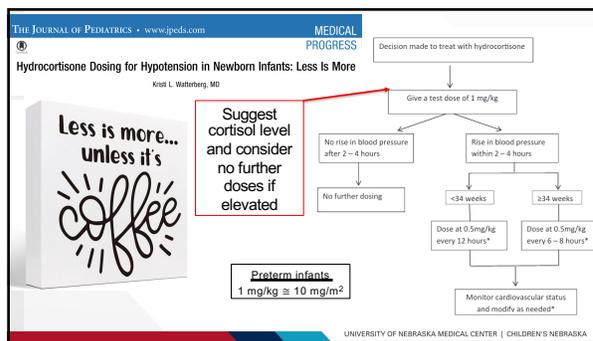
Preterm infants, 1 mg/kg \approx 10 mg/m²

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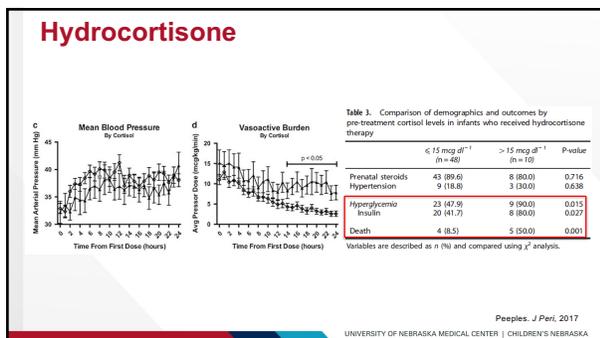
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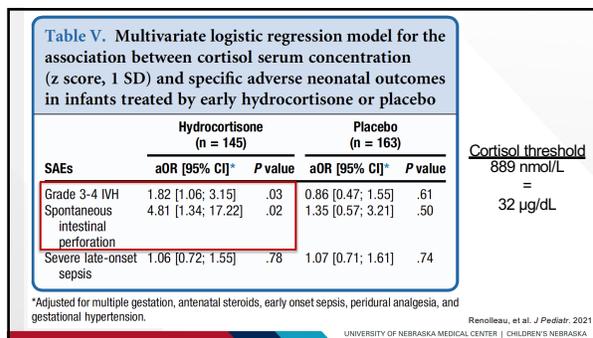
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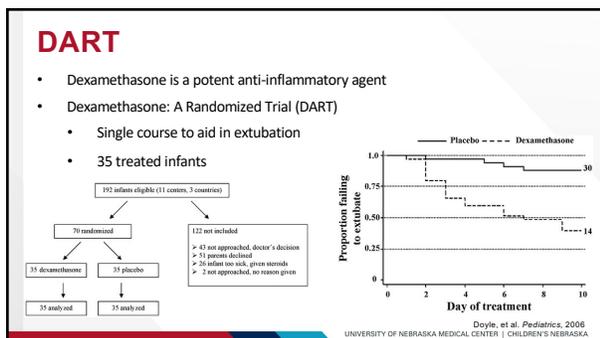
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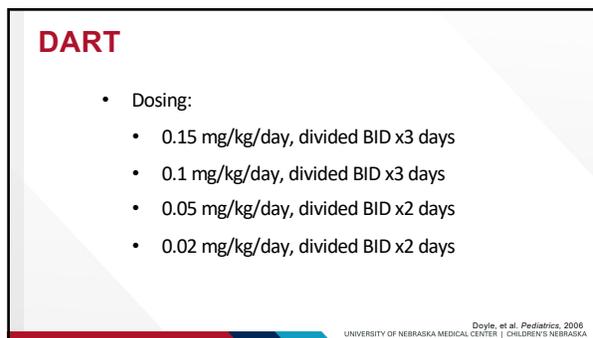
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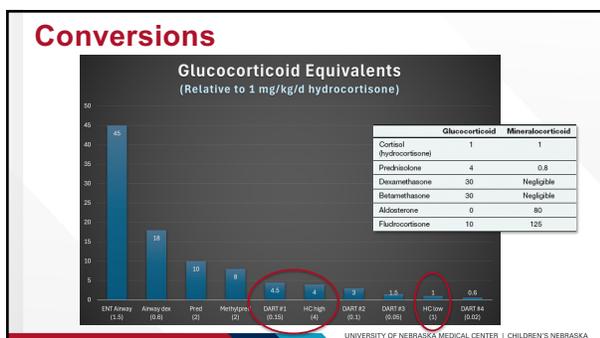
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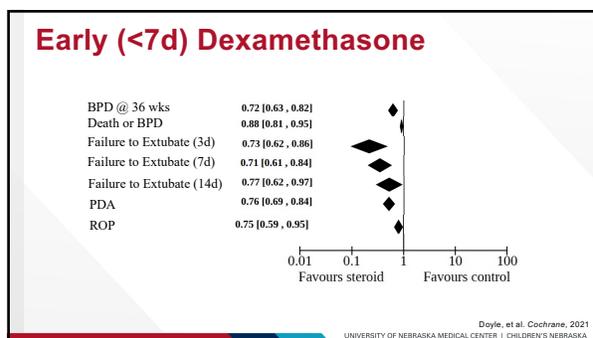
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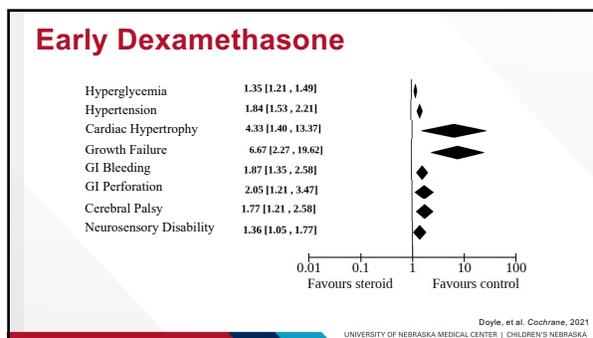
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Early Dexamethasone

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Late (>7d) Dexamethasone

BPD @ 36 wks	0.76 [0.66, 0.87]
Death or BPD	0.75 [0.67, 0.84]
Failure to Extubate (3d)	0.76 [0.69, 0.84]
Failure to Extubate (7d)	0.66 [0.60, 0.73]
Failure to Extubate (14d)	0.63 [0.45, 0.90]
Home on Oxygen	0.71 [0.54, 0.94]

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Late Dexamethasone

Hyperglycemia	1.53 [1.26, 1.85]
Hypertension	2.45 [1.48, 4.06]
Cardiac Hypertrophy	2.76 [1.33, 5.74]
GI Bleeding	1.38 [0.99, 1.93]
GI Perforation	0.36 [0.02, 8.05]
Cerebral Palsy	1.12 [0.79, 1.60]
Neurosensory Disability	1.17 [0.85, 1.60]

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Late Dexamethasone

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Risk Modification

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Risk Modification

NEONATAL RESEARCH NETWORK

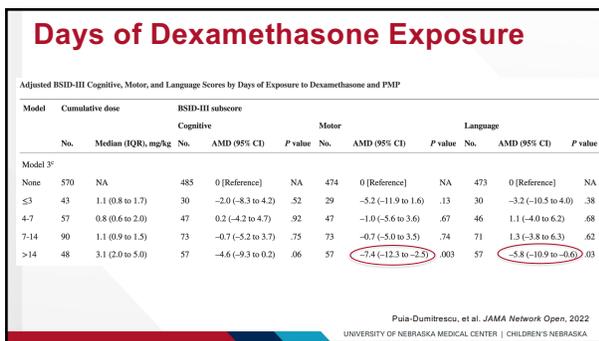
Neonatal BPD Outcome Estimator (2022)
Infants with GA 25-30 weeks & Birth Weight 500-1200g

Postnatal Day	1
Gestational Age (Weeks)	24
Birth Weight (Grams)	600
Sex	Male
AMS	Yes
Surgical Neonatology Enterocolitis	N/A
Respiratory Support Type	HFV (high frequency ventilator)
FIQ2	00

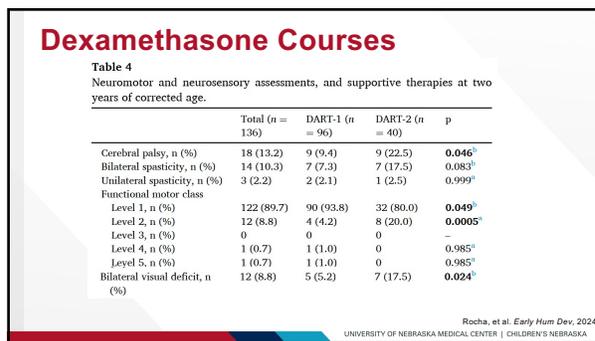
	Grade 3 BPD	Grade 2 BPD	Grade 1 BPD	No BPD
Death	33.81	12.69	31.17	20.24
				1.99

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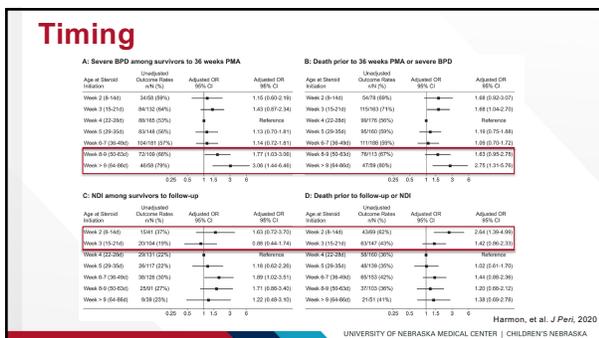
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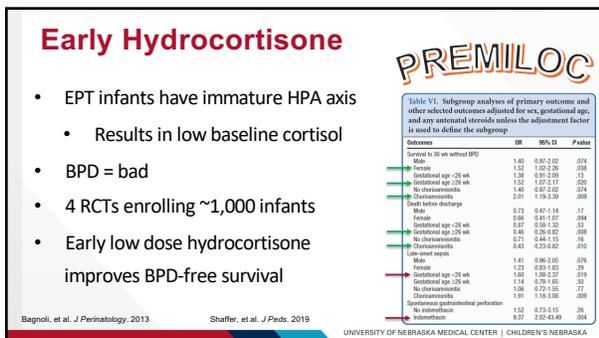
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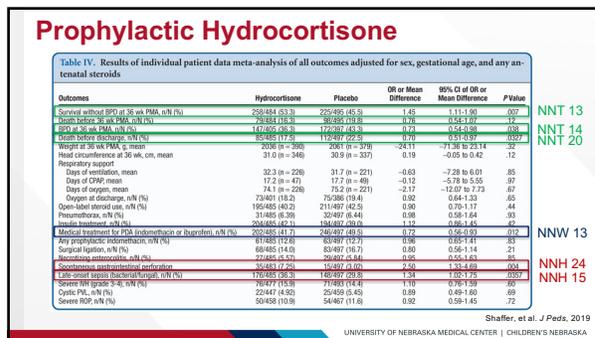
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NEUROSIS Study

- 1059 infants <28 weeks GA
- Budesonide+surfactant vs. placebo
- Survival without BPD:
 - 26% tx vs 23% placebo
 - Death 17% vs 19%
- “Early intratracheal budesonide may have little to no effect on survival free BPD”

Manley, et al. JAMA, 2024
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Drug, Route, and Timing of Initiation	Death or BPD at 36 Weeks PMA	BPD at 36 Weeks PMA	Death at the Last Reported Age	Death or Cerebral Palsy	Cerebral Palsy
Systemic					
<7 days of age (33)					
Dexamethasone	0.88 (0.81-0.95) 17 trials, n=2791	0.72 (0.63-0.82) 15 trials, n=1948	1.02 (0.90-1.16) 20 trials, n=2940	1.18 (1.01-1.37) 7 trials, n=921	1.85 (1.31-2.61) 7 trials, n=587
Hydrocortisone	0.90 (0.82-0.99) 9 trials, n=1376	0.89 (0.78-1.02) 9 trials, n=1145	0.80 (0.65-0.99) 11 trials, n=1433	0.86 (0.71-1.05) 6 trials, n=1002	1.01 (0.65-1.58) 6 trials, n=742
>7 days of age (34/32)					
Dexamethasone	0.75 (0.67-0.84) 12 trials, n=553	0.80 (0.69-0.93) 7 trials, n=278	0.85 (0.66-1.11) 19 trials, n=993	0.95 (0.77-1.16) 15 trials, n=855	1.14 (0.75-1.74) 15 trials, n=591
Hydrocortisone ^a	0.97 (0.92-1.02) 3 trials, n=1235	0.98 (0.92-1.04) 3 trials, n=1059	0.83 (0.64-1.06) 3 trials, n=1235	0.95 (0.75-1.19) 3 trials, n=1184	1.25 (0.85-1.83) 3 trials, n=951
Inhaled					
≤24 hours of age (62/63)					
Budesonide	0.86 (0.75-1.00) 1 trial, n=665	0.74 (0.60-0.91) 1 trial, n=728	1.37 (1.01-1.86) 1 trial, n=613	Not reported	1.18 (0.67-2.07) 1 trial, n=670
≤14 days of age (1/61)					
Budesonide	0.86 (0.75-0.99) 6 trials, n=1285	0.76 (0.62-0.92) 6 trials, n=1285	1.36 (1.02-1.81) 3 trials, n=1127	1.26 (1.00-1.58) 3 trials, n=1127	1.05 (0.67-1.65) 3 trials, n=1127
Intratracheal					
<8 days of age (64)					
Budesonide	0.59 (0.50-0.70) 6 trials, n=771	0.64 (0.55-0.74) 12 trials, n=1377	0.63 (0.43-0.93) 6 trials, n=771	Not reported ^d	Not reported ^d

Jensen & Watterberg. Neuroreviews. 2023
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Conclusions

AAP COFN (Cummings, et al. *Pediatrics*, 149(6))

- Routine use of steroids cannot be recommended
- Decision should be individualized and made together with parents
- If give, low dose for a short, predefined duration (e.g. extubations) is recommended
- If no clinical response within 72 hours, continuation not recommended
- High-dose steroids not recommended to prevent or treat CLD
- Indomethacin should not be used concurrently with steroids

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Conclusions

Early (<7d)

- Avoid dexamethasone
- PREMILOC likely improves BPD and mortality
 - Avoid concurrent NSAID use (especially if SGA, other high-risk)
 - ?baseline cortisol?
 - Use with care if <26 weeks due to increased sepsis risk
- Possible increased mortality with budesonide alone
- Budesonide+surfactant shown inconsistent results, awaiting NRN BiB study

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Conclusions

Late (>7d)

- No clear role for hydrocortisone
- Consider single course of DART at 3-4 wks (15-28d) of life for extubations
 - Consider infant's risk of BPD (>40%)
- If additional course needed:
 - Consider shorter course (3-5 days)
 - Counseling with family
 - Reserve for extubation (i.e. not non-invasive ventilation)
- Unknown pred/methylpred benefits/risks (specifically ND outcomes)

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References

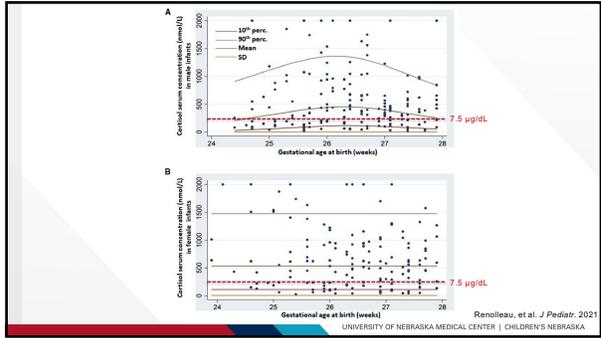
- Asik M, Urahaki T, Nagano N, Aoki R, Morikawa I. Association of Plasma Cortisol Levels with Gestational Age and Anthropometric Values at Birth in Preterm Infants. *International Journal of Environmental Research and Public Health*. 2022; 19(15):11448.
- Bassler, Dirk, et al. "Early inhaled budesonide for the prevention of bronchopulmonary dysplasia." *New England Journal of Medicine* 373.16 (2015): 1497-1506.
- Bhandari, Anita, et al. "Effect of a short course of prednisolone in infants with oxygen-dependent bronchopulmonary dysplasia." *Pediatrics* 121.2 (2008): e344-e349.
- Doyle LW, Cheong J, Hay S, Manley BJ, Halliday HL. Early (< 7 days) systemic postnatal corticosteroids for prevention of bronchopulmonary dysplasia in preterm infants. *Cochrane Database Syst Rev*. 2021 Oct 21;16(10):CD011466.
- Jørgen, Erik A., and Krisis L. Watterberg. "Postnatal corticosteroids to prevent bronchopulmonary dysplasia." *Neoreviews* 24.11 (2023): e691.
- Linfaller, A., Cui, A., Liu, C., Ostleir, A., Trigg, W. E., Sampath, V., & Qvistman, A. (2019). Extended course of prednisolone in infants with severe bronchopulmonary dysplasia. *Early Human Development*, 140, 1-10.
- Manley BJ, et al. "Early intratracheal budesonide mixed with surfactant for extremely preterm infants: the PLUS randomized clinical trial." *Lancet Respiratory Medicine*. 2021; 9(10):1009-1018.
- Orland, Wes, 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* 321.4 (2019): 354-363.
- Parikh, Nehal A., et al. "Pilot randomized trial of hydrocortisone in ventilator-dependent extremely preterm infants: effects on regional brain volumes." *The Journal of pediatrics* 192.4 (2013): 686-690.
- Parikh, Nehal A., et al. "Neurodevelopmental outcomes of extremely preterm infants randomized to stress dose hydrocortisone." *PLoS One* 10.9 (2015): e0137051.
- Peeples ES. An evaluation of hydrocortisone dosing for neonatal refractory hypotension. *J Perinatol*. 2017;37(8):943-946.
- Peples ES, Comstock BA, Heagerty PJ, Juhl SE. Preterm Extracranial Neuroprotection (PENUT) Trial Investigators. Blood pressure values and hypotension management in extremely preterm infants: a multi-center study. *J Perinatol*. 2022; 32(9):1709-1719.
- Renshaw C, Toumazd A, Bourmaud A, et al. Association between Baseline Cortisol Serum Concentrations and the Effect of Prophylactic Hydrocortisone in Extremely Preterm Infants. *J Pediatr*. 2021;234:65-70.e3.
- Rocha, Gustavo, et al. "The use of two or more courses of low-dose systemic dexamethasone to extubate ventilator-dependent preterm infants may be associated with a higher prevalence of cerebral palsy at two years of corrected age." *Early Human Development* 194 (2015): 100-107.
- Scott SM, Watterberg KL. Effect of gestational age, postnatal age, and illness on plasma cortisol concentrations in premature infants. *Pediatr Res*. 1995;37(1):12-16.
- Shaffer, Michelle L., et al. "Effect of prophylaxis for early adrenal insufficiency using low-dose hydrocortisone in very preterm infants: an individual patient data meta-analysis." *The Journal of pediatrics* 207 (2019): 136-142.
- Trousson, Clémence, et al. "Neurocognitive outcomes at age 5 years after prophylactic hydrocortisone in infants born extremely preterm." *Developmental Medicine & Child Neurology* 65.7 (2023): 526-532.
- Watterberg KL. Hydrocortisone Dosing for Hypotension in Newborn Infants: Less Is More. *J Pediatr*. 2016;174:23-26.e1.
- Watterberg KL, et al. "Hydrocortisone to improve survival without bronchopulmonary dysplasia." *New England Journal of Medicine* 373.16 (2015): 1497-1506.
- Zhang H, Guo H, Han X, et al. "Prevention of support-free type II bronchopulmonary dysplasia in extremely low birth weight infants." *Neuroreviews*. 2023; 24(11):e691.

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