ADRENAL INSUFFICIENCY - EMERGENCY MANAGEMENT

PRACTICE GUIDELINE ©

DOCUMENT SUMMARY/KEY POINTS

- Acute adrenal insufficiency can occur in patients with known adrenal (primary) disease, hypothalamo- pituitary (secondary) disorders or after adrenal suppression from glucocorticoid therapy. It should also be considered as a new diagnosis in any unwell neonate or child.
- The management of acute adrenal crisis involves the immediate administration of intramuscular (IM) or intravenous (IV) hydrocortisone ***(do not delay treatment, if IV access is difficult give an IM dose)***, fluid resuscitation and treatment of hypoglycaemia and electrolytes disturbances (low sodium, high potassium) if present.
- Patients with known adrenal insufficiency require additional steroid during intercurrent illness, significant injury, surgery or anaesthesia.
- **It is recommended that children with a known Adrenal Insufficiency be given a minimum triage category of 3 for all mild to moderate illnesses and a minimum triage category of 2 for moderate to severe illnesses or injures.**
- When in doubt, err on the side of giving stress cover.
- Trebling or quadrupling the usual dose of hydrocortisone may not be sufficient especially in patients with secondary or iatrogenic adrenal insufficiency as low maintenance doses, 5-10 mg/m^2/day of hydrocortisone are commonly used in these patients.
- This document provides empiric guidelines for stress doses in emergency situations. However, after the emergency resuscitation phase it is preferable to refer to the patient's individualised stress letter and discuss with the endocrinologist on call.
- An Emergency Management Plan and an Alert should be placed in the patient's electronic Medical Records.

Approved by:	SCHN Policy, Procedure and Guideline Committee	
Date Effective:	1st December 2020	**Review Period:** 3 years
Team Leader:	Clinical Nurse Consultant	**Area/Dept**: Endocrinology

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CHANGE SUMMARY

- Existing SCHN guideline due for mandatory review.
- Triage categories added for Adrenal Insufficiency management.
- Other minor changes throughout.
- Replaces 2017 version.

READ ACKNOWLEDGEMENT

- All clinical staff working in any SCHN Emergency Departments or Intensive Care areas or Endocrinology are to read and acknowledge they understand the contents of this document.

TABLE OF CONTENTS

1 What is adrenal insufficiency?

Adrenal insufficiency occurs when the adrenal gland is unable to produce sufficient glucocorticoid and/or mineralocorticoid hormones.

In health, the adrenal glands produce approximately 6-8 mg/m^2/day of cortisol. However, during illness there is a physiological rise in cortisol production, and substantially more is secreted. Therefore, in patients with adrenal insufficiency, glucocorticoid doses **must be** increased during times of illness.

2 Types of adrenal insufficiency

Primary: diseases of the adrenal gland

ACTH is high (in the untreated state), for example in congenital adrenal hyperplasia, Addison's disease or adrenoleukodystrophy. These patients will likely have features of glucocorticoid and mineralocorticoid deficiency.

Secondary: diseases of the pituitary or hypothalamus

ACTH is deficient e.g. idiopathic hypopituitarism, craniopharyngioma/other sellar or suprasellar tumours. These patients will predominantly have features of glucocorticoid deficiency.

Iatrogenic: chronic corticosteroid use

This is a subgroup of secondary adrenal insufficiency and can occur following withdrawal of supraphysiological corticosteroid use (duration 2 weeks or more) or as anti-inflammatory doses of corticosteroids are tapered, e.g. Crohn's disease, juvenile arthritis, systemic lupus erythematosus (SLE), asthma, nephrotic syndrome and autoimmune based neurological disorders. These patients will predominantly have features of glucocorticoid deficiency.

3 Assessment of suspected or known Adrenal Insufficiency

Children with adrenal insufficiency may present to the Emergency Department as a new diagnosis or, in existing patients, during intercurrent illness or injury.

New presentations of adrenal insufficiency: Consider in any unwell neonate or child. An intercurrent illness or other stress (e.g. surgery) may precipitate an adrenal crisis.

Clinical features may include:

- weakness & lethargy
- weight loss
- depression, anorexia, vomiting
- pigmentation (only in primary adrenal insufficiency due to excess adrenocorticotropic hormone [ACTH] production)
- hypotension (often with postural drop), collapse
- hypoglycaemia (fingerprick blood glucose level [BGL])

Biochemical features may include:

- Low sodium and high potassium (in the presence of aldosterone deficiency in primary adrenal insufficiency e.g. Congenital Adrenal Hyperplasia [CAH] or Addison's)
- Elevated serum urea and creatinine (from associated dehydration)
- Hypoglycaemia (from lack of glucocorticoid)
- Elevated plasma renin (as an index of volume depletion)
- Elevated plasma ACTH (in primary adrenal insufficiency)

4 Investigation of new onset adrenal insufficient patients

- Discuss with Senior Emergency doctor and Endocrine team.
- Try to get these investigations *before* giving hydrocortisone **if clinical condition permits**.
- Please refer to the table below as there are different sample requirement at the Westmead and Randwick laboratories.

Table 1: Investigations in new onset adrenal insufficient patients

	Westmead Campus	**Randwick Campus**
EUC	1mL lithium hep tube	1mL serum (or lithium hep tube)
Blood gas	Take specimen in blood gas syringe to one of the wards with blood gas analyser (on ice)	Send to Lab or take specimen in blood gas syringe to one of the wards with blood gas analyser (on ice)
BGL **(immediate glucometer, or from blood gas & then formal glucose)**	0.5mL in lithium heparin	0.5mL in lithium heparin or fluoride oxalate (FLOX) tube (use FLOX tube if transport likely to be delayed)
Cortisol & 17OH-Progesterone	2mL in serum or lithium hep tube (must be non-gel tubes as gel causes interference with Mass spec analysis)	1mL in serum tube
Aldosterone	2mL in lithium hep tube, ON ICE, to be spun down ASAP	1mL in serum tube, NOT on ice
ACTH	2mL in EDTA tube, ON ICE, to be spun down ASAP	1mL in EDTA tube, ON ICE, to be spun down ASAP
Renin	2mL in EDTA tube, NOT on ice	1mL in EDTA tube, NOT on ice
Urine steroid profile*	10mL in yellow top container	30mL in yellow top container

***Note:** if the patient is not a neonate and not acutely unwell a 24 hour collection should be performed (24hr urine bottle, preservative free, available from Pathology. Send full collection or 10-20mL in yellow top container with total volume recorded).*

EDTA: ethylenediaminetetraacetic acid

EUC: electrolytes, urea and creatinine.

5 Investigation of known adrenal insufficient patients

- Electrolytes, urea and creatinine [EUC] and BGL (immediate bedside glucometer and then formal glucose)
- Consider venous or capillary acid-base if very unwell. Regular monitoring of the patient's blood pressure

6 Management of Acute Adrenal Crisis

1. **GIVE STRESS HYDROCORTISONE COVER IM or IV** (see Flowchart for dose):
   Give as a single STAT dose, and then continue stress cover in 3-4 divided doses per day.
   In a known adrenally insufficient patient do not delay administration to secure venous access.

   NB: Fludrocortisone is not usually required acutely as high doses of hydrocortisone give sufficient mineralocorticoid cover.

2. **Fluids:**

   If the patient is shocked give 10-20 mL/kg 0.9% sodium chloride IV bolus and repeat as necessary. Ongoing maintenance plus deficit for dehydration given as 0.9% sodium chloride with 5% glucose.

3. **Check BGL hourly initially:**

   If BGL is less than 3.5mmol/L give 2 mL/kg of 10% glucose; check BGL in 30minutes and repeat if necessary.

4. **Check sodium and potassium:** The reference range for plasma potassium for children over the age of one month is 3.5 to 5.5mmol/L.
   (For children less than one week it is 4.5 to 6.5mmol/L, and for one week to one month it is 3.8 to 6mmol/L. This is due to both sampling artefact and neonatal physiology).

   If potassium is greater than 5.5mmol/L place on a cardiac monitor, perform a 12 lead electrocardiogram [ECG] and treat as below (Refer to Potassium Management guideline).

   Potassium greater than 5.5mmol/L without ECG changes: cardiac monitor, discuss with senior doctor or endocrinologist to consider if medical management is required.

   Potassium greater than 5.5mmol/L with ECG changes (peaked T waves, wide QRS) **or potassium greater than 6.5mmol/L *regardless* of ECG findings**, manage as above plus:

   - *Discuss with Consultant* to consider further management of hyperkalaemia (including the following).
   - Administration of IV calcium gluconate or IV calcium chloride as below.
     NB: Calcium gluconate is better tolerated and causes less phlebitis than calcium chloride.

- **If using calcium gluconate injection (0.22 mmol calcium/mL, comes in 10 mL vial):**
- IV calcium 0.11- 0.13 mmol/kg (max 4.4 mmol), inject undiluted over 5 minutes[10,12]

  (= 0.5 mL/kg, max 20 mL) per dose), inject undiluted over 5 minutes[12]
- **If using calcium chloride injection (0.68 mmol calcium/mL, comes in 10mL vial):**
  - ❖ IV calcium 0.11-0.13 mmol/kg (max 6.8 mmol), inject undiluted slowly at a maximum rate of 0.68 mmol of calcium per minute

    (= 0.2 mL/kg max 10 mL per dose), inject undiluted slowly at a maximum rate of 1 mL per minute

- **Central administration of IV calcium is preferred. If central access is not available discuss with senior doctor. If peripheral access needs to be used, ensure that a large peripheral vein is used, the IV line is patent, and flush the line after delivery. Avoid extravasation as necrosis may occur. Extravasation is managed according to the SCHN Intravenous Extravasation Management Practice Guideline.**
- *Glucose*, 5 – 10 mL/kg bolus push of 10% glucose solution. The insulin response to the glucose bolus is the most potent temporary treatment for hyperkalaemia.
- *Insulin*, 0.1 units/kg IV bolus (ultra-short acting (Novorapid or Humalog) or short acting insulin (Actrapid or Humulin R), may be necessary with the glucose. However, the patient will need to be monitored for hypoglycaemia so check BGL every 30 minutes for 4 hours.
- *Salbutamol*, either via nebuliser or intravenously.
  Note that there can be a small increase (approximately 0.1 mmol/L) in potassium within the first 3 minutes of administration.
  - *NB: Salbutamol should be considered after ECG changes have reversed*
  - Nebulised salbutamol:
    - ❖ 2.5 mg if patient weighs less than 25 kg
    - ❖ 5 mg if patient weighs greater than 25 kg

    OR
  - IV salbutamol: 4 micrograms/kg (max 250 micrograms) over 15-20 minutes
- *Intravenous sodium bicarbonate 8.4% (only useful in reducing potassium level if patient has a metabolic acidosis).*
  Note: each mL of 8.4% sodium bicarbonate solution contains 84 mg of sodium bicarbonate which gives 23 mg (or 1 mmol) of sodium and 61 mg (or 1 mmol) of bicarbonate.
  - 1 mmol/kg sodium bicarbonate 8.4%, slow IV injection

As the 8.4% solution is hypertonic and may be painful through small veins, consider dilution to 4.2% with Water for Injection (WFI) in patients less than 2 years of age.

- *Resonium A® (polystyrene sulfonate sodium),* 1 g/kg orally (or rectally in neonates)
  - Oral route is slower in onset, but longer lasting in effect compared with rectal administration.

    If given rectally mix each 1 g with 5 mL of glucose 10% or water

    Resonium should only be used rectally in term neonates and is ***contraindicated in neonates with reduced gastric motility, ileus, recent abdominal surgery or perforation and in all Oncology/Haematology patients unless approved by the treating oncologist***.

5. **Look for underlying cause**, for example sepsis or non-compliance with medication.
6. **Consider repeating the IV or IM steroid dose** if there is a poor response to initial resuscitation.

7 Management of patients with or at risk of Adrenal Insufficiency in the Emergency department

Patients with known adrenal insufficiency must be given increased doses of replacement hydrocortisone at times of physical stress. Parents should be well educated about what they need to do, but may need assistance. Some patients will have a letter that states their stress dose of hydrocortisone. Children at risk also includes those who are weaning off long term steroid medications, as the use of such medication will suppress the adrenal glands for 6-12 months post having their steroids ceased completely.

There should be a low threshold to up triage and escalating care.

It is recommended that no Child with a known Adrenal Insufficiency should be left in the waiting room.

Moderate to severe illness: (see Table 2 and Flowchart for more information)

- If the child has vomiting or diarrhoea, drowsiness or is unconsciousness, pale/mottled, has a serious injury (burn, fracture, head injury)
  - Give hydrocortisone intramuscularly or intravenously
  - Recommend a minimum triage category 2
- If the child's parents have given an injection of hydrocortisone prior to arriving it is recommended that they still be triaged as a minimum category 2 regardless of their presentation. This is due to the increased risk of rapid deterioration
- Give additional glucose containing fluids e.g. fruit juice, cordial or IV glucose if vomiting persists, to avoid hypoglycaemia.
- Treatment should continue for at least 24 hours after the child has recovered from the illness/episode.

Mild to moderate illness (see Table 2 and Flowchart for more information).

- If presenting with a mild to moderate illness such as poor appetite, or is generally unwell and/or fever >38^{o}C, AND not vomiting:
    - Give stress dose of hydrocortisone orally
    - Recommend a minimum triage category 3.
- If the child's parents have given an oral hydrocortisone stress dose prior to and they are reporting a mild illness it is recommended that they still be triaged as a minimum category 3. This is due to the increased risk of rapid deterioration.

8 Patients with known Adrenal Insufficiency Peri and Post-Anaesthetic/Operation

- At induction give single dose IV stress hydrocortisone (see Table 2). Some patients will require stress hydrocortisone for the next 24 hours or longer (given 6-8 hourly), depending on whether there is ongoing post-operative pain or other physical stress.

GENERAL IMPORTANT POINTS:

- When in doubt, err on the side of giving stress cover
- Trebling or quadrupling the usual dose of hydrocortisone may not be sufficient especially in patients with secondary or iatrogenic adrenal insufficiency at low maintenance doses, 5-10 mg/m^2/day of hydrocortisone are commonly used in these patients.
- When stress doses of steroids are required for prolonged periods of time, consider prophylactic use of proton pump inhibitor or histamine [H_2] receptor antagonist (for prevention of peptic ulceration) and blood glucose monitoring to detect hyperglycaemia.
- Patients with iatrogenic adrenal insufficiency due to long term steroid use may already be receiving a steroid dose that is equivalent to a stress dose of hydrocortisone. Therefore they may not require an increase during stress if they are still tolerating and absorbing oral steroids. However, they may still need IM hydrocortisone in episodes of diarrhoea, vomiting or any situation where they cannot take oral steroids.
  Refer to Table 3 (Relative Glucocorticoid Potency) to calculate hydrocortisone equivalents and the need for additional stress doses.
- Hydrocortisone is the steroid of choice for stress dosing. Methylprednisolone and dexamethasone (IV or oral) have no mineralocorticoid activity and are unsuitable.
- Important to have a low threshold for obtaining senior paediatric review/endocrine consultation.

Consider Intensive Care referral when children not responding to test dose steroids, for severe electrolyte or glucose abnormalities, haemodynamic instability and staff worried about the care of child.

Table 2: Empiric hydrocortisone stress doses to be used when individualised patient dose letter is not available or may be out-dated

Stress Doses for Age and Weight		
Age and Weight (kg)	**Dose of hydrocortisone for injection* (IM or IV) single stat dose (may be repeated if clinically indicated)**	**Dose of oral hydrocortisone* (maintenance dose to continue stress cover)**
Less than 6 months (less than 7 kg)	25 mg	8 mg every 8 hours
6months to 2 years (8-12 kg)	50 mg	16 mg every 8 hours
3-10 years (13-30 kg)	75 mg - 100 mg	24 mg every 8 hours
Greater than 10 years (greater than 30kg)	100 mg - 200 mg	40 mg every 8 hours

If available, please use the patient's individualised stress letter. *The doses above are based on 60-100 mg/m^2/day of stress hydrocortisone (adapted from Maguire A, Craig M et al. Management of Emergency or 'Stress' Situations where Hypoglycaemia or Cortisol Deficiency Occur. Hormones and Me Booklet, Merck Serono 2011.*

However, after the initial dose is given it is important to discuss ongoing dosing with the endocrinologist on call (as prescribing practices vary and the evidence guiding practice is empiric).

Table 3: Relative glucocorticoid potency

Natural/Synthetic Glucocorticoid	Relative glucocorticoid potency
Hydrocortisone	**1**
Prednisolone	**4**
Methylprednisolone	**5**
Dexamethasone	**25**

Example: *A 14 year old boy (150cm, 35kg, BSA= 1.2m^2) with Crohn's Disease on 40 mg prednisolone orally daily, who develops a high fever is already receiving the equivalent of 160 mg hydrocortisone per day (calculation 40 x 4=160). This is equivalent to 133 mg/m^2/day hydrocortisone, therefore no additional stress dosing required unless there is concern about oral absorption, vomiting or diarrhoea.*

Consider dose of steroids for patients who are on other medications affecting steroid requirements, such as phenytoin, carbamazepine, rifampicin, azoles (ketoconazole)

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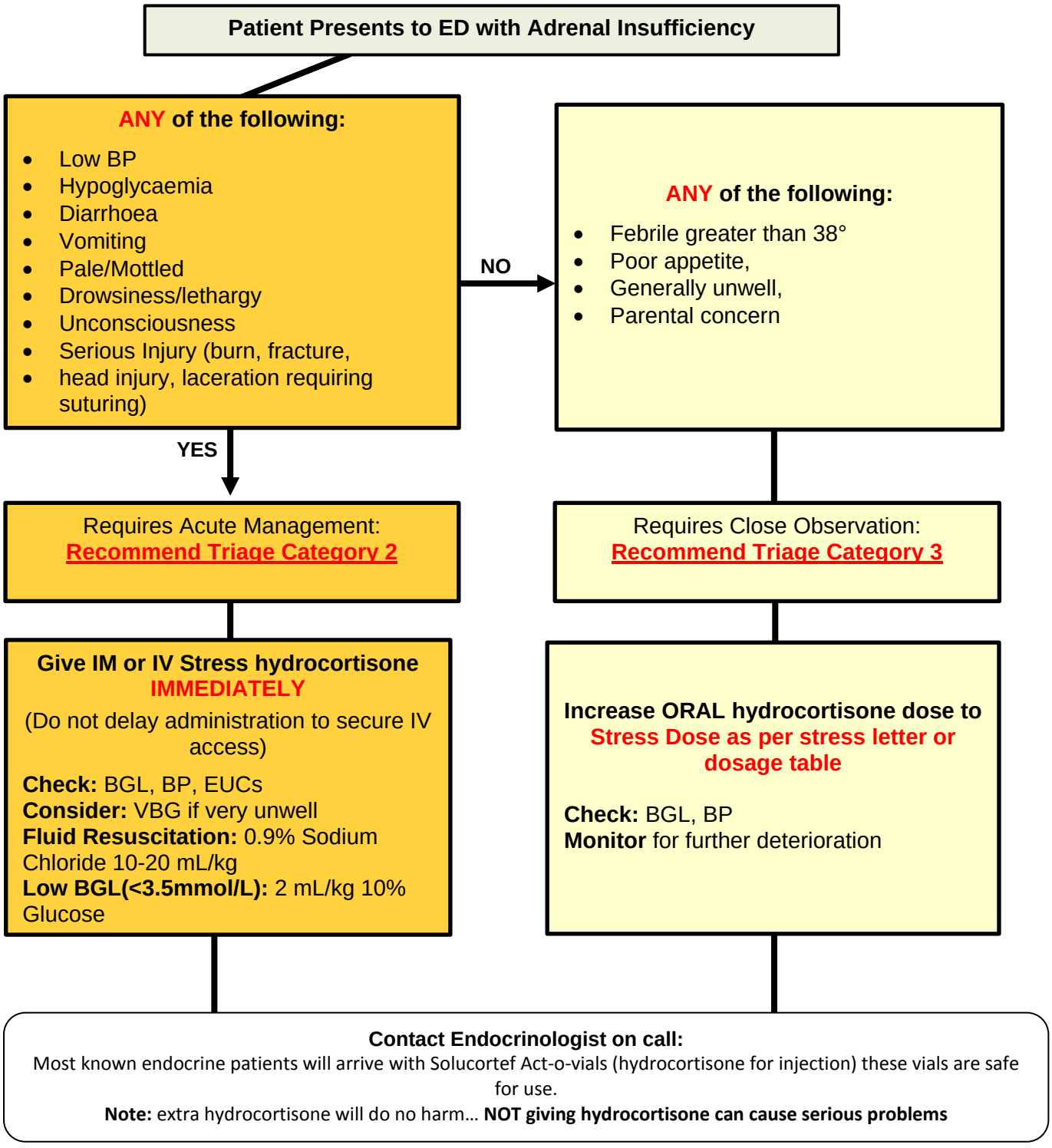
Flowchart for the Emergency Management of Adrenal Insufficiency



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Other Teams with patients who are at risk of an adrenal crisis

- Teams such as Renal, Respiratory, Gastroenterology and Metabolic who have patients who are on a long term steroid medication regime also need to prepare their patients for a possible adrenal crisis.
- Such preparation includes
  - An Emergency Letter highlighting their required dose of Hydrocortisone or Prednisolone
  - Education on what to do in times of illness
  - A travel letter if the family plan on traveling
  - Scripts for oral Hydrocortisone and IMI Hydrocortisone
  - Contact the Endocrine CNC/CNS for Hydrocortisone injection kits