



CLINICAL PRACTICE GUIDELINE

Guideline coverage includes NICU KEMH, NICU PMH and NETS WA

Cortisol Estimation and ACTH Stimulation Testing

This document should be read in conjunction with the [Disclaimer](#)

Adrenal insufficiency in neonates can be divided into 2 categories:

Relative Adrenal Insufficiency (RAI)

- A temporary condition in critically ill neonates which occurs when the cortisol response is inadequate for the patient's degree of stress and has a reported incidence of 37-86%.
- It is defined as a random or baseline cortisol level $<414\text{nmol/L}$ or an ACTH stimulated (short synacthen test, 1mcg IV) Δ -cortisol (peak - baseline) of $<250\text{nmol/L}$ or a peak $<550\text{nmol/L}$.
- It should be considered in any critically ill neonate with conditions such as severe sepsis, HIE, MAS, PPHN, CDH and severe RDS, particularly in those with vasopressor-resistant hypotension (BP mean $<$ gestational age despite fluid bolus and inotropic support). It is common in 25% term newborns following cardiac surgery (cardiopulmonary bypass) as well.
- Diagnosis of RAI and treatment with hydrocortisone are controversial and presently there is a lack of good evidence in the literature. However, it is known that:
 - Severe prolonged hypotension is associated with increased mortality and central nervous system morbidity.
 - Inotropic support may lead to decreased organ perfusion causing decreased cerebral perfusion, renal and cardiac failure and fluid boluses are associated with pulmonary oedema and PDA.
- It has been shown that:
 - Hydrocortisone therapy results in haemodynamic stability and reduced use and of vasopressors and fluid boluses; with rapid tapering of inotropic support.
 - Treatment with hydrocortisone should be weighed up with the potential risks particularly in preterm neonates where there has been shown to be increased rates of GI perforation (in those treated alongside indomethacin therapy). Evidence from a recent trial (Premiloc) involving extremely preterm infants indicated that hydrocortisone did not show the detrimental effects on growth and neurodevelopmental outcome seen with dexamethasone treatment.

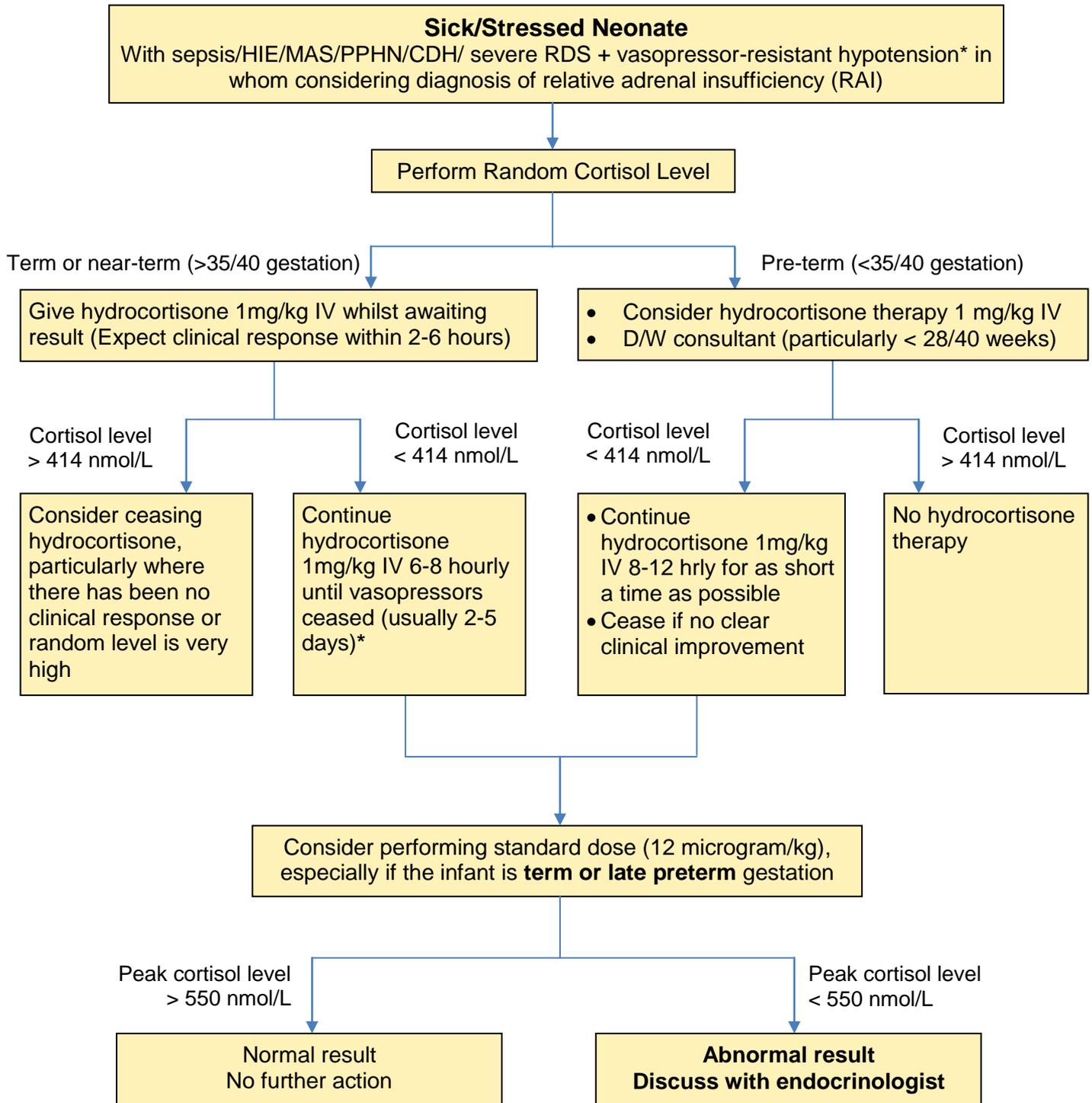
Primary/Secondary Adrenal Insufficiency

- Conditions are primary adrenal such as congenital adrenal hyperplasia or congenital hypoplasia or secondary adrenal/central such as hypopituitarism.

- Suspected in patients with ambiguous genitalia, hyponatraemia, hypoglycaemia, and an abnormal head scan (absent pituitary/mal-placed pituitary/septo-optic dysplasia/ midline defects).

Flowchart for adrenal investigation in the sick/stressed neonate with vasopressor-resistant hypotension in whom a diagnosis of relative adrenal insufficiency (RAI) is being considered:

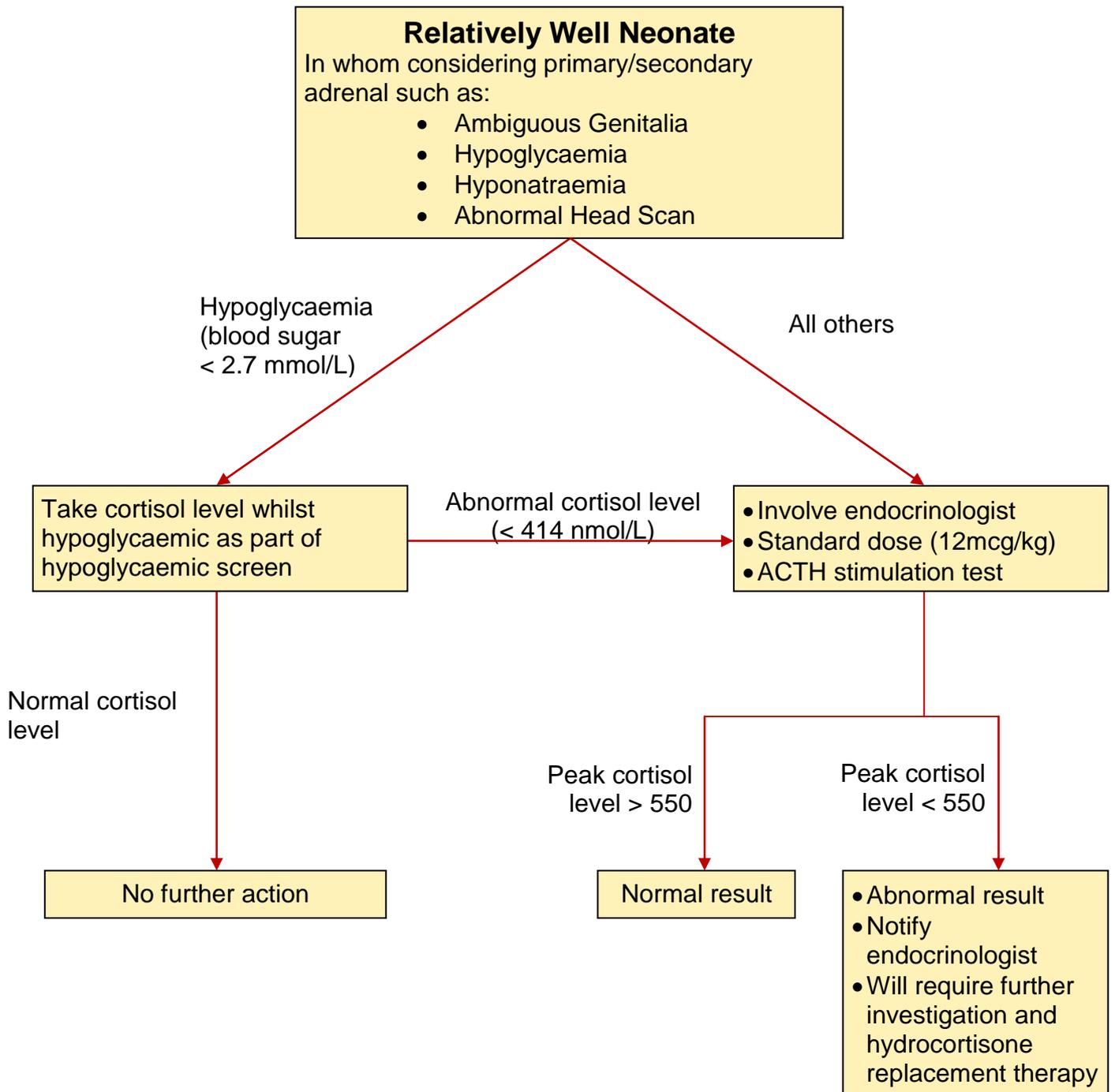
*Vasopressor-resistant hypotension defined as mean BP < gestational age despite > 20mL/kg fluid bolus and on > 10mcg/kg/min dopamine and/or > 10mcg/kg/min dobutamine or multiple other inotropes.



Flowchart for Adrenal Investigation in the Relatively Well Neonate in Whom a Diagnosis of Primary or Secondary Adrenal Insufficiency is being considered:

***Note:** If hydrocortisone was not given for > 3 days, it can be discontinued without tapering, otherwise within 24 hours after a positive response to hydrocortisone therapy with improved BP and urine output and tolerance of reduced vasopressor support, it is recommended that hydrocortisone dose be reduced to 0.5 mg/kg/dose 8-12 hrly.

Refer to Neonatal Medication Protocol - [Hydrocortisone](#)



ACTH Stimulation Testing (Short Synacthen Test)

The short Synacthen test is a test of adrenal insufficiency which can be used as a screening procedure in the non-critically ill patient. The test is based on the measurement of serum cortisol before and after an injection of synthetic ACTH (also known as Tetracosactrin).

The dose of synacthen to use for the testing remains controversial. Our standard practice is to use standard dose of 12 microgram/kg, unless there is a special request by the endocrinologist to use a different dose

Standard Dose Test (for establishing cause of primary/ secondary adrenal insufficiency, diagnosis of congenital adrenal hyperplasia and for checking adrenal cortical function post recovery from acute illness and off hydrocortisone therapy).

- 12mcg/kg Tetracosactrin intramuscularly (IMI) or intravenously (IV) if available.

Refer to Neonatal Medication Protocol: [Tetracosactrin](#).

References

1. Baud O, Trousson C, Biran V, Leroy E, Mohamed D, Alberti C; PREMILOC Trial Group. Association Between Early Low-Dose Hydrocortisone Therapy in Extremely Preterm Neonates and Neurodevelopmental Outcomes at 2 Years of Age. *JAMA*. 2017 Apr 4; 317(13):1329-1337.
2. Crawford JH, Hull MS, Borasino S, Steenwyk BL, Hock KM, Wall K, Alten JA. Adrenal insufficiency in neonates after cardiac surgery with cardiopulmonary bypass. *Paediatr Anaesth*. 2017 Jan; 27(1):77-84.
3. Johnson PJ. Hydrocortisone for Treatment of Hypotension in the Newborn. *Neonatal Netw*. 2015; 34(1):46-51.
4. Finken MJ, van der Voorn B, Heijboer AC, de Waard M, van Goudoever JB, Rotteveel J. Glucocorticoid Programming in Very Preterm Birth. *Horm Res Paediatr*. 2016;85(4):221-31
5. Robert SM, Borasino S, Dabal RJ, Cleveland DC, Hock KM, Alten JA. Postoperative Hydrocortisone Infusion Reduces the Prevalence of Low Cardiac Output Syndrome After Neonatal Cardiopulmonary Bypass. *Pediatr Crit Care Med*. 2015 Sep; 16(7):629-36.
6. Bone M, Diver M, Selby A, Sharples A, Addison M, Clayton P. Assessment of adrenal function in the initial phase of meningococcal disease. *Pediatrics*. Sep 2002;110(3):563-569.
7. Fernandez E, Schrader R, Watterberg K. Prevalence of low cortisol values in term and near-term infants with vasopressor-resistant hypotension. *Journal of perinatology : official journal of the California Perinatal Association*. Feb 2005;25(2):114-118.
8. Fernandez EF, Montman R, Watterberg KL. ACTH and cortisol response to critical illness in term and late preterm newborns. *Journal of perinatology : official journal of the California Perinatal Association*. Dec 2008;28(12):797-802.
9. Fernandez EF, Watterberg KL. Relative adrenal insufficiency in the preterm and term infant. *Journal of perinatology : official journal of the California Perinatal Association*. May 2009;29 Suppl 2:S44-49.
10. Heckmann M, Hartmann MF, Kampschulte B, et al. Cortisol production rates in preterm infants in relation to growth and illness: a noninvasive prospective study using gas chromatography-mass spectrometry. *The Journal of clinical endocrinology and metabolism*. Oct 2005;90(10):5737-5742.
11. Heckmann M, Wudy SA, Haack D, Pohlandt F. Serum cortisol concentrations in ill preterm infants less than 30 weeks gestational age. *Acta paediatrica*. Sep 2000;89(9):1098-1103.
12. Huysman MW, Hokken-Koelega AC, De Ridder MA, Sauer PJ. Adrenal function in sick very

preterm infants. *Pediatric research*. Nov 2000;48(5):629-633.

13. Jett PL, Samuels MH, McDaniel PA, et al. Variability of plasma cortisol levels in extremely low birthweight infants. *The Journal of clinical endocrinology and metabolism*. Sep 1997;82(9):2921-2925.
14. Kamath BD, Fashaw L, Kinsella JP. Adrenal insufficiency in newborns with congenital diaphragmatic hernia. *The Journal of pediatrics*. Mar 2010;156(3):495-497 e491.
15. Ng PC. Is there a "normal" range of serum cortisol concentration for preterm infants? *Pediatrics*. Oct 2008;122(4):873-875.
16. Ng PC. Effect of stress on the hypothalamic-pituitary-adrenal axis in the fetus and newborn. *The Journal of pediatrics*. Feb 2011;158(2 Suppl):e41-43.
17. Pizarro CF, Troster EJ, Damiani D, Carcillo JA. Absolute and relative adrenal insufficiency in children with septic shock. *Critical care medicine*. Apr 2005;33(4):855-859.
18. Soliman AT, Taman KH, Rizk MM, Nasr IS, Alrimawy H, Hamido MS. Circulating adrenocorticotrophic hormone (ACTH) and cortisol concentrations in normal, appropriate-for-gestational-age newborns versus those with sepsis and respiratory distress: Cortisol response to low-dose and standard-dose ACTH tests. *Metabolism: clinical and experimental*. Feb 2004;53(2):209-214.
19. Tantivit P, Subramanian N, Garg M, Ramanathan R, deLemos RA. Low serum cortisol in term newborns with refractory hypotension. *Journal of perinatology : official journal of the California Perinatal Association*. Jul-Aug 1999;19(5):352-357. Watterberg KL. Adrenocortical function and dysfunction in the fetus and neonate. *Seminars in neonatology* : SN. Feb 2004;9(1):13-21.

Related WNHS policies, procedures and guidelines

Neonatal Medication Protocol: [Tetracosactrin](#)
[Hydrocortisone](#)

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