JOHNS HOPKINS ALL CHILDREN'S HOSPITAL

Heart - Stress Corticosteroids in Pediatric Cardiac Disease Clinical Pathway

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Stress Corticosteroids in Pediatric Cardiac Disease Clinical Pathway

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Johns Hopkins All Children's Hospital

Stress Corticosteroids in Pediatric Cardiac Disease Clinical Pathway

Rationale:

This clinical pathway was developed by a consensus group of Johns Hopkins All Children's Hospital (JHACH) surgeons, physicians, advanced practice providers, nurses, and pharmacists to guide the use of corticosteroids in pediatric cardiac disease. It addresses the following clinical questions or problems:

1. Define adrenal insufficiency (AI) and diagnosis of AI
2. Management of patients requiring stress corticosteroids for hemodynamics
3. Management of patients with AI requiring stress corticosteroids
4. Weaning of patients requiring stress corticosteroids

Background:

Adequate adrenocortical function is essential for survival in critical illness. Most critically ill patients display elevated plasma cortisol concentrations, which reflect activation of the hypothalamic-pituitary-adrenal (HPA) axis and are considered a homeostatic adaptation. However, many critically ill patients have 'relative' or 'functional' AI, which is characterized by an inadequate production of cortisol with an increased demand during periods of severe stress.

During severe illness and stress, the activity of the HPA axis is generally enhanced, and the release of cortisol from the adrenal cortex is stimulated. Exposure to stressors, such as severe infection, trauma, burns, and surgery, results in a series of coordinated responses that enhance survival. This stress response is mainly mediated by two systems that are functionally related: the sympathoadrenal system and the HPA axis.

The sympathoadrenal system includes the sympathetic nervous system and the adrenal medulla. Its activation results in the secretion of epinephrine and norepinephrine from the adrenal medulla.

Activation of the HPA axis results in increased secretion of both corticotrophin-releasing hormone (CRH) and arginine vasopressin (AVP) from the hypothalamic paraventricular nucleus. CRH and AVP act synergistically to stimulate the release of adrenocorticotrophic hormone (ACTH) from the anterior pituitary. In turn, ACTH stimulates the production of cortisol, adrenal androgens, and, to a lesser extent, mineralocorticoids from the adrenal cortex. Many factors modulate CRH secretion during stress, including adrenergic agonists, opioids, and inflammation cytokines: interleukin (IL)-1, IL-2, IL-6, and tumor necrosis factor-α (TNF-α). Of note, cytokines,

as well as catecholamines, angiotensin II, serotonin, and vasoactive intestinal peptide (VIP), also act directly on the pituitary to stimulate ACTH secretion. In addition, the reduction, during stress, of the negative feedback from cortisol to the hypothalamus-pituitary results in increased cortisol concentrations roughly proportional to the severity of the illness. Furthermore, stress also results in decreased secretion of corticosteroid-binding globulin (CBG), leading to an increase in free cortisol concentrations.

Many critically ill patients have ‘relative' or ‘functional' AI, which is characterized by an inadequate production of cortisol with an increased demand during periods of severe stress. Recently, the term ‘critical illness-related corticosteroid insufficiency' (CIRCI) was coined. CIRCI occurs as a result of a decrease in adrenal steroid production or tissue resistance to glucocorticoids.

Given the high prevalence of AI in critically ill patients and variable management strategies, this clinical pathway was developed based on a review of existing literature, discussion with specialists, and review of other protocols to help guide providers in the JHACH Heart Institute.

Inclusion criteria:

- Patients with cardiac disease being cared for in the JHACH Heart Institute requiring stress-dose steroids

Clinical Management:

Given the variety of patients and individualized care in a critical state of illness, the clinical parameters described below should not supersede clinical judgment.

Please consult Pediatric Endocrinology for the following scenarios:

- For peri-operative corticosteroid therapy plans for patients with confirmed AI
- For corticosteroid weaning plans for patients with AI or when steroids have been on for > 14 days

Of note, it is important to be mindful of the corticosteroids, the relative glucocorticoid and mineralocorticoid activity, the approximate equivalent doses, and physiologic dose references as outlined below for patient management.

Glucocorticoid	Approximate equivalent dose (mg)	Relative glucocorticoid activity	Relative mineralocorticoid activity	Physiologic dose (mg/m^2)
Short-acting				
hydrocortisone	20	1	1	10 mg/m^2/**day**
Intermediate-acting				
prednisone/prednisolone	5	4	0.8	2 mg/m^2/**day**
methylprednisolone	4*	5	Minimal	2 mg/m^2/**day**
Long-acting				
dexamethasone	0.75	30	Minimal	0.4 mg/m^2/**day**
*Technical conversion of prednisone/prednisolone to methylprednisolone is 1.25 to 1 ratio. In clinical practice, it is not uncommon to use a 1:1 ratio for ease of conversion.				

Suspected AI:

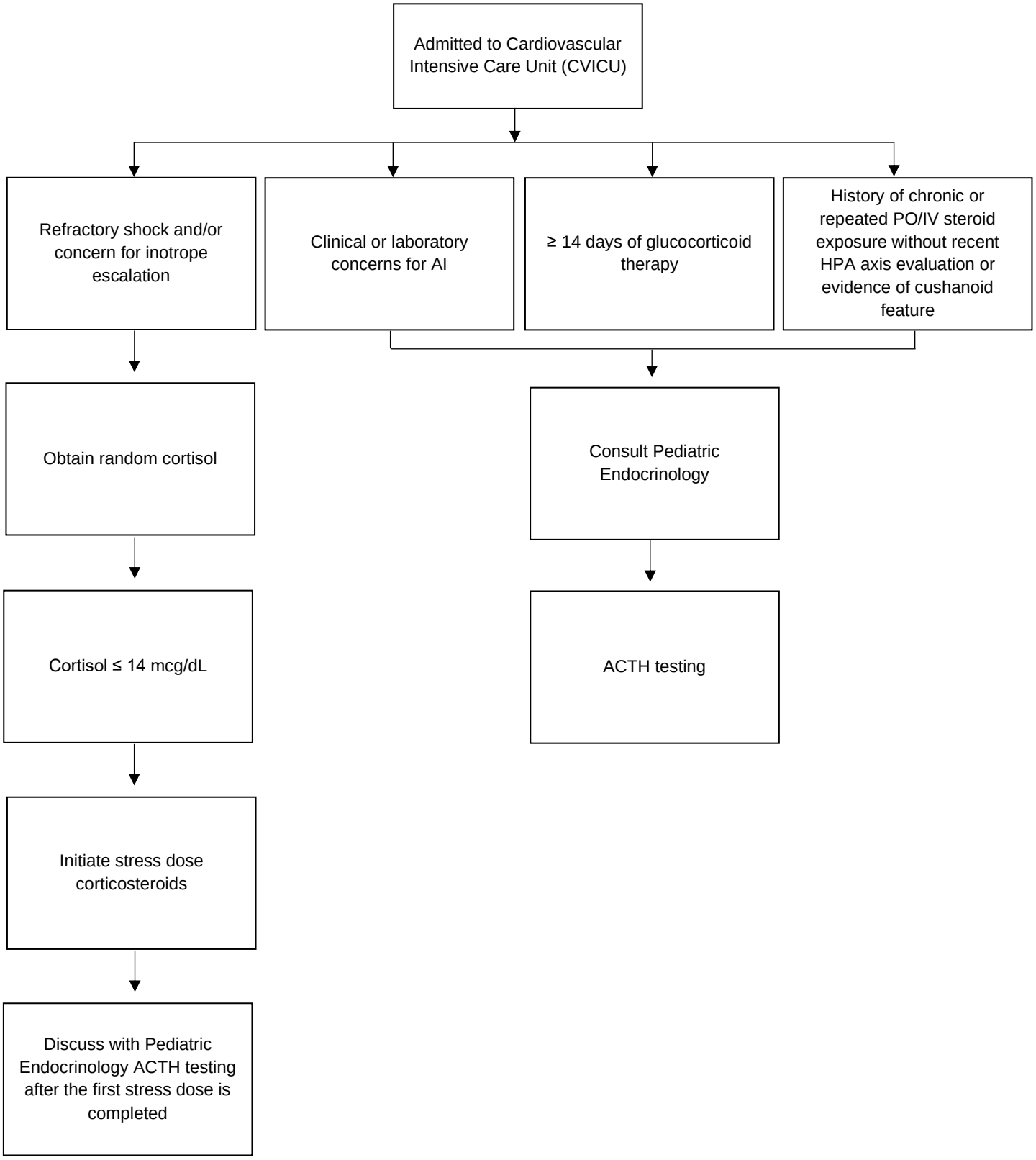
When to send random cortisol:

- Catecholamine refractory shock and/or concern for inotrope escalation

When to consider ACTH testing:

- Random cortisol OR post-cosyntropin cortisol ≤ 14 mcg/dL
- The patient had symptoms concerning for AI
    - Patient clinical factors
        - Lethargy, abdominal pain, vomiting, tachycardia, hypotension, cyanosis, cold skin
    - Laboratory markers
        - Metabolic acidosis, hypoglycemia, hyponatremia
        - Hyperkalemia indicates an additional mineralocorticoid defect as seen in primary AI
        - Serum potassium may be normal in steroid-induced or central AI
- ≥ 14 days of glucocorticoid therapy *(discuss with Pediatric Endocrinology before testing*):
        - hydrocortisone: > 10 mg/m^2/**day**
        - prednisone/prednisolone/methylprednisolone: any dose
        - dexamethasone: any dose
- History of chronic or repeated enteral (PO)/intravenous (IV) steroid exposure within the past 12 months without recent HPA axis evaluation (e.g., 3 – 5-day pulse courses of PO/IV steroids more than 6 times per year), or those with evidence of cushingoid features on physical examination (*discuss with Pediatric Endocrinology before testing)*

Random Cortisol and HPA Axis Testing



Diagnosis of AI:

An ACTH stimulation test is the gold standard for the evaluation of adrenal function and diagnosis of AI

- An ACTH-stimulation test can be normal in the setting of acute onset (< 4 weeks) central AI
- ACTH-stimulation test considerations
    - When performing an ACTH-stimulation test in patients receiving hydrocortisone, a period of ≥ 24 hours from the last dose of hydrocortisone to the pre-cosyntropin cortisol is preferred to enhance the accuracy of the response
    - When performing an ACTH-stimulation test in patients receiving feeds or dextrose-containing IV fluids (IVF) – the ideal condition is not receiving feeds or dextrose during the test:
        - Bolus feeds: if receiving multiple bolus feedings, perform the test 1 hour before the next feed and complete the test before the next feed started
        - Continuous feeds: if receiving continuous feeds, hold feeds for 1 hour before the test and during the test
            - If the patient can't tolerate being off feeds for 2 hours, at least hold feeds during the test
        - Dextrose-containing IVF: if the patient can tolerate it, hold IVF 1 hour before and during the test
            - If can't tolerate being off for that long, at least hold IVF during the test if possible
- Normal adrenal function is supported by random or post-cosyntropin cortisol of > 14 mcg/dL
- ACTH-stimulation test:
    - The ACTH-stimulation test can be used for primary or secondary diagnosis.
        - Primary adrenal insufficiency: the adrenal glands do not produce enough steroid hormones (e.g., Addison's Disease)
            - The ACTH-stimulation test uses cosyntropin, and dosing is based on age:
                - < 2 years: 15 mCg/kg (max dose: 125 mCg/dose) IV once
                - ≥ 2 years: 250 mCg/dose IV once
        - Secondary adrenal insufficiency: the pituitary gland does not produce enough ACTH, and therefore, the adrenal glands do not make enough steroid hormones (e.g., chronic steroid use)
            - The ACTH-stimulation test uses cosyntropin, and dosing is based on age:
                - 1 mCg
    - Obtain cortisol levels as follows:
        - Before administration of cosyntropin
        - 30 minutes after administration of cosyntropin
        - 60 minutes after administration of cosyntropin
    - If peak cortisol is > 14 mCg/dL, the HPA axis is normal
    - If peak cortisol is ≤ 14 mCg/dL, the HPA axis is not normal

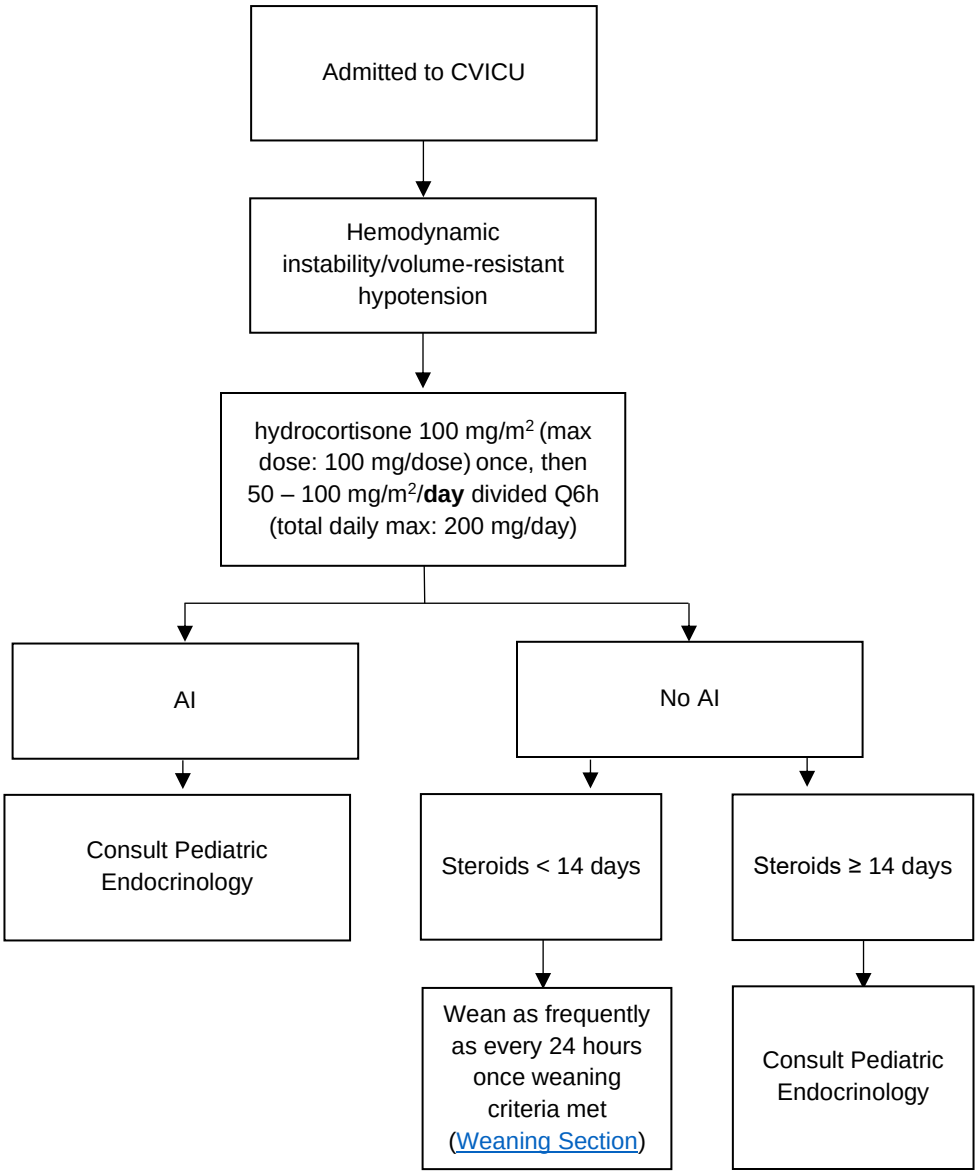
- Consult Pediatric Endocrinology (if not already consulted)
- Initiate stress steroids (in a stress state, **Appendix A**) or consult Pediatric Endocrinology for further guidance on the need for physiologic dosing in a non-stressed patient

Hemodynamic instability and pressor/volume-resistant hypotension:
Initiation of scheduled stress-dose hydrocortisone, with cessation or a taper as clinically tolerated, should be considered in either of the following circumstances:

- Persistent hemodynamic instability in the setting of escalating vasoactive therapy and volume resuscitation
- Recommended by Pediatric Endocrinology

Dosing:
This is typically ordered as a one-time dose of 100 mg/m^2 (max dose: 100 mg/dose), followed by scheduled 50 – 100 mg/m^2/day divided Q6h (total daily max: 200 mg/day) stress-dose hydrocortisone and subsequent taper or wean.

Corticosteroids for Hemodynamic Instability or Volume-Resistant Hypotension



Management of patients with AI:

Physiologic adrenal replacement (hydrocortisone):

- Consult Pediatric Endocrinology
- Physiologic hydrocortisone treatment should be considered in non-ill, non-stressed patients suspected of having ongoing AI
- Agent and dosing:
    - hydrocortisone is the preferred agent
    - Do NOT use dexamethasone or methylprednisolone for stress dosing as it has minimal corticoid activity
    - For patients on alternative agents, refer to **Appendix B** and discuss with Pediatric Endocrinology

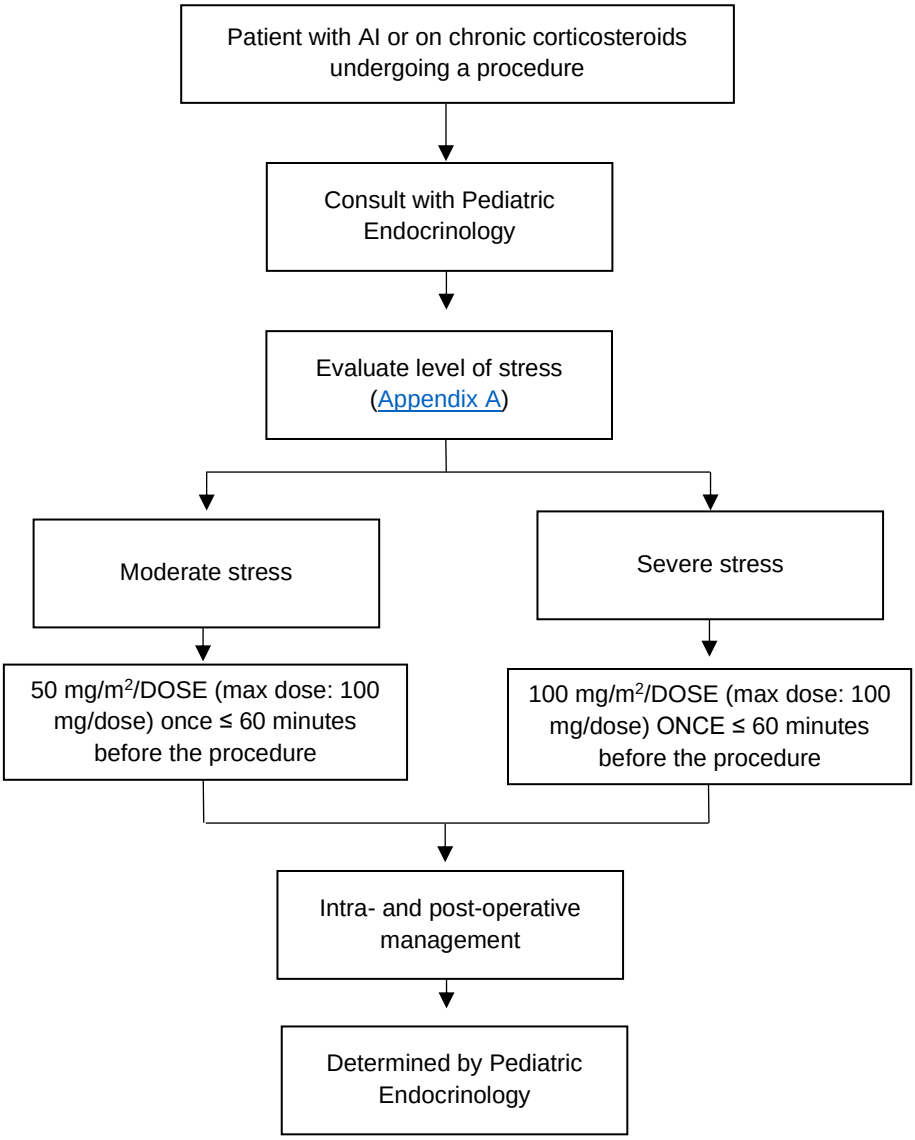
- Initial physiologic hydrocortisone dosing is as follows:
    - Body surface area (BSA) < 1.2 m^2: 8 – 10 mg/m^2/**day** divided three times daily (TID)
    - BSA ≥ 1.2 m^2: 10 – 20 mg/**day** divided TID or twice daily (BID) in adolescent patients
- Physiologic dosing can be adjusted, as per Pediatric Endocrinology

Peri-operative hydrocortisone stress dosing for patients with AI:

Patients with AI should be treated with peri-operative stress-dose hydrocortisone, for procedures associated with moderate-to-severe physiologic stress. This is typically a pre-operative dose of hydrocortisone ≤ 60 minutes before the procedure, and an intra- and post-operative plan dictated by Pediatric Endocrinology.

- Peri-operative (see **Appendix A** for stress levels)
    - Moderate stress: hydrocortisone 50 mg/m^2/DOSE (max dose: 100 mg/dose) once per Pediatric Endocrinology and typically administered by Anesthesia
    - Severe stress: hydrocortisone 100 mg/m^2/DOSE (max dose: 100 mg/dose) once per Pediatric Endocrinology and typically administered by Anesthesia
- Intra-operative
    - Discuss with Pediatric Endocrinology
- Post-operative
    - Post-operative plan determined by Pediatric Endocrinology

Patients with AI Undergoing Procedures



Duration and weaning of corticosteroids:

Weaning of corticosteroids depends on the duration of therapy, the presence of AI, or chronic corticosteroid therapy.

- Consult Pediatric Endocrinology who will assist with weaning of steroids and develop a physiologic/stress dose steroid plan for patients with one or more of the following:
    - Receiving ≥ 14 days of stress-dosed corticosteroid therapy
    - Confirmed AI
    - Chronic corticosteroid therapy
- For steroids courses < 14 days, in patients withOUT AI or chronic corticosteroid therapy, initiate weaning when the patient is hemodynamically stable and has low dose single agent vasoactive support requirements. If the total steroid course is < 14 days, consider weaning outlined below as frequently as every 24 hours
    - Patients receiving < 14 days of stress-dosed corticosteroid therapy:
        - 100 mg/m^2/**day** divided Q6h →
        - 50 mg/m^2/**day** divided Q6h →
        - 37.5 mg/m^2/**day** divided Q6h →
        - 25 mg/m^2/**day** divided Q6h →
        - 12.5 mg/m^2/**day** divided Q6h →
        - STOP

    ****Please ensure to keep steroid interval Q6h, and only change the dose****
- For weaning of corticosteroids other than hydrocortisone, please consult with Pediatric Endocrinology or discuss with pharmacy for assistance

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Outcome Measures:

- Pathway utilization
- Endocrine consults

Clinical Pathway Team

Stress Corticosteroids in Pediatric Cardiac Disease Heart Institute Clinical Pathway

Johns Hopkins All Children's Hospital

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Also Reviewed by:

Heart Institute Clinical Practice Council
Cardiac ICU Physicians
Pediatric Endocrinology

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Disclaimer:

Appendix A: Stress level examples

Stress Level	Examples
Moderate	▪ Minor/brief surgery ▪ Anesthesia or sedation for simple/routine procedures (e.g., endoscopy, bone marrow biopsy, lumbar puncture, tooth extraction) ▪ Persistent diarrhea ▪ Fever > 38 °C (100.5 °F) ▪ Single episode vomiting ▪ Pneumonia ▪ Broken bone ▪ Seizure ▪ Concussion ▪ Prolonged/intense exercise (e.g., all-day sports tournament, running marathon)
Severe	▪ Major surgery ▪ Prolonged anesthesia or deep sedation for complex/time-consuming procedures (e.g., cardiacsurgery, bowel resection, thyroidectomy) ▪ Major trauma – motor vehicle accident, head trauma ▪ Severe sepsis/septic shock ▪ Repeated emesis ▪ Pronounced dehydration ▪ Altered mental status ▪ Loss of consciousness

Appendix B: Transitioning from chronic steroid therapy in the setting of moderate and severe stress

Chronic Glucocorticoid Therapy	Stress Level	Bolus Dose	Subsequent Dosing Regimen	Home Dosing
hydrocortisone	Severe	hydrocortisone 100 mg/m^2 (max dose: 100 mg/dose) [A]	• IV: hydrocortisone 100 mg/m^2/**day** divided Q6h (25 mg/m^2/dose) • Begin 6 hours after stress dose	Hold
	Moderate	Not necessary	• IV: hydrocortisone 50 mg/m^2/**day** divided Q6h (12.5 mg/m^2/dose), up to 12.5 mg/dose • PO: hydrocortisone 50 mg/m^2/**day** divided TID (max dose: 15 mg/dose)	Hold
prednisone/prednisolone/ methylprednisolone[B]	Severe	hydrocortisone 100 mg/m^2 (max dose: 100 mg/dose) [A]	• IV: hydrocortisone 100 mg/m^2/**day** divided Q6h (25 mg/m^2/dose) • Begin 6 hours after stress dose	Continue
	Moderate	Not necessary	• IV: hydrocortisone 50 mg/m^2/**day** divided Q6h (12.5 mg/m^2/dose), up to max dose of 12.5 mg/dose • PO: ○ hydrocortisone 50 mg/m^2/**day** divided TID (max dose: 15 mg/dose) OR ○ prednisolone/prednisone 12 mg/m^2/day divided BID (max dose: 6 mg/dose) [B]	Continue
dexamethasone[C]	Severe	hydrocortisone 100 mg/m^2 (max dose: 100 mg/dose) [A]	• IV: hydrocortisone 100 mg/m^2/**day** divided Q6h (25 mg/m^2/dose) • Begin 6 hours after stress dose	Continue
	Moderate	Not necessary	• IV: hydrocortisone 50 mg/m^2/**day** divided Q6h (12.5 mg/m^2/dose), up to max dose of 12.5 mg/dose • PO: ○ hydrocortisone 50 mg/m^2/**day** divided TID (max dose: 15 mg/dose) OR ○ prednisolone/prednisone 12 mg/m^2/**day** divided BID (max dose: 6 mg/dose) [B]	Continue

[A]If calculated BSA is unavailable/unknown, may consider the following dosing: 0 – 24 months: hydrocortisone 25 mg/dose, > 24 months to 10 years: 50 mg/dose, > 10 years: 100 mg/dose
[B]Avoid methylprednisolone given minimal mineralocorticoid activity; prednisolone/prednisone have mineralocorticoid activity
[C]Avoid dexamethasone given minimal mineralocorticoid activity