Newborn Critical Care Center (NCCC) Clinical Guidelines

Prophylactic Hydrocortisone for the Prevention of BPD in 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% vs 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 neurodevelopment 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. In infants <28 weeks gestational age, administer hydrocortisone 0.5 mg/kg twice a day for 7 days, followed by 0.5 mg/kg per day for 3 days (10 days total) starting on the first postnatal day
2. Avoid the use of indomethacin during the treatment period, and for 48 hours post-treatment. Ibuprofen or acetaminophen is acceptable.
3. In infants who may need hydrocortisone ***stress dosing*** (e.g. vasopressor resistant hypotension), please refer to the Hydrocortisone Stress Dosing Guideline, as the dose is higher than the early or prophylactic dose.

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.