Newborn Critical Care Center (NCCC) Clinical Guidelines

Prophylactic Hydrocortisone for ELBW Infants

BACKGROUND

Early or prophylactic low-dose systemic hydrocortisone may counteract the state of relative adrenal insufficiency (AI) that is experienced by extremely preterm infants and thereby reduce the risk of certain neonatal morbidities, including death.[1]

The following are points for consideration for early or prophylactic hydrocortisone:

- PREMILOC[2], the largest of the early or prophylactic hydrocortisone trials, randomized 523 infants to receive either 8.5 mg/kg of hydrocortisone or placebo for 10 days and demonstrated that infants receiving hydrocortisone had a significantly higher incidence of survival without BPD (60% versus 51%, respectively; OR 1.48 (1.02 to 2.16, p=0.04)).
- In a single-patient meta-analysis of five trials of early or prophylactic hydrocortisone, preterm infants treated with early hydrocortisone had a significantly higher chance of survival without BPD compared to those infants treated with placebo (53 versus 46%, NNT = 13) [3]
- In the Cochrane review of early corticosteroids, hydrocortisone reduced mortality without evidence of adverse effect at two years.[4]
- Early or prophylactic hydrocortisone use was associated with higher incidence of spontaneous GI perforation when used concurrently with indomethacin. GI perforation did not occur with ibuprofen for PDA treatment.
- Early or prophylactic hydrocortisone use was associated with higher incidence of late-onset sepsis, particularly in infants exposed to chorioamnionitis. There were no adverse effects observed in terms of mortality or 2-year neurodevelopmental outcomes.
- Early or prophylactic hydrocortisone did not have an adverse effect on neurodevelopment when assessed at 2 years[5], and may reduce moderate to severe neurodevelopmental impairment in infants at 24-25 week gestation.[6] In a small subset of infants followed to 5 years[7], there was no adverse effect.

DOSING AND CONSIDERATIONS

UNC will provide early or prophylactic hydrocortisone per the PREMILOC trial, as follows:

1. Infants < 28 weeks gestational age AND < 72 hours
    a. ***Inborn*** infants: begin on admission
    b. ***Outborn*** infants: begin on admission if < 72 hours old
2. Hydrocortisone dosing:
    a. 0.5 mg/kg Q12 hours for 7 days (14 doses) followed by
    b. 0.5 mg/kg Q24 hours for 3 days (3 doses) for 10 days total
3. Avoid the use of indomethacin during the treatment period, and for 48 hours post-treatment. Ibuprofen and acetaminophen are **not** contraindicated.
4. For infants who may need hydrocortisone *stress dosing* (e.g. vasopressor resistant hypotension), refer to the Hydrocortisone Stress Dosing Guideline.
5. For infants who receive stress dose hydrocortisone and would be ready to wean off physiologic dosing prior to DOL 10, physiologic dosing should be provided through the end of DOL 9 (10 postnatal days)
6. ***Special attention should be given to the units of dosing for prophylactic hydrocortisone (mg/kg/day) vs stress and physiologic dosing (mg/m2/day)***

References:

1. Jensen EA, Watterberg KL. Postnatal Corticosteroids To Prevent Bronchopulmonary Dysplasia. *Neoreviews.* 2023;24(11):e691-e703.

2. Baud O, Maury L, Lebail F, 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(10030):1827-1836.

3. Shaffer ML, Baud O, Lacaze-Masmonteil T, Peltoniemi OM, Bonsante F, Watterberg KL. Effect of Prophylaxis for Early Adrenal Insufficiency Using Low-Dose Hydrocortisone in Very Preterm Infants: An Individual Patient Data Meta-Analysis. *J Pediatr.* 2019;207:136-142 e135.

4. Doyle LW, Cheong JL, 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;10(10):CD001146.

5. Baud O, Trousson C, Biran V, et al. Association Between Early Low-Dose Hydrocortisone Therapy in Extremely Preterm Neonates and Neurodevelopmental Outcomes at 2 Years of Age. *JAMA.* 2017;317(13):1329-1337.

6. Baud O, Trousson C, Biran V, et al. Two-year neurodevelopmental outcomes of extremely preterm infants treated with early hydrocortisone: treatment effect according to gestational age at birth. *Arch Dis Child Fetal Neonatal Ed.* 2019;104(1):F30-F35.

7. Trousson C, Toumazi A, Bourmaud A, Biran V, Baud O. Neurocognitive outcomes at age 5 years after prophylactic hydrocortisone in infants born extremely preterm. *Dev Med Child Neurol.* 2023;65(7):926-932.

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