Yorkshire & Humber Pan-Network Neonatal Clinical Guideline

Title: Early Hydrocortisone Treatment to Improve Neonatal Outcomes

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Date written: May 2022

Review date: September 2027

This clinical guideline has been developed to ensure appropriate evidence based standards of care throughout the Yorkshire & Humber Neonatal Operational Delivery Network. The appropriate use and interpretation of this guideline in providing clinical care remains the responsibility of the individual clinician. If there is any doubt discuss with a senior colleague.

A. Guideline summary

1. Aims

To describe the use of low dose hydrocortisone as prophylaxis for early adrenal insufficiency in infants ≤27+6 in an NICU or those who are receiving care in a Local Neonatal Unit (LNU). Benefits include reducing rates of bronchopulmonary dysplasia (BPD), reduced need for patent ductus arteriosus (PDA) ligation and improved survival to discharge.

2. Best Practice Recommendations

This guideline is intended to support clinical decision-making and facilitate the use of low-dose hydrocortisone where appropriate.

- Use prophylactic IV hydrocortisone from the first day of life, in infants ≤ 27+6 who are not clinically septic or receiving indomethacin for 10 days.
- Use with caution if co-administering ibuprofen and hydrocortisone.
- Monitor BP and blood glucose in infants receiving hydrocortisone

The Yorkshire and Humber Neonatal Operational Delivery Network

B Full guideline and evidence

1. Background

Preterm infants can experience adrenal insufficiency for multiple reasons including an immature hypothalamic pituitary adrenal (HPA) axis and a reduced ability of the adrenal glands to produce cortisol. Low cortisol levels in the first postnatal week have been linked to cardiovascular instability and BPD. BPD is a leading cause of mortality and morbidity in extreme preterm infants. Trials have been conducted including the PREMILOC study, demonstrating low dose hydrocortisone from the first day of life can reduce BPD, need for PDA treatment and mortality.

Guideline:

Eligible infants:

Infants born 22+0 to 27+6.

Treatment.

It is a 10 day course of treatment, starting from the first day of life.

Ideally the first dose should be given within 12 hours of birth.

The treatment regime is the low dose regime used in the PREMILOC study.

Following consultant discussion and decision making, update parents.

Drug	**Dosing**	**Days duration**
Hydrocortisone (IV)	1mg/kg/day divided into two doses per day (i.e 0.5mg/kg BD)	First 7 days. Followed by the below:
Hydrocortisone (IV)	0.5mg/kg/day OD	3 days

The majority of studies have used IV dosing for the full 10 day course. Other centres have found most patients will still need IV access by day 10 of life. However, substitution of enteral hydrocortisone for IV treatment in patients who do not need IV access may be reasonable, but is not well established nor is optimal dosing understood. Also the minimum number of IV doses recommended prior to switching to enteral is unknown. If the neonatal team has decided to do an enteral conversion for the above reasons, as enteral hydrocortisone has near 100% bioavailability, it is a 1:1 conversion for dosing i.e. the same dose as IV dosing.

Evidence base

Preterm infants can experience adrenal insufficiency due to a combination of factors including an immature HPA axis, with reduced ability of the adrenal glands to produce cortisol. This is thought to be due to intermediate enzyme deficiency in the steroidogenesis pathway. It is described as transient adrenocortical insufficiency of prematurity and typically resolves by 2 weeks of age. There is also relative adrenal insufficiency, where a limited ability to produce adequate cortisol results in inappropriately low levels for the degree of stress or illness[1,2]. Sick preterm infants have been shown to have biochemical evidence of reduced adrenal function when compared to their well counterparts or term infants[3,4].

Low cortisol levels in first postnatal week have been linked to cardiovascular instability and BPD development[5], with lower cortisol leading to reduced ability to dampen the inflammatory response. Cortisol response to adrenocorticotropic hormone (ACTH) stimulation at the end of week 1 of life is significantly lower in babies that develop BPD[3,4].

BPD is a leading cause of mortality as well as short and long term respiratory morbidity, including pulmonary hypertension, in extreme preterm infants (22+0 to 27+6 weeks gestation). It is also associated with poor neurodevelopment outcomes. BPD is multifactorial in nature and a combination of lung inflammation with abnormal growth and development of the alveoli[5-9].

Hydrocortisone has been researched as a potentially safer alternative to dexamethasone in BPD prevention. Dexamethasone treatment is not recommended before 7 days of life[5,6,10].

Trials have demonstrated early low dose hydrocortisone from day 1 of life can reduce incidence of BPD, need to treat PDA and mortality pre- discharge[5,11-13]. Low dose hydrocortisone has also been shown not to suppress adrenal function[11]. The PREMILOC study used lower doses and shorter duration of hydrocortisone than previous studies; after a 10-day course from day 1 of life there was improved BPD free survival[5].

The PREMILOC follow up study demonstrated no statistically significant difference in head circumferences at 36 weeks corrected gestational age, brain tissue or volume, neurodevelopment or rates of cerebral palsy at 2 years in hydrocortisone versus placebo groups[14-19]. In comparison between gestational age groups, there was a statistically significant improvement in neurodevelopmental outcomes in infants born at 24 and 25 weeks compared to 26 and 27 weeks[14-16].

Key adverse outcomes with use of early low dose hydrocortisone include a statistically significant increase in spontaneous intestinal perforation (SIP) in the hydrocortisone treated group. However, this occurred in patients who also received indomethacin treatment (95% CI 1.33-4.69; p= 0.004)[16] and was not found if given hydrocortisone only. In studies where ibuprofen for PDA treatment was used simultaneously with hydrocortisone there was no effect on SIP rates[20]. The other key adverse outcome is late onset bacterial or fungal sepsis, particularly in the more extreme preterm group (24+0 to 25+6 week gestation) (95% CI 1.09-3.21; p=0.02)[5]. This was statistically significant in infants with histological evidence of chorioamnionitis[5,16].

Despite these risks, they do not negate the overall benefit of using hydrocortisone in the extreme preterm infants, with survival without BPD increasing (OR, 2.01; 95% CI, 1.19-3.39) and mortality before discharge decreased (OR, 0.43; 95% CI, 0.23-0.82)[16].

Caution and monitoring:

Risk of spontaneous intestinal perforation:

Due to the increased risk of spontaneous intestinal perforation (SIP), combined use indomethacin and hydrocortisone should be avoided. Caution should be exercised with respect to co-administration of ibuprofen and hydrocortisone, as currently there are no studies reporting SIP with ibuprofen and hydrocortisone use.

Risk of late onset sepsis (LOS):

Start hydrocortisone with caution if an infant is clinically septic (can be used if clinically well with risk factors for infection) or those with strong suspicion of or confirmed chorioamnionitis who are less than 26 weeks. This should be a senior clinical decision, made on an individual patient basis. Current evidence suggests that despite an increased risk of late onset infection, prophylactic hydrocortisone treatment offers net benefits to patients.

All extremely preterm infants should be closely monitored for signs of developing late onset infections, with a low threshold for screening and starting antibiotics if concerned. This includes babies treated with prophylactic hydrocortisone.

Risk of hypertension:

Monitor blood pressure 6 hourly minimally to assess for hypertension whilst on the hydrocortisone, although the low doses of hydrocortisone recommended are not expected to cause significant hypertension. Hypertension is defined as elevation in systolic blood pressure greater than 95th centile for age, weight and gender. See Appendix 1 and 2.
If hypertensive when receiving hydrocortisone

1. Repeat blood pressure measurement should be performed, and (if non-invasive BP measurement then repeat on a different limb)
2. If systolic BP remains greater than 95th centile withhold hydrocortisone and continue to monitor BP.
3. Consider restarting hydrocortisone if blood pressure normalises. If deciding to restart, it is a 10 day course starting first day of life to day 10 of life, not a total of 10 days. For example, if stopping due to hypertension on day 5 and restarting day 7 of life, the hydrocortisone course would still finish day 10 of life even though missed 2 days. This is based on Watterberg et al's study of hydrocortisone use from day 14 to 28 of life which demonstrated no statistically significant improvement in survival without moderate or severe BPD[22].

If persisting hypertension despite stopping hydrocortisone, further review and investigation may be warranted.

The hypotensive neonate:

If hypotensive and needing to commence hydrocortisone treatment at the higher 2.5mg/kg 4-6hourly regime, we suggest stopping the prophylactic dose of hydrocortisone. As the patient improves and tolerates reducing the hydrocortisone dosing for hypotension, please remember to revert back to the prophylactic dose of hydrocortisone if still applicable.

Hyperglycaemia:

Monitor blood glucose for signs of hyperglycaemia, being aware these infants are at risk not just due to steroid use but also due to fluid requirements, losses and parental nutrition (PN) use. Recommended minimum 6 hourly blood glucose checks, though timing may vary depending on stability of baby and their blood sugars.

Currently, it is not recommended to start a PPI or ranitidine whilst receiving low dose hydrocortisone, as this is meant to be a small physiological dose of hydrocortisone and PPIs and ranitidine are not without risks.

2. Areas outside remit

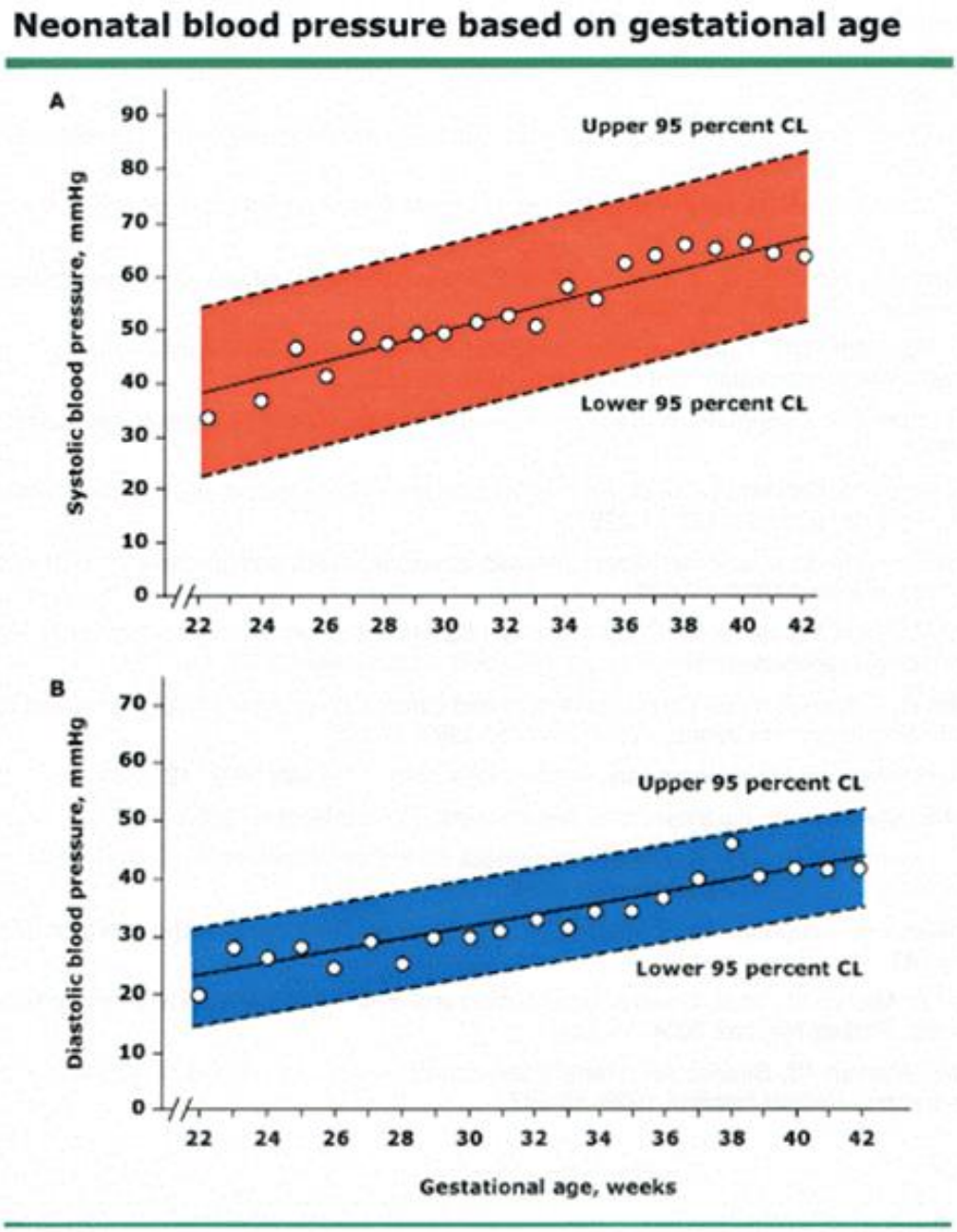
Infants born at or greater than 28+0 weeks gestation.

3. Audit Criteria.

Audit infants receiving low dose hydrocortisone for BPD prophylaxis including rates of SIP, LOS and the outcome at discharge for them, using local patient records and badger.net system. Results can be shared at local clinical governance and at regional meetings.

4. Appendices

Appendix 1: Systolic and diastolic blood pressures (mean and 95% confidence intervals) on day 1 at various gestational ages[23].



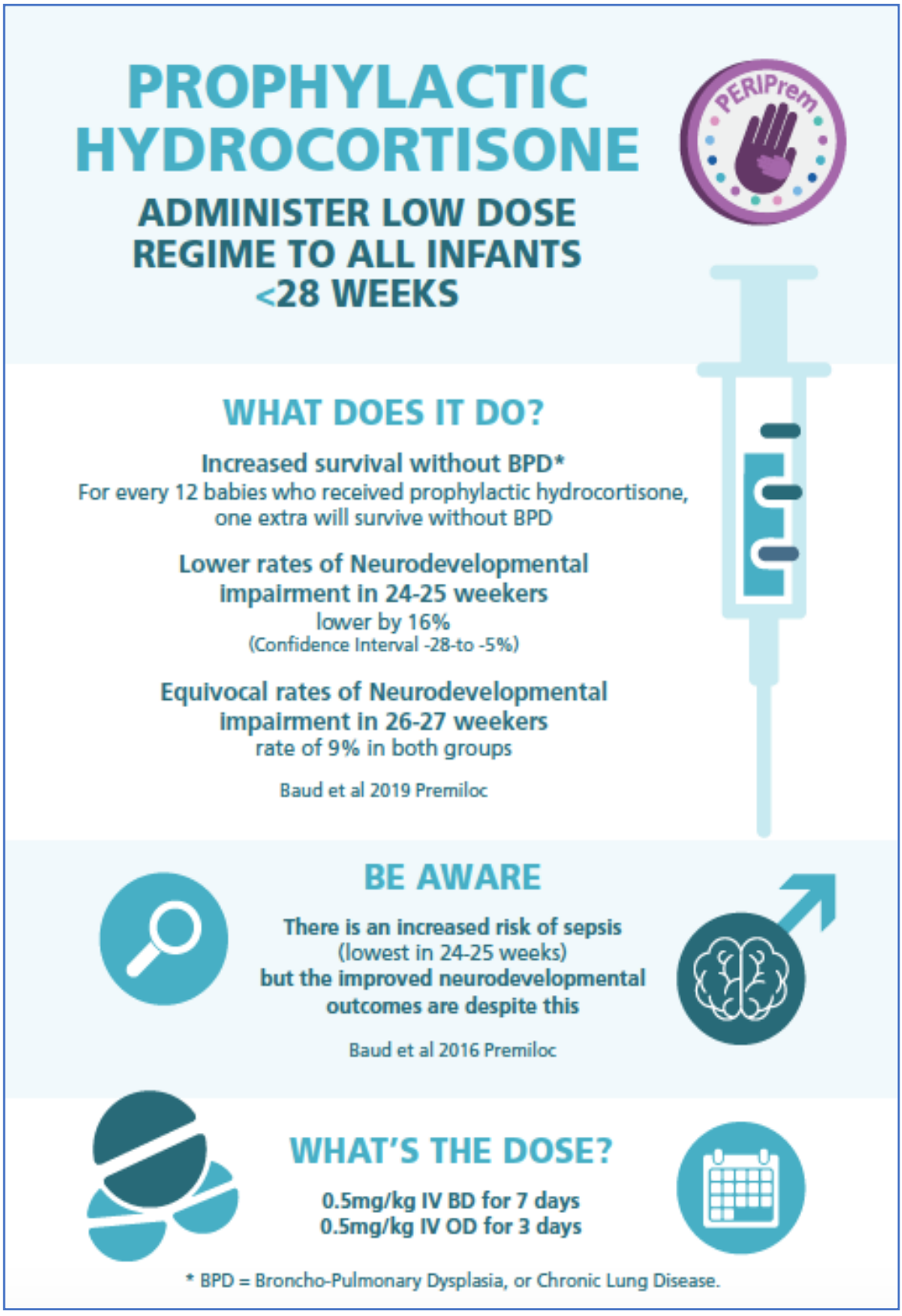
Appendix 2: Neonatal blood pressure reference ranges[24].

MABP- Mean arterial Blood pressure.

Birth Weight	Average MABP (mmHg)	95% upper confidence limit (mmHg)
500-750 grams	35	44
750-1000 grams	38	47
1000-1250 grams	39	48
1250-1500 grams	40	49
2000-2999 grams	41	50
3000-3999 grams	47	55
4000 grams	52	62

Appendix 3: Periprem poster for prophylactic hydrocortisone[25].

Please use these posters in your clinical areas to support and educate team members. They can be downloaded at: https://www.weahsn.net/our-work/transforming-services-and-systems/periprem/periprem-bundle-prophylactic-hydrocortisone/



5. Contributors and Sources

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6. References

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25. Periprem poster available as free download at <https://www.weahsn.net/our-work/transforming-services-and-systems/periprem/periprem-bundle-prophylactic-hydrocortisone/>