East of England Neonatal ODN
(Hosted by Cambridge University Hospitals)

Clinical Guideline: Use of Hydrocortisone to reduce incidence of chronic lung disease in neonates

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For use in: For use within local neonatal services

Used by: Doctors and ANNPs

Key Words: Hydrocortisone, Chronic Lung Disease

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Approved by:

Neonatal Clinical Oversight Group	
Clinical Lead Matthew James	**Matthew James**

Ratified by

Date of meeting	

Audit Standards: All premature babies born below 28 weeks' gestation in the East of England should receive prophylactic hydrocortisone to reduce the incidence of chronic lung disease

Audit points:
Hydrocortisone given and documented in accordance to guidance within 24 hours of birth or as soon as practical after admission if already 24-72 hours of life**
Hydrocortisone course completed in accordance to guidance.**
****Where hydrocortisone has not been given or has been stopped there is a clear written audit trail of when and why this decision was made.**

CONTENTS:

1. Abbreviations

BD Twice a day
BPD Bronchopulmonary dysplasia
CLD Chronic lung disease
OD Once a day
PDA patent ductus arteriosus

2. Purpose.

Hydrocortisone is being recommended for routine use in the first 7 days of life in all premature babies born below 28 weeks' gestation with the aim of reducing the incidence of bronchopulmonary dysplasia/chronic lung disease (BPD/CLD) within this cohort.

3. Introduction.

BPD/CLD among extremely premature infants is a significant cause of mortality and morbidity. The largest randomised controlled trial of prophylactic hydrocortisone, the PREMILOC trial, published in 2016, reported increased survival without BPD in the group receiving prophylactic hydrocortisone.[1] This finding was confirmed in a meta-analysis in 2019, with the only reported adverse effect being an increase in gastrointestinal perforation associated with hydrocortisone and indomethacin (but not ibuprofen).[2] Antenatal steroids given to mothers are accepted within our current practice to improve neonatal outcomes. Similarly, treatment with steroids, for example dexamethasone from 8 days of age onwards, or inhaled budesonide, are already recognised treatments for babies who show early evidence of evolving BPD/CLD by remaining ventilated or having high oxygen requirements. Hydrocortisone given to all preterm infants less than 28 weeks' gestation is therefore a prophylactic treatment aimed at preventing BPD/CLD.

Many studies have focused on the use of dexamethasone, however the choice of hydrocortisone rather than dexamethasone for this intervention is both as a

physiological replacement dose and for its lower side-effect profile compared to dexamethasone. While studies on the use of dexamethasone have shown a reduction in the number of days on the ventilator and a reduction in the incidence of BPD at 36 weeks corrected gestational age, they also show evidence of an increased incidence of hypertension, intestinal perforation and a suggestion, within the largest study, of an increased incidence of cerebral palsy.[3] Conversely there was no evidence of increased hypertension, intestinal perforation or worse neurodevelopment outcomes in studies looking at prophylactic hydrocortisone use. [2,4] The rationale of prophylactic steroid use to improve BPD/CLD outcomes is based upon the hypothesis that extremely premature infants are cortisol insufficient and that preterm delivery and chorioamnionitis can trigger an inflammatory cascade within the neonatal lungs. This is then exacerbated by oxidative stress and barotrauma from mechanical ventilation. The effect of this damage leads to the development of BPD/CLD. This intervention aims to supplement the endogenous cortisol production of the extreme preterm neonate with hydrocortisone, thereby reducing the subsequent inflammatory cascades within the preterm lung which contribute to BPD/CLD.

4 Use of hydrocortisone:

*****Inform parents why hydrocortisone is being used and answer any questions they may have about its use*****

4.1 Indication.

All preterm infants <28 weeks of age admitted to the NICU within the first 72 hours of life.

4.2 Regime:

This has been based around the PREMILIOC study [1](see cautions below for indications outside the clinical trial design). This is a total **10-day course** to be started within the **first 24 hours of life** (or as soon as practical after admission if already 24-72 hours of life). There is no evidence regarding the benefit of starting prophylactic hydrocortisone beyond 72 hours of life.

Hydrocortisone IV 0.5mg/kg BD for 7 days.

Followed by:

Hydrocortisone IV 0.5mg/kg OD for 3 days.
(This will be a total cumulative dose of 8.5mg/kg).

Antifungal prophylaxis will also need to be prescribed in accordance with the usual neonatal antifungal guidelines

4.3 Contraindications:

Starting:

There are no absolute contraindications to starting hydrocortisone in infants <72 hours of age.

Continuing:
Absolute: Intestinal perforation.
Relative: Suspected necrotising enterocolitis.

Stopping:
When stopping prophylactic hydrocortisone before completing the 10-day course it can be stopped immediately and there is no need to wean the dosage.

4.4 Cautions:

Infants <24 weeks gestation.
The PREMILOC study did not recruit infants <24 weeks' gestation. However, given the high-risk of BPD in these infants, it would not be unreasonable to consider commencing hydrocortisone in these infants.

Infants with preterm prolonged rupture of membranes <22 weeks' gestation.
These infants were not recruited to the PREMILOC study, however given the high-risk of BPD in these infants it would not be unreasonable to consider commencing hydrocortisone in this situation.

Infants with evidence of perinatal hypoxia-ischaemia – defined by an initial pH <7.0 or Apgar score <3 at 5 minutes.
These infants were not recruited to the PREMILOC study. Given the potential risk of gastrointestinal perforation or necrotising enterocolitis following perinatal hypoxia-ischaemia, the decision to commence prophylactic hydrocortisone in these infants should be at the attending clinician's discretion.

Hydrocortisone and ibuprofen.
The published data to date have shown no association between prophylactic hydrocortisone, ibuprofen and intestinal perforation, although there was an increased risk of intestinal perforation with prophylactic hydrocortisone and indomethacin administration. In a preterm infant <10 days of age with a clinically significant PDA where the decision has been made to treat, it will be up to the attending clinician to decide whether to continue prophylactic hydrocortisone.

Hypertension, hyperglycaemia, renal failure
Careful monitoring is required for babies with hypertension, hyperglycaemia and renal failure as hydrocortisone could exacerbate these conditions

4.5 Exceptions in episodes of severe hypotension.

If a baby requires hydrocortisone for blood pressure management, as per the current neonatal hypotension guidelines, then that should take precedence. The dosing and

duration of hydrocortisone should follow the neonatal hypotension guideline in that circumstance. Once blood pressure has stabilised, the dose should be adjusted to the BPD/CLD dose above to complete the 10-day course.

5. Monitoring compliance with and the effectiveness of this document.

The standards set out within this guideline will be periodically monitored by audit of infants on the neonatal unit that meet the criteria for use of hydrocortisone as per this guideline. The results will be reviewed by the senior nursing and medical teams and disseminated amongst staff.

6. References.

1. 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, randomized trial. Lancet 2016;387:1827-36.
2. Shaffer ML, Baud O, Lacaze-Masmonteil T, et al. Effect of prophylaxis for early adrenal insufficiency using low-dose hydrocortisone in very preterm infants: an individual patient data meta-analysis. Pediatr. 2019;207:136-142.
3. Shinwell ES, Karplus M, Reich D, et al. Early postnatal dexamethasone treatment and increased incidence of cerebral palsy. Arch Dis Child Fetal Neonatal Ed. 2000;83:F177-81.
4. 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;317:1329-37.
5. NICE Cochrane Review 2018: Specialist Neonatal respiratory care for babies born preterm

document only applies to the East of England region with due process followed in agreeing the content.

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Exceptional Circumstances Form

Form to be completed in the **exceptional** circumstances that the Trust is not able to follow ODN approved guidelines.

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