UC DAVIS HEALTH | CHILDREN'S HOSPITAL

Adrenal Insufficiency in Neonates: Evaluation and Management

What signs/symptoms raise concern for adrenal insufficiency?

- Hypotension
- Unexplained hypoglycemia
- Cholestasis

NOTE: Hyponatremia and hyperkalemia are *not* typical signs of adrenal insufficiency in the NICU population since the primary etiologies of their adrenal insufficiency (prematurity and iatrogenic) do not affect the mineralocorticoid axis. Conditions affecting the mineralocorticoid axis in neonates are exceedingly rare.

How to test for adrenal insufficiency in premies and young infants? Premie and neonatal cortisol levels do not follow a diurnal pattern and are not established for the first several months of life. Thus, a low cortisol level could be due to adrenal insufficiency or because the lab was drawn at a physiologic nadir. There is also evidence to suggest that among infants at risk for iatrogenic AI, cortisol levels do not correlate with results of ACTH stim testing nor clinical findings (Rosano et al., 2024, Wittekind et al., 1993). This may differ from infants with suspected central AI, where there is some evidence to suggest that random cortisols can be used for diagnosis in term neonates (Bulan et al., 2023).

In summary, random cortisol levels cannot be used reliably in this population to assess adrenal function and we would recommend against obtaining random cortisol levels as well as starting hydrocortisone based off of only a low random cortisol level. If there is clinical concern for adrenal insufficiency, we recommend starting hydrocortisone, quickly tapering off glucocorticoids once their status has improved (see below for weaning protocol), and monitoring clinically after discontinuation. If the infant develops hypotension or hypoglycemia after stopping glucocorticoids, a cortisol and ACTH should be drawn, then hydrocortisone restarted.

Who is at risk of iatrogenic adrenal insufficiency?

High risk: hydrocortisone at doses of ≥8 mg/m2/day (or equivalent) for ≥ 4 weeks

Moderate risk: hydrocortisone at doses of 8-12 mg/m2/day for 2-4 weeks

Low risk: <2 weeks of glucocorticoid at any dose

Risk is stratified in terms of body surface area (can be determined using the dot phrase .BSA) and hydrocortisone dosing. For those who received glucocorticoids other than hydrocortisone, their doses will need to be converted to determine their risk:

Hydrocortisone (mg)	= 26 x mg dexamethasone
	= 5 x mg methylprednisolone
	= 4 x mg prednisone
	= 4 x mg prednisolone

Who is at risk of adrenal insufficiency of prematurity? Infants ≤ 32 weeks GA are at greatest risk. The fetal adrenal gland consists of a fetal zone (80-90%), which lacks the 3ßHSD2 enzyme needed to produce cortisol, and a definitive/adult zone (10-20%), that acts much like an adult adrenal. Fetal cortisol production is low until about 32 weeks gestation, when levels begin to rise in anticipation of delivery (Regelmann, 2018).

Who is at highest risk of central (secondary) adrenal insufficiency? Infants with CNS abnormalities (ectopic posterior pituitary, optic nerve hypoplasia, agenesis or hypoplasia of the corpus callosum or septum pellucidum, etc.), midline facial defects, microphallus, and pituitary deficiencies.

Proposed glucocorticoid weaning protocol

The following protocols apply to stable infants with iatrogenic adrenal insufficiency or adrenal insufficiency of prematurity. Note that for infants who received steroids of any dose for less than 2 weeks, no wean is needed.

For infants who received >15 mg/m2/day hydrocortisone (or equivalent) for 2-4 weeks:

1. Days 1-2: Decrease to 10 mg/m2/day divided q8hrs
2. Days 3-4: Decrease to 8 mg/m2/day divided q8hrs
3. Days 5-6: Decrease to 6-7 mg/m2/day divided q8hrs
4. Days 7-8: Decrease to 6-7 mg/m2/day divided q12hrs
5. Day 9: Discontinue glucocorticoids

For infants who received >15 mg/m2/day hydrocortisone (or equivalent) for 4 weeks – 3 months:

1. Days 1-4: Decrease to 10 mg/m2/day divided q12hrs
2. Days 5-8: Decrease to 8 mg/m2/day divided q12hrs
3. Days 9-12: Decrease to 6 mg/m2/day divided q12hrs
4. Day 13: Discontinue glucocorticoids

For infants who received >15 mg/m2/day hydrocortisone (or equivalent) for greater than 3 months:

1. Days 1-7: Decrease to 10 mg/m2/day divided q12hrs
2. Days 8-14: Decrease to 8 mg/m2/day divided q12hrs
3. Days 15-21: Decrease to 6 mg/m2/day divided q12hrs
4. Day 22: Discontinue glucocorticoids

**NOTE: Infants who are receiving < 30 mg/m2/day of hydrocortisone or have completed their wean but not yet passed an ACTH stimulation test still require empiric stress dosing during periods of acute illness. Once the stressor has resolved, the wean can be restarted where they had left off prior to the stress.

Stress dosing for surgical procedures

Stress dosing is indicated for infants undergoing operations and/or anesthesia to avoid hypotension and adrenal crisis. The degree of stress dosing used may vary based on the invasiveness of the procedure, so pediatric endocrinology should be contacted for infants with known adrenal insufficiency who have upcoming procedures.

There are not studies that specifically evaluate the role of peri-operative stress dosing on wound healing in adrenally insufficient neonates. However, adult studies have shown that wound healing is not significantly affected, nor are infection rates significantly increased by a short course of high-dose glucocorticoids in the perioperative period (Wang et al., 2013; Brown & Buje, 2001).

Timing of ACTH stimulation tests

In infants who are off glucocorticoids, perform an ACTH stim test at 36 weeks CGA or one week prior to discharge, provided that at least 1 week has passed since discontinuation of physiologic dose glucocorticoids. If the response is inadequate (see below for stim test interpretation), repeat the ACTH stim 1 week prior to discharge. At least 24 hours must have passed between their last course of stress dose glucocorticoids and the stim test. The stim test can be performed at any time of day.

In infants who have been unable to wean off glucocorticoids due to clinical instability, the ACTH stim test should be performed 1-2 weeks prior to discharge, after at least 12 hours have passed since their last glucocorticoid dose.

ACTH stimulation test protocol

Cosyntropin dosing depends on the suspected underlying etiology of adrenal insufficiency. If a central etiology is suspected, use low-dose (1mcg). If a primary etiology is suspected, use standard dosing (15 mcg/kg, max dose for ≤2 years old is 125 mcg).

If performing a 15 mcg/kg stim test, either IM or IV can be used. Dosing is equivalent and the timing of blood draws does not need to be adjusted (Ozsu et al, 2020). If IM dosing is used, an IV does not need to be placed.

If performing a low-dose stim, IV is preferred.

Timing of labs:

1. Baseline: no labs necessary
2. Give cosyntropin
3. 30 minutes: cortisol
4. 60 minutes: cortisol

30 and 60 minute values are critical; the 30 minute is very helpful and should be included unless there is concern for blood volume. Ledrew et al (2020) found that cortisol peaked at the 30-minute mark for 27% of neonates and at 60 minutes for 69% of neonates.

ACTH Stimulation Test Interpretation

Historically, a peak of 18 µg/dL has been used as the threshold for diagnosis of adrenal insufficiency, utilizing a polyclonal antibody assay. However, we now have newer assays (LC/MS and monoclonal antibody) that have greater specificity and recent data suggests that using a threshold of 18 results in unnecessary prolongation of glucocorticoid use. At UC Davis, blood samples are analyzed using a monoclonal antibody assay. Based on recent studies (Javorsky et al, 2021; Cortez et al, 2023), we propose a threshold of 14 µg/dL for assessing adrenal sufficiency.

- If peak cortisol is < 14 and the infant is clinically unstable, start stress dose glucocorticoids. Once stress dosing is complete, the infant should then receive physiologic dose hydrocortisone.
- If peak cortisol is < 14 and the infant is well, PRN stress dose only.
- If peak cortisol is ≥14, the infant is adrenally sufficient. No glucocorticoids (physiologic or stress) are needed.

Please consult pediatric endocrinology to review results of ACTH stimulation tests, if not already consulted.

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