

PEDIATRIC EMERGENCY MEDICINE PRACTICE

AN EVIDENCE-BASED APPROACH TO PEDIATRIC EMERGENCY MEDICINE ▲ EB MEDICINE.NET

An Evidence-Based Assessment Of Pediatric Endocrine Emergencies

It's 2:30 AM on a slow Thursday night when the triage nurse brings in an ill-appearing, tachypneic, and febrile 2-year-old with markedly delayed capillary refill. As you are listening to inspiratory crackles in the child's left lung, you notice that her medications list includes hydrocortisone and fludrocortisone. You ask the child's mother about these uncommon medications, and she informs you that her daughter has congenital adrenal hyperplasia. As you struggle to recall the specifics of this relatively rare condition, the nurse asks you whether this diagnosis is going to change the management of this critically ill child.

Most emergency clinicians are quite comfortable treating diabetic ketoacidosis (DKA) in children, but other rarer endocrine disorders in this population are likely to cause anxiety in even the most well-read emergency clinician. In addition to their complex pathophysiologies, these disorders present with an array of nonspecific complaints — the most ominous of which is an altered mental status. This issue of *Pediatric Emergency Medicine Practice* reviews the diagnosis and management of these uncommon disorders, which, if left untreated, can cause significant morbidity.

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CME Objectives

Upon completion of this article, you should be able to:

1. Cite the presentation, evaluation, and treatment of adrenal insufficiency in children.
2. Cite the presentation, evaluation, and treatment of pheochromocytoma in children.
3. Cite the presentation, evaluation, and treatment of disorders involving antidiuretic hormone (ADH) in children, including diabetes insipidus and the syndrome of inappropriate antidiuretic hormone (SIADH).
4. Cite the presentation, evaluation, and treatment of hypothyroidism and hyperthyroidism in children.

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Abbreviations

ACTH: Adrenocorticotrophic hormone
ADH: Antidiuretic hormone
BUN: Blood urea nitrogen
CAH: Congenital adrenal hyperplasia
CNS: Central nervous system
CSW: Cerebral salt wasting
DKA: Diabetic ketoacidosis
GI: Gastrointestinal
ED: Emergency department
EMS: Emergency Medical Services
FSH: Follicle-stimulating hormone
ICU: Intensive care unit
IM: Intramuscularly
IV: Intravenously
LH: Luteinizing hormone
MMI: Methimazole
PO: "per os" by mouth
PTO: Propylthiouracil
SIADH: Syndrome of inappropriate antidiuretic hormone
T₃: Triiodothyronine
T₄: Thyroxine
tid: "ter in die" three times a day
TRH: Thyrotropin-releasing
TSH: Thyroid-stimulating hormone

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Part I. Adrenal Insufficiency

Critical Appraisal Of The Literature

A literature search was performed using Ovid MEDLINE® and PubMed. Keywords included *adrenal insufficiency, congenital adrenal hyperplasia, 21-hydroxylase deficiency, and stress-dose corticosteroids*. Similar searches were performed in the Cochrane Database of Systematic Reviews and the National Guideline Clearinghouse.

Most of the literature on pediatric adrenal insufficiency published within the past 20 years has addressed its 2 main causes: congenital adrenal hyperplasia and adrenal suppression due to chronic corticosteroid use. Unfortunately, most of these articles are case series or observational studies, with few clinical trials. Within the last decade, adrenal insufficiency in critically ill children has become a hot topic, resulting in some well-designed studies that are covered in this article.

Anatomy, Epidemiology, And Pathophysiology

Acute adrenal insufficiency occurs when the adrenal cortex fails to produce enough cortisol in response to stress, which is often triggered by infection or trauma. Patients classically present with inappropriate and rapid decompensation in the presence of a stressor, but in some cases, symptoms develop with no obvious inciting event.¹ The most common cause of acute adrenal insufficiency in North America is the sudden discontinuation of or noncompliance with medication or emesis in patients who are on long-term glucocorticoid therapy.² Adrenal insufficiency also occurs in patients receiving such therapy who are subjected to stressors such as sepsis, trauma, or surgery. Although it is seen most commonly in patients who are taking long-term oral glucocorticoids, significant adrenal suppression has also been described with chronic use of high-dose inhaled, topical, and intranasal preparations.³⁻⁷

Congenital adrenal hyperplasia (CAH) is an inherited defect of cortisol synthesis and the most common cause of primary adrenal insufficiency in children.¹ A description of the pathophysiology of CAH is beyond the scope of this article, but it should be noted that these patients require long-term glucocorticoid replacement and many also require mineralocorticoid replacement. Newborn screening for CAH is now carried out in most parts of the United States.⁸ Many females with this disorder can be identified clinically at birth because of the associated virilization of their genitalia. In contrast, in unscreened males, the diagnosis is often not made until school age or later.⁹⁻¹¹

The pertinent anatomy and physiology of the adrenal gland are shown in **Figures 1 and 2**.

Differential Diagnosis

Children with acute adrenal insufficiency classically present with dehydration, hypotension, hypoglycemia, or altered mental status.¹ Since these episodes are often triggered by infection or trauma — conditions which by themselves may produce these nonspecific findings — making the diagnosis of acute adrenal insufficiency is extremely difficult on the basis of clinical signs alone. Consider adrenal insufficiency when reviewing the differential diagnoses for children with hypotension and altered mental status. (See **Tables 1 and 2**.)

Prehospital Care

Given its rarity and nonspecific symptoms, pediatric adrenal insufficiency is unlikely to be recognized by Emergency Medical Services (EMS) personnel. However, many children with acute adrenal insufficiency initially present with hypotension, hypoglycemia, and altered mental status — symptoms frequently

Figure 1. Adrenal Gland

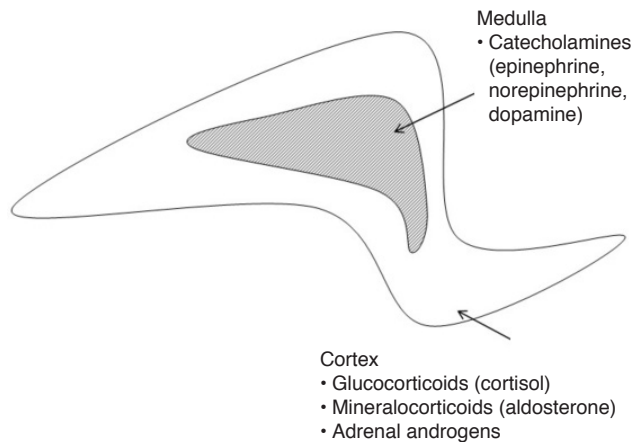
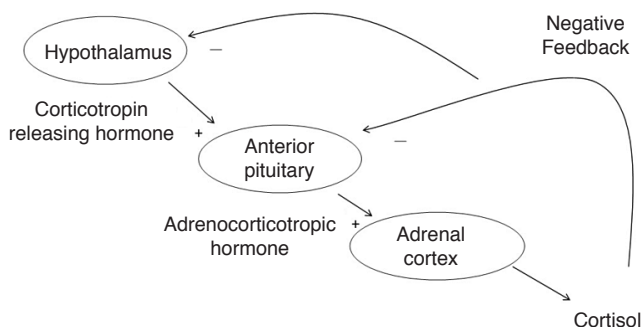


Figure 2. The Hypothalamic–Pituitary–Adrenal Axis



encountered in the prehospital setting. Fluid resuscitation with isotonic saline, correction of hypoglycemia, and a standard protocol for altered mental status should be initiated.

Emergency Department Evaluation

Initial Stabilization

Children with acute adrenal insufficiency will frequently require resuscitative efforts in the emergency department (ED). One of the first clues to adrenal insufficiency may be hypotension unresponsive to appropriate fluid resuscitation, such as in a child with presumed sepsis. As with any child with hypotension due to dehydration, 20 mL/kg of isotonic saline boluses should be administered intravenously (IV) until adequate tissue perfusion is restored. Hypoglycemia is common in young children¹ and can be corrected by infusing 5 mL/kg of dextrose 10% in water (D10) in infants, 2 mL/kg of D25 in toddlers, and 1 mL/kg of D50 in older children. Of note, children with presumed sepsis who require intubation should not receive etomidate as an induction agent. Etomidate-induced adrenal suppression is a well-described phenomenon in adults, and 2 pediatric studies have documented an increased risk of death in children with sepsis after a single bolus of etomidate during intubation.^{24,83}

Table 1. Differential Diagnosis For Children With Hypotension

Hypovolemia Dehydration Vomiting and diarrhea Glycosuric diuresis Sunstroke Burns Peritonitis Blood loss	Distributive Shock Anaphylaxis Toxic ingestions Sepsis
	Cardiogenic Shock Aortic coarctation and various other ductal-dependent lesions Aortic stenosis Myocarditis Conduction abnormalities
	Neurogenic Shock Central nervous system and spinal injuries

Table 2. Differential Diagnosis For Children With Altered Mental Status

AEIOU Tips

- A** = Alcohol abuse
- E** = Electrolytes, encephalopathy
- I** = Infection
- O** = Overdose
- U** = Uremia
- T** = Trauma
- I** = Insulin/hypoglycemia, intussusception, inborn errors of metabolism
- P** = Psychogenic (rare in young children)
- S** = Seizures, shock, shunt (ventricular shunt malfunction)

History

It is vital to determine whether there is a history of corticosteroid use when confronted with a child who is clinically unstable or appears to have sepsis. Although it is difficult to reliably estimate the degree of adrenal suppression based on the dose or duration of corticosteroid therapy, a treatment course longer than 2 weeks is typically necessary to suppress endogenous cortisol production.^{1,25} Adrenal suppression may persist for 6 to 9 months after long-term glucocorticoid therapy has been discontinued. Patients taking corticosteroids for CAH or other conditions may be wearing an identification bracelet indicating their condition. Common symptoms of chronic adrenal insufficiency are listed in **Table 3**.^{1,26-28}

Physical Examination

The physical findings in acute adrenal insufficiency are typically characteristic of the precipitating illness rather than specifically suggestive of adrenal insufficiency. Hypotension unresponsive to fluid resuscitation is characteristic of, although not pathognomonic for, acute pediatric adrenal insufficiency.^{22,23} Other findings include an altered mental status, orthostatic hypotension, and other signs of dehydration such as sunken eyes and dry mucous membranes.

The physical findings in chronic adrenal insufficiency vary widely depending on the cause. In children with primary adrenal insufficiency, increased skin pigmentation is a key finding; it is most pronounced in scars, flexion creases, areolae, gums, and nonexposed areas of skin. Physical findings in primary adrenal insufficiency and CAH are listed in **Table 3**.^{1,27,28} Children with adrenal suppression from chronic corticosteroid use may have cushingoid features (eg, truncal obesity, rounded faces, striae, and acne).

Table 3. Findings On History And Physical Examination In Chronic Adrenal Insufficiency

History	Physical Examination
Chronic fatigue	Primary adrenal insufficiency
Nausea	Increased skin pigmentation
Anorexia	Evidence of recent weight loss
Vomiting	Congenital adrenal hyperplasia
Weight loss	In girls:
Recurrent abdominal pain	Enlarged clitoris
Behavioral changes	Fused labial folds
Depression	In boys:
Reduction in school performance	Enlarged penis
Salt craving	Small testes
	In both sexes:
	Premature pubic hair

Diagnostic Studies

Laboratory Testing

Chemistry Panel

A chemistry panel may be the most useful routine test when considering the possibility of childhood adrenal insufficiency. Hypoglycemia is the most consistent laboratory finding in young children.¹ Low serum sodium levels (hyponatremia) and high serum potassium levels (hyperkalemia) will typically be present in cases of primary adrenal failure or CAH when the production of both cortisol and aldosterone is impaired. Other classic findings of aldosterone insufficiency include a reduced serum bicarbonate level and an increased chloride level (a non anion-gap metabolic acidosis). Secondary adrenal failure due to withdrawal from chronic glucocorticoid therapy or to adrenocorticotropic hormone (ACTH) deficiency will present with cortisol deficiency only.

Illness-Specific Testing

Ideally, adrenal insufficiency is a diagnosis to be suspected in the ED and confirmed after admission to the hospital. Once suspected, it is important to collect urine and blood for confirmatory testing before administering glucocorticoids, if at all possible,^{1,27,28} and it is wise to consult with a pediatric endocrinologist when ordering these highly specialized tests. (**See Table 4.**) At some institutions, serum cortisol can be measured in the ED. A random cortisol value may not be helpful in ruling out adrenal insufficiency, since a single low value does not definitively confirm the diagnosis; however, a serum cortisol concentration less than 10 mcg/dL in children who are not acutely ill or less than 18 mcg/dL in those who are acutely ill is highly suggestive of adrenal insufficiency.^{1,28,33-35, 82}

Treatment

The first priority in children with presumed adrenal insufficiency is restoration of tissue perfusion and correction of hypoglycemia, as previously discussed. Some patients with primary adrenal insufficiency will have clinically significant hyponatremia and

Table 4. Laboratory Tests In The Evaluation Of Suspected Adrenal Insufficiency

- Serum electrolytes and glucose
- Serum cortisol
- Serum ACTH
- Plasma renin activity
- Serum aldosterone
- 17-hydroxyprogesterone (if CAH is suspected)
- Urine sodium, potassium, and creatinine

Abbreviations: ACTH, adrenocorticotropic hormone; CAH, congenital adrenal hyperplasia

hyperkalemia due to aldosterone deficits. Patients with a serum potassium level greater than 6 mEq/L should be treated with one or several of the options listed in **Table 5**.²⁷

Very few pediatric studies have looked at corticosteroid dosing in children with acute adrenal insufficiency, and most current recommendations are empiric and extrapolated from adult studies. Hydrocortisone at a dose of 50 mg/m² (about 3 mg/kg) IV or intramuscularly (IM) is recommended by several authors as the initial treatment of choice.^{1,27,28,37, 82} Hydrocortisone has a mineralocorticoid effect in addition to its glucocorticoid effect (eg, 30 mg of hydrocortisone has the mineralocorticoid effect of 0.1 mg of fludrocortisone). Methylprednisolone 10 to 15 mg/m² (about 1 mg/kg) IV or IM or dexamethasone 1.5 to 2 mg/m² (about 0.1 mg/kg) IV or IM may also be given, although neither of these agents has intrinsic mineralocorticoid activity. If the child can tolerate oral medication, fludrocortisone (0.1-0.2 mg) can be given to provide mineralocorticoid activity if primary adrenal failure is suspected.

Some controversy exists as to when and how to give “stress doses” of corticosteroids to patients on chronic corticosteroid therapy. Current recommendations are to double or triple the daily dose in patients with simple febrile illnesses, such as an upper respiratory infection or streptococcal pharyngitis, for the duration of the illness.³⁸⁻⁴⁰ Children who cannot be given oral medication because of vomiting or those being treated just prior to surgery can be given IV hydrocortisone as follows: 25 mg for children under 3 years of age, 50 mg for children ages 3 to 12, and 100 mg for adolescents. Following the initial dose, these children should receive the same amount per day in divided doses. Children with more severe and life-threatening conditions, such as pneumonia, meningitis, or major trauma, require higher doses of IV hydrocortisone, up to 100 mg/m²/day (about 7 mg/kg) divided every 6 hours.^{10,38,39,41}

Disposition

With rare exception, children with new-onset adrenal insufficiency will require admission to the hospital. Often the disease process that is exacerbating the insufficiency will itself warrant admission (eg, gastroenteritis with dehydration or pneumonia with hypoxia). Children who are hemodynamically

Table 5. Treatment Of Hyperkalemia In Children

- Sodium bicarbonate 1-2 mEq/kg IV over 10 minutes
- Calcium gluconate 50-100 mg/kg (maximum dose 1 g) IV over 10 minutes
- 2 mL/kg IV bolus of D25 plus 0.1 unit/kg IV regular insulin
- Sodium polystyrene sulfonate 1 g/kg orally or rectally

cally unstable (ie, a serum sodium level less than 125 mg/dL or a serum potassium level greater than 6 mEq/dL) must be admitted to an intensive care unit (ICU).

Children with known adrenal insufficiency who present with a mild illness (eg, otitis media) and no clinical evidence of acute adrenal insufficiency can be managed as outpatients, as previously discussed, if they are able to tolerate oral medication without emesis. Close follow-up, preferably within 48 hours, should be arranged for these children prior to ED discharge. Instruct parents to return if the child’s condition worsens, specifically in the case of altered mental status or excessive vomiting.

Part II. Pheochromocytoma

Clinical Appraisal Of The Literature

A literature search was performed using Ovid MEDLINE® and PubMed using the keyword *pheochromocytoma*. Similar searches were performed of the Cochrane Database of Systematic Reviews and the National Guideline Clearinghouse. The vast majority of papers published on pediatric pheochromocytoma in the past 40 years consists of case series. Given the rarity of this illness, clinical trials focused on its management would be extremely difficult.

Anatomy, Epidemiology, And Pathophysiology

Pheochromocytomas are rare childhood tumors that arise from the chromaffin tissue of the adrenal medulla and sympathetic ganglia.¹² Pheochromocytomas originating outside the adrenal gland are often called paragangliomas. Pheochromocytomas are malignant in 12% to 40% of childhood cases, and the average age at presentation is 9 to 11 years.¹³⁻¹⁷ Pediatric pheochromocytomas are associated with familial syndromes, including multiple endocrine neoplasia, Sipple’s syndrome, Sturge-Weber syndrome, von Hippel-Lindau disease, tuberous sclerosis, and neurofibromatosis.^{13, 14, 16-21} Excess catecholamine secretion from pheochromocytomas causes symptoms such as hypertension, tachycardia, and headaches.

Differential Diagnosis

Children with pheochromocytoma most commonly present with signs and symptoms related to hypertension.¹⁵ The presence of hypertension in a child with otherwise nonspecific complaints opens up a broad differential diagnosis. (See **Table 6 on page 6.**)

Emergency Department Evaluation

History

The most common presenting symptoms related to catecholamine excess in children include headache, usually described as throbbing, and inappropriate sweating.^{12, 13, 16, 17, 21, 29-31} Other symptoms of pheochromocytoma are listed in **Table 7**. Consider pheochromocytoma when presented with children who have these nonspecific symptoms and a known multiple endocrinopathy or neurocutaneous syndrome.

Physical Examination

Sustained hypertension is the most consistent physical finding in children with pheochromocytoma, being present 88% to 93% of the time.^{12, 13} Other physical findings are listed in **Table 7**.^{13, 15-18, 29, 31} Of note, in a small percentage of cases of pediatric pheochromocytoma, the tumor mass will be palpable in the neck or abdomen.^{12, 31, 32}

Diagnostic Studies

Laboratory Testing

Normal results on a chemistry panel may help distinguish pediatric pheochromocytoma from renal causes of childhood hypertension, and fasting blood sugar will typically be elevated in children with this tumor.¹⁷

Illness-Specific Testing

As with adrenal insufficiency, the emergency clinician's role in diagnosing pediatric pheochromocytoma is primarily to consider it when the setting seems appropriate. Once suspected, diagnostic studies are of 2 types: biochemical and anatomic. The biochemical diagnosis relies on detecting an elevated level of catecholamines or their metabolites in the blood or urine and can establish the diagnosis in over 95% of patients.¹⁵ Since pheochromocytomas are a heteroge-

Table 6. Hypertension In Children

Age Group	Causes Of Hypertension
Newborns and infants	Life-threatening: Coarctation of the aorta, congenital adrenal hyperplasia, valvular insufficiency, renal vascular disease, renal parenchymal disease Non-life-threatening: Congenital renal malformations, bronchopulmonary dysplasia
Children	Life-threatening: Renal vascular disease, renal parenchymal disease, coarctation of the aorta, increased intracranial pressure, bacterial endocarditis Non-life-threatening: Essential hypertension
Adolescents	Life-threatening: Renal parenchymal disease, pre-eclampsia, toxicities Non-life-threatening: Essential hypertension

neous group of catecholamine-secreting tumors, no biochemical test is 100% sensitive.¹³ The confirmatory blood and urine tests for pheochromocytoma are listed in **Table 8**.³⁶ The availability of these tests varies by institution, and it is wise to consult a pediatric endocrinologist before ordering them. Imaging studies to determine tumor location (ideally magnetic resonance imaging) are obtained at a later date if results of initial biochemical tests are positive.

Treatment

Control of blood pressure in children with suspected pheochromocytoma is necessary to reduce the risk of end-organ damage until definitive treatment (ie, surgical resection) is possible. Unfortunately, no controlled studies in children have been published comparing the efficacy of antihypertensives used for this purpose. In children requiring admission, IV nitroprusside at a starting dose of 0.3 to 0.5 mcg/kg/min or phentolamine at a dose of 0.05 to 0.1 mg/kg has been used at some institutions, with the addition of a beta blocker such as propranolol 0.01 to 0.1 mg/kg/dose IV, if needed, to control the heart rate.^{17, 20} Labetalol (0.2-1 mg/kg IV every 10 minutes as needed) has both alpha- and beta-blocking effects and has been used by some centers, although others have had little success with it.^{16, 21, 31, 42} In children who are to be discharged pending further work-up, phenoxybenzamine at a starting dose of 0.2 mg/kg/day is advocated in many sources.^{15-21, 30, 42, 43} Calcium-channel blockers and prazosin at a starting dose of 25 mcg/kg/day are other outpatient options.^{15-17, 31, 43}

Table 7. Findings On History And Physical Examination In Pediatric Pheochromocytoma

History	Physical Examination
<ul style="list-style-type: none">• Headache• Sweating• Blurry vision• Palpitations• Dizziness• Tremors• Abdominal pain• Vomiting• Anorexia• Constipation	<ul style="list-style-type: none">• Hypertension• Tachycardia• Hyperthermia• Inappropriate sweating• Flushed or mottled skin• Dilated pupils• Hypertensive retinal changes

Table 8. Laboratory Tests In The Evaluation Of Suspected Pheochromocytoma

- Plasma
- Fractionated metanephrines
- Catecholamines
- Urine (24-hour collection)
- Fractionated metanephrines
- Catecholamines
- Total metanephrines
- Vanillylmandelic acid

Ideally, the choice of an antihypertensive agent for these children should be discussed with a pediatric endocrinologist or nephrologist.

Disposition

Children with suspected pheochromocytoma require admission if there is any clinical or laboratory evidence of end-organ damage. Children with mild symptoms may be discharged if appropriate follow-up has been arranged, ideally with a pediatric endocrinologist. Outpatient antihypertensive therapy should be discussed with the referral physician and should be begun before the child is discharged from the ED.

Part III. Disorders Involving Antidiuretic Hormone

Critical Appraisal Of The Literature

A literature search was performed using Ovid MEDLINE® and PubMed. Keywords included *diabetes insipidus*, *SIADH*, *cranial salt-wasting*, *hypernatremia*, and *hyponatremia*. Articles and studies from the pediatric literature were selected preferentially. Similar searches were performed of the Cochrane Database of Systematic Reviews and the National Guideline Clearinghouse.

Pediatric syndrome of inappropriate antidiuretic hormone (SIADH) and diabetes insipidus have not been well studied. Most publications on these topics have been case series, with a few studies addressing long-term treatment, and many of the management recommendations discussed in review articles are extrapolated from the adult literature. Perhaps of greater importance to the emergency clinician are the results of some good animal and human research on the treatment of symptomatic hyponatremia and hypernatremia.

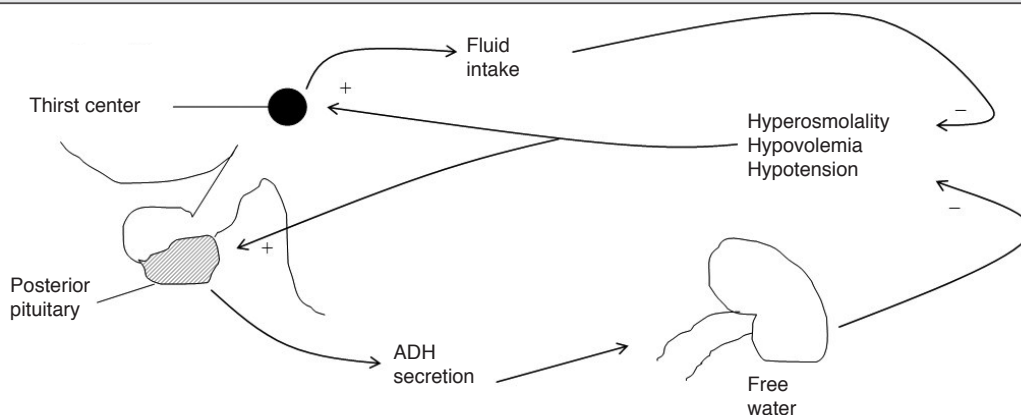
Anatomy, Epidemiology, And Pathophysiology

Antidiuretic hormone (ADH) is produced by neurosecretory neurons that originate in the hypothalamus and extend into the posterior pituitary gland. Water balance in the body is regulated by ADH and thirst. (See Figure 3.)

Diabetes insipidus is a condition defined as the passage of large volumes of dilute urine, in excess of 150 mL/kg/day in newborns, 110 mL/kg/day at 2 years of age, and 40 mL/kg/day in older children.⁴⁴ Diabetes insipidus can be divided into 2 main categories: central diabetes insipidus, caused by inadequate secretion of ADH, and nephrogenic diabetes insipidus, characterized by the inability of the kidneys to concentrate urine in response to ADH. Not surprisingly, polydipsia, polyuria, and symptoms of dehydration are the main symptoms. Table 9 on page 8 lists the causes of diabetes insipidus in children. Intracranial tumors and idiopathic causes have been the main etiologies of pediatric diabetes insipidus in most published case series.⁴⁵⁻⁴⁸ It has been observed that many children with central diabetes insipidus also have dysfunction of the anterior pituitary, with deficiencies of thyroid-stimulating hormone (TSH), growth hormone, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) or ACTH.^{45,48-50}

Syndrome of inappropriate antidiuretic hormone is caused by excessive secretion of ADH and is uncommon in children. Excess ADH results in increased free water reabsorption by the kidneys, with subsequent hypervolemia and dilutional hyponatremia. A “nephrogenic syndrome of inappropriate antidiuresis” has also been described in infants; the clinical picture is the same as that of SIADH but with low serum ADH levels.⁵¹ Clinical criteria used to diagnose SIADH are listed in Table 10 on page 8.⁵² Syndrome of inappropriate antidiuretic hormone in children is usually a transient and self-limited phe-

Figure 3. Maintenance Of Water Balance



Abbreviation: ADH, antidiuretic hormone

nomenon, with only a few case reports describing it as a chronic condition.^{53,54} The causes of SIADH in children are listed in **Table 11**.^{52,55} Although these causes have not been formally studied, some authors believe that the most common cause is the administration of vasopressin or its synthetic analogue, desmopressin.⁵⁶ These medications are commonly used to treat diabetes insipidus, von Willebrand disease, hemophilia, and bed wetting.

Differential Diagnosis

Intense polyuria and polydipsia are the most common symptoms in children with diabetes insipidus. These symptoms may not be as readily apparent in infants who are more likely to present with poor growth and symptoms of dehydration.⁵⁷ New-onset diabetes mellitus with uncontrolled hyperglycemia is a much more common cause of this clinical picture in children. Other conditions that present with symptoms similar to those of diabetes insipidus are listed in **Table 12**.

Symptoms and signs of hyponatremia without evidence of hypovolemia predominate in children with SIADH. **Table 13 on page 9** lists other conditions that can cause hyponatremia in children.^{58,59} The symptoms of hyponatremia in children are generally nonspecific and include anorexia, vomiting, lethargy, and weakness. More severe cases may present with obtundation and seizures. Syndrome of inappropriate antidiuretic hormone is an uncommon cause of hyponatremia in children, with gastrointestinal losses and water intoxication being much more common. Consider SIADH when treating a child with hyponatremia but no clinical signs of dehydration.

Table 9. Causes Of Diabetes Insipidus In Children

Central Diabetes Insipidus	Nephrogenic Diabetes Insipidus
<ul style="list-style-type: none"> Intracranial tumor (most commonly germinoma, craniopharyngioma, and optic glioma) Idiopathic Langerhans cell histiocytosis (histiocytosis X) Cerebral malformations (most commonly septo-optic dysplasia and holoprosencephaly) Trauma Infection (encephalitis and meningitis) Familial Sarcoidosis Autoimmune Hypoxia/ischemia Drugs (most commonly ethanol and phenytoin) 	<ul style="list-style-type: none"> Familial Osmotic diuresis (most commonly hyperglycemia) Metabolic (hypocalcemia and hyperkalemia) Renal disease (most commonly polycystic disease and sickle cell nephropathy) Drugs (eg, lithium, amphotericin B)

Cerebral salt-wasting (CSW) is a recently defined clinical entity with characteristics of both diabetes insipidus and SIADH.⁶⁰ (See **Table 14 on page 10**.) Like diabetes insipidus and SIADH, CSW can occur after central nervous system (CNS) insults such as trauma, infection, surgery, or tumors.^{61,84} Symptoms typically begin within 1 week of the insult and last for 2 to 4 weeks. Cerebral salt wasting is thought to be caused by atrial natriuretic peptide, a hormone which decreases the tubular reabsorption of sodium in the kidney, resulting in increased urine and sodium excretion. The net result is the inability to prevent sodium and water loss despite the presence of hyponatremia and hypovolemia. Cerebral salt wasting is marked by low serum sodium, high urine output, and renal salt loss. This is in contrast to SIADH in which hyponatremia is accompanied

Table 10. Diagnostic Criteria For Syndrome Of Inappropriate Antidiuretic Hormone

- Hyponatremia (< 135 mEq/L)
- Serum hypo-osmolality (< 280 mOsm/kg)
- Urine sodium > 25 mEq/L
- Urine osmolality > serum osmolality in the absence of renal, adrenal, or thyroid disease or dehydration

Table 11. Causes Of Syndrome Of Inappropriate Antidiuretic Hormone In Children

Central Nervous System Disorders

- Infection (encephalitis and meningitis)
- Trauma
- Hypoxia/ischemia
- Intracranial tumors
- Congenital malformations

Intrathoracic Disorders

- Infection (pneumonias and tuberculosis)
- Positive-pressure ventilation
- Decreased left atrial pressure (most commonly in asthma or cystic fibrosis)

Medications

- Desmopressin or exogenous vasopressin
- Acetaminophen
- Chemotherapeutic agents (vincristine, vinblastine, and cisplatin)
- Anticonvulsants (carbamazepine, oxcarbamazepine, and valproic acid)
- Tricyclic antidepressants
- Selective serotonin-reuptake inhibitors
- Phenothiazines

Table 12. Conditions With Symptoms Similar To Diabetes Insipidus

- New-onset diabetes mellitus
- Sickle cell disease
- Medications (eg, methylxanthines, diuretics, carbamazepine)
- Renal disease (interstitial nephritis, renal tubular acidosis)
- Electrolyte abnormalities (hypercalcemia, hypokalemia)
- Primary polydipsia (hypothalamic lesions, psychogenic causes)

by low urine output. It is important to distinguish between SIADH and CSW, since the fluid management of each differs considerably.

Emergency Department Evaluation

Initial Stabilization

Many children with diabetes insipidus will present with characteristic signs of dehydration. Treat this type of hypovolemia in standard fashion with 20 mL/kg isotonic saline boluses until adequate fluid volume has been restored.

The most critically ill children with SIADH will present with signs of cerebral edema and herniation caused by hyponatremia. Seizures and respiratory arrest are the most serious manifestations.⁵⁹ Seizures should be initially managed in standard fashion with supplemental oxygen, rapid glucose testing, and the administration of benzodiazepines. (Keep in mind that the hyponatremic etiology of the seizure will rarely be apparent until after formal laboratory testing.) Respiratory arrest, even when managed in an appropriate fashion, has an exceptionally grim prognosis.⁵⁹

History

Most older children with diabetes insipidus present with the classic symptoms of polyuria and polydipsia. Nocturia and new-onset bed wetting may also be present. Infants are more likely to present with symptoms of dehydration and poor growth, since they don't have free access to fluids.⁵⁷ Consider diabetes insipidus in children with these symptoms and a known intracranial tumor, cerebral malformation, or recent CNS infection or trauma. Ask about a family history of similar illnesses in children with these symptoms, since 5% of cases of diabetes insipidus in children are familial.⁴⁵ In reality, diabetes insipidus will probably be the first diagnosis considered in the child with classic symptoms of new-onset diabetes mellitus who has a surprisingly normal blood glucose level.

Symptoms of hyponatremia predominate in children with SIADH. Most children remain asymptomatic until the serum sodium level drops below 125 mEq/L,^{55,62,63} and symptoms are more likely to become apparent when levels have dropped rapidly. Unfortunately, the symptoms of hyponatremia are

rather nonspecific. Headache, nausea, vomiting, and generalized weakness are the most consistent findings.^{55,58,59,62} Progressive neurologic abnormalities include lethargy, confusion, and agitation as hyponatremic encephalopathy progresses. Consider SIADH when a child is found to be hyponatremic in combination with a recent history of a CNS insult or use of desmopressin.

Physical Examination

In children with diabetes insipidus, physical findings, if any, reflect a volume-contracted, hypernatremic state. Dry mucous membranes, sunken eyes, tachycardia, and listlessness may be present. In severe cases, the child may be comatose, with reduced skin turgor, causing the abdominal skin to have a doughy texture. Hyponatremia in children may result in increased muscle tone, nuchal rigidity, and brisk reflexes.

Infants with diabetes insipidus can have a failure-to-thrive appearance with wasted extremities and a protuberant abdomen. Vision may be impaired in children whose diabetes insipidus is caused by an intracranial tumor. Since many children with diabetes insipidus have associated anterior pituitary dysfunction, look for signs of coexisting endocrinopathies. (See Table 15 on page 10.)

The physical findings in SIADH are primarily due to hyponatremia, with most signs indicative of CNS dysfunction. Generalized weakness, hyporeflexia, dilated pupils, and progressive alteration of mental status from mild confusion to coma typically occur.^{59,63} Note that these symptoms occur in children without evidence of dehydration, a fact that distinguishes SIADH from many other causes of hyponatremia in children.

Diagnostic Studies

Laboratory Testing

Chemistry Panel

Hyponatremia is typically present in infants with diabetes insipidus owing to the loss of free water. In older children, who are able to increase their fluid intake, serum sodium may not be elevated. Children who are dehydrated on presentation will usually have an elevated blood urea nitrogen (BUN)-to-

Table 13. Causes Of Hyponatremia In Children

Hypovolemia	Normovolemia/Hypervolemia	States of Apparent Hyponatremia
GI losses (vomiting and diarrhea)	SIADH	Hyperosmolar DKA, nonketotic hyperglycemia)
Diuretics	Renal failure	Factitious (hyperlipidemia and hyperproteinemia)
Cerebral salt-wasting	Water intoxication	
Skin losses (burns and cystic fibrosis)	Nephrotic syndrome	
Mineralocorticoid deficiency	Cirrhosis	
Salt-wasting nephropathies	Hypothyroidism	
	Glucocorticoid deficiency	
	Congestive heart failure	

Abbreviations: DKA, diabetic ketoacidosis; SIADH, syndrome of inappropriate antidiuretic hormone

creatinine ratio (> 20:1), as is typical of a volume-depleted state.⁶⁴ As previously stated, a normal serum glucose quickly rules out diabetes mellitus.

The chemistry panel in children with SIADH reflects their diluted, hypervolemic state. Hyponatremia (serum sodium < 135 mEq/L) is present by definition. The BUN-to-creatinine ratio is usually less than 10:1.^{54,65}

Urine Specific Gravity

Although this test is neither sensitive nor specific for either of these disorders, a urine specific gravity can usually be measured rapidly by dipstick and is of value in the diagnosis of diabetes insipidus and SIADH in the ED. Children with diabetes insipidus will typically have dilute urine with a specific gravity of less than 1.005 mOsm/kg.⁶⁴ Those with SIADH, on the other hand, will have a concentrated urine, usually with a specific gravity above 1.030 mOsm/kg.

Urine Osmolality And Serum Osmolality

If available to the emergency clinician, measurements of urine and serum osmolalities are extremely valuable in diagnosing diabetes insipidus and SIADH. (See Table 16 on page 12.)

Treatment

In most cases, the diagnosis of diabetes insipidus will not be known at the time of presentation and

Table 14. Characteristics Of SIADH, CSW, And Diabetes Insipidus

Variable	SIADH	CSW	Diabetes Insipidus
Intravascular volume	Hypervolemic	Hypovolemic	Hypovolemic
Serum sodium	Low	Low	High
Urine output	Low	High	High
Urine sodium	High	High	Normal
Primary treatment	Fluid restriction	Sodium and fluid resuscitation	Fluid resuscitation

Abbreviations: CSW cerebral salt wasting; SIADH, syndrome of inappropriate antidiuretic hormone

Table 15. Anterior Pituitary Endocrinopathies

Hormonal Deficiency	Symptoms and Clinical Findings
ACTH	Fatigue, weight less, postural hypotension, hypoglycemia
TSH	Poor growth, lethargy, constipation, dry skin
Growth hormone	Poor growth, hypoglycemia, truncal obesity
FSH / LH	Delayed puberty, micropallus

Abbreviations: ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; TSH, thyroid-stimulating hormone

will be considered only after initial resuscitation with isotonic saline. At this point, treat these patients the same as those being treated for hypernatremic dehydration. Although correction of hypernatremia is necessary to prevent long-term sequelae such as myelinolysis and cellular necrosis in the brain, correction must take place at a controlled rate.⁶⁶ Overly zealous correction of hypernatremia results in cerebral edema, which can cause seizures, coma, permanent neurologic damage, and death.^{59,62,66-69} The correction rate for serum sodium should not exceed 0.5 mEq/L/hr when treating hypernatremia in children,^{70,71} and most studies have suggested correcting pediatric hypernatremia over a 48- to 72-hour period.^{66,72,73} Hypotonic fluid (0.2% sodium chloride or 0.45% sodium chloride, depending on the level of hypernatremia) can be used for this purpose, with no particular regimen having been proved to be superior to another. Given this fact, it is wise to discuss the particular treatment approach with a pediatric intensivist. Although desmopressin is the treatment of choice for diabetes insipidus, its use in the ED should be restricted to those children confirmed to have diabetes insipidus. This is another treatment option that should be used only after consultation with an appropriate subspecialist.

Like diabetes insipidus, SIADH in children is usually first considered once the initial laboratory results are known. Since hyponatremia is the main cause of morbidity in SIADH, treatment should be focused on correcting this electrolyte abnormality. Fluid restriction is the mainstay of therapy. In children with signs of cerebral edema, including altered mental status, seizures, or coma, more rapid correction is necessary. Although the use of 0.9% sodium chloride (154 mEq/L) would seem to be a reasonable option to correct severe hyponatremia, its use in SIADH specifically may, paradoxically, make the hyponatremia worse.^{63,74} Instead, 3% sodium chloride should be administered to increase the serum sodium level in children with symptomatic hyponatremia. Keep in mind that the key to using 3% sodium chloride is to raise the serum sodium level quickly enough to reverse the neurologic symptoms but not so quickly that it causes the dreaded complication of cerebral osmotic demyelination,⁷⁵⁻⁷⁷ which leads to various permanent neurologic disabilities and often death. The optimal rate at which to correct symptomatic hyponatremia is a matter of some controversy.^{63,78,79} Many authorities have suggested an infusion rate of 1 to 2 mL/kg/hr of 3% sodium chloride until neurologic symptoms improve or the serum sodium level exceeds 125 mEq/L.^{59,62,63,65,80} This should cause a rise in the serum sodium level of approximately 1 to 2 mEq/L/hr. Furosemide (1 mg/kg IV) can also be given to increase free water loss by the kidney.⁶³ Check serum electrolytes every 2 hours in children who are being treated with 3% sodium chloride.

Many authorities recommend not exceeding a serum sodium correction rate of more than 8 to 12 mEq/L/day.^{58,62,63,65,77,78,80,81}

Disposition

Admit any child in whom diabetes insipidus or SIADH is suspected. A fluid deprivation test may be necessary to confirm the diagnosis of diabetes insipidus. A search for other endocrinopathies may be necessary in both diabetes insipidus and SIADH. The close monitoring of fluid intake and output and of serum electrolytes is of more immediate importance in both conditions. Children with hemodynamic instability, any evidence of cerebral dysfunction, or a serum sodium level less than 125 mEq/L should be admitted to an intensive care setting.

Part IV. Thyroid Disorders

Critical Appraisal Of The Literature

A literature search was performed using Ovid MEDLINE® and PubMed. Keywords included *acquired hypothyroidism, congenital hypothyroidism and hyperthyroidism, Graves' disease, thyrotoxicosis, and thyroid storm*. Similar searches were performed of the Cochrane Database of Systematic Reviews and the National Guideline Clearinghouse.

The majority of studies on pediatric hypothyroidism in recent decades have addressed congenital hypothyroidism, evaluating both programs that screen for this disorder and treatment options. Pediatric hyperthyroidism is a relatively rare disorder, with virtually all papers published on this topic being case series, and most recommendations about the treatment are individual or consensus opinions. Thyroid storm is exceptionally rare in children, with only a few case reports published; therefore, guidelines for managing this condition must be extrapolated from the adult literature.

Anatomy, Epidemiology, And Pathophysiology

Hypothyroidism is classified as primary (ie, resulting from a failure of the thyroid gland to produce thyroid hormones), secondary (ie, due to a lack of production of thyroid-stimulating hormone [TSH] by the pituitary), or tertiary (ie, caused by the failure of the hypothalamus to produce thyrotropin-releasing hormone [TRH]). Pediatric hypothyroidism can be congenital (when thyroid hormone production is inadequate at birth) or acquired (when it develops after the child has reached 6 months of age). Since thyroid hormones influence all aspects of normal development, including nervous system myelination, it

is not surprising that untreated hypothyroidism is a significant cause of mental retardation worldwide.

Congenital hypothyroidism occurs in 1:3000 to 1:4000 newborns, and the female-to-male prevalence is 2:1.⁸⁵ The majority of cases are due to dysgenetic or ectopic thyroid glands. The presenting symptoms are few and often nonspecific soon after birth, making it extremely difficult to diagnose clinically in the first few weeks of life.⁸⁵ For this reason, newborn screening programs were developed in the 1970s and are now implemented in most industrialized nations. As with most screening programs, however, a small number of newborns who have congenital hypothyroidism are not detected.^{86,87}

Acquired hypothyroidism starting after 2 years of age does not carry the risk of permanent mental retardation associated with congenital hypothyroidism. Since the routine addition of iodine to foods, the incidence of acquired hypothyroidism has decreased significantly in most developed countries. Autoimmune (Hashimoto) thyroiditis is the most common pediatric cause of acquired hypothyroidism in the United States.⁸⁹ This illness occurs twice as often in females as males and usually presents in early to mid puberty. The incidence of Hashimoto thyroiditis during adolescence is approximately 1% to 2%.⁹⁰ Other causes of acquired hypothyroidism are listed in **Table 17 on page 13**.

A review of the key anatomic and physiologic features of the hypothalamic–pituitary–thyroid axis can be found in **Figure 4 on page 13**.

Hyperthyroidism occurs much less commonly than hypothyroidism in children. Thyrotoxicosis defines the clinical response to excessive amounts of thyroid hormones. Like hypothyroidism, pediatric hyperthyroidism can be divided into 2 main categories: congenital (neonatal) and acquired. Thyrotoxicosis factitia, hyperthyroidism caused by the ingestion of excessive amounts of thyroid hormone, has been reported with diet pill use among adolescents and accidental ingestions by toddlers.⁹⁷ Other causes of pediatric hyperthyroidism are listed in **Table 18 on page 13**.

Neonatal hyperthyroidism is caused by the transplacental passage of thyroid-stimulating immunoglobulins in pregnant women with Graves' disease and rarely Hashimoto thyroiditis. It is estimated that less than 2% of infants born to mothers with Graves' disease will manifest symptoms of hyperthyroidism.⁹⁸ Neonatal thyrotoxicosis usually presents within a few days after birth but may be delayed for a week or more in infants born to mothers who are taking antithyroid medication.^{98,99} The duration of congenital hyperthyroidism is determined by the persistence of the maternal antibodies in the newborn, and the condition usually remits after 8 to 20 weeks.¹⁰⁰ Although typically transient in nature, congenital hyperthyroidism may cause prolonged intellectual impairment.¹⁰¹

The vast majority of cases of acquired hyperthyroidism in developed countries are due to Graves' disease, and it is estimated that only about 5% of all patients with this disease are diagnosed before age 18.¹⁰² Graves' disease is caused by the production of antibodies directed against the thyroid hormone receptor on the thyroid gland as well as antigens in the orbital tissues. Given this fact, it is not surprising that up to 60% of children with Graves' disease will have a family history of autoimmune thyroid disease.¹⁰³ Pediatric Graves' disease is rare in prepubertal children, peaks during adolescence, and affects girls approximately 4 times more often than it does boys.⁹⁶ Uncontrolled hyperthyroidism in children may cause behavioral problems, emotional lability, accelerated bone maturation, and high-output cardiac failure.

Thyroid storm, also called thyrotoxic crisis, is a loosely defined clinical condition caused by excessive thyroid hormone release in a patient with preexisting hyperthyroidism. Patients present with tachycardia, fever, abdominal pain, emesis, and altered mental status ranging from agitation to seizures and coma. Although rare in children, this condition has a 20% mortality rate in adults. Thyroid storm typically results from a precipitating event such as surgery, severe infection, DKA, or trauma. Thyroid storm has also been reported in children after the discontinuation of antithyroid medication and after radioactive iodine therapy.¹⁰⁴

Differential Diagnosis

Of all the symptoms and signs of hypothyroidism in children, lethargy in a neonate is the one situation most likely to lead to an ED visit. Although hypothyroidism is not common in the Western world, it should be considered a possibility in the differential diagnosis of a lethargic infant. (See Table 19 on page 13).

Many symptoms of pediatric hyperthyroidism are nonspecific and include weight loss, emotional lability, decreased school performance, frequent bowel movements, and feeling warm. One helpful finding, if present, is thyroid enlargement, which is present in most affected children. Be certain to check for thyromegaly in any child with unexplained tachycardia or tremor.

The predominant symptoms of thyroid storm (hyperpyrexia, mental status changes, and arrhyth-

mias) can mimic several other illnesses, most notably CNS infections, sepsis, and anticholinergic or sympathomimetic ingestions. Children with thyroid storm may have a history of hyperthyroidism, but some rarely present with these symptoms because of a delay in the diagnosis. Review of systems in previously undiagnosed hyperthyroidism should be positive for the symptoms noted above, and the finding of a palpable goiter is further indication of the disease.

Emergency Department Evaluation

Initial Stabilization

Children with hypothyroidism who present to the ED with lethargy should undergo finger-stick blood sugar testing and pulse oximetry; if opioid toxicity is suspected, IV or IM naloxone (0.1 mg/kg if < 20 kg and 2 mg if > 20 kg) should be administered.

Children with hyperthyroidism may require rapid treatment for hyperpyrexia and tachyarrhythmias, especially atrial fibrillation. Treat febrile children suspected of having hyperthyroidism with acetaminophen and with external cooling measures if fever is severe. Salicylates specifically should be avoided, since they displace thyroid hormone from binding proteins in the serum, resulting in an increase in free thyroid hormone.¹⁰⁵ To achieve rate control in children with sinus tachycardia and atrial fibrillation, administer propranolol 0.01 to 0.1 mg/kg/dose IV or esmolol 0.1 to 0.5 mg/kg load IV, followed by an infusion of 25 to 100 mcg/kg/min. For children in whom beta-blockers are contraindicated, such as in severe asthma, diltiazem 0.25 mg/kg IV or digoxin 5 to 15 mcg/kg IV can be used for rate control in cases of atrial fibrillation.¹⁰⁶

History And Physical Examination

The common findings on history and physical examination in hypothyroidism are listed in Table 20 on page 14.^{89,91-94} Since the vast majority of newborns with congenital hypothyroidism will not have clinical manifestations at birth, universal neonatal screening is essential to permit early intervention. If neonatal hypothyroidism is suspected, it is important to test thyroid function, since screening may not be done when infants are born at home or outside the United States. In addition, human error in screening labs or failure to follow up on abnormal results can occur.

Table 16. Urine And Serum Osmolalities in Diabetes Insipidus And SIADH

	Urine Osmolality	Serum Osmolality	Relationship
Diabetes insipidus	< 300 mOsm/L	> 300 mOsm/L	Serum osmolality > Urine osmolality
SIADH	> 100 mOsm/L	< 275 mOsm/L	Serum osmolality < Urine osmolality

Abbreviation: SIADH, syndrome of inappropriate antidiuretic hormone

The onset of symptoms in children with acquired hypothyroidism is often very subtle and may be apparent only to the primary care physician who follows a child's maturation and development. The presence of goiter may be the only sign that would lead an emergency clinician to consider hypothyroidism. As with many autoimmune illnesses, thyroiditis may occur in association with other autoimmune disorders such as type I diabetes mellitus, celiac disease, or systemic lupus erythematosus. Be sure to ask about medications and a family history of thyroid disorders when considering a diagnosis of hypothyroidism in children. (See **Table 17**.)

The characteristic history and physical findings in hyperthyroidism are summarized in **Table 21** on

Table 17. Causes Of Acquired Hypothyroidism In Children

Autoimmune (Hashimoto) thyroiditis

- Increased incidence with Turner, Klinefelter, and Down syndromes

Iodine deficiency

- The most common cause globally, although rare in developed nations

Surgical excision

- May occur with resection of thyroglossal duct cyst

Thyroid irradiation

- External irradiation of nonthyroid tumors
- Therapeutic radioiodine

Medication effects

- Thionamides (propylthiouracil, methimazole, carbimazole)
- Lithium
- Dilantin
- Amiodarone

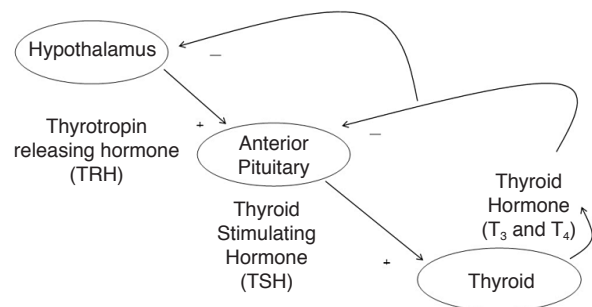
Late-onset congenital hypothyroidism

- Thyroid dysgenesis
- Thyroid hormone resistance

Secondary and tertiary causes

- Central nervous system tumors
- Neurosurgery
- Cranial irradiation
- Head trauma

Figure 4. The Hypothalamic–Pituitary–Thyroid Axis



Abbreviations: T₃, triiodothyronine; T₄, thyroxine

page 14.^{101,107-112} A thorough prenatal history may be the initial clue to the diagnosis of neonatal hyperthyroidism. The vast majority of infants with neonatal hyperthyroidism will be born to mothers with a history of current or prior treatment for Graves' disease. Keep this fact in mind when evaluating a neonate for being "jittery" or "not feeding well."

Many children diagnosed with acquired hyperthyroidism will, in retrospect, have had subtle symptoms for months or even years. Many of the early signs, such as restlessness, irritability, and decreased school performance, may be attributed to behavioral problems or even attention deficit–hyperactivity disorder.⁹⁶ The most readily identifiable clinical signs of hyperthyroidism in children are goiter and unexplained tachycardia, both of which will be present in the majority of cases. The thyroid gland is usually diffusely and symmetrically enlarged. Roughly half of all children with hyperthyroidism will have pro-

Table 18. Causes Of Pediatric Hyperthyroidism

Neonatal

- Maternal Graves' disease and Hashimoto thyroiditis

Acquired

- Graves' disease
- Thyroiditis
- Iodine-induced hyperthyroidism
- McCune–Albright syndrome
- Thyroid hormone ingestion (thyrotoxicosis factitia)
- Thyroid neoplasms
- Thyroid-stimulating hormone hypersecretion (often caused by a pituitary tumor)
- Pituitary resistance to thyroid hormones

Table 19. Causes Of Lethargy In Infants

- **Infectious diseases**
 - Sepsis
 - Meningitis
- **Cardiac disease**
 - Congenital heart disease
 - Supraventricular tachycardia
- **Adrenal insufficiency**
- **Metabolic disorders**
 - Hyponatremia, hypernatremia
 - Inborn errors of metabolism
 - Hypoglycemia
- **Toxins**
- **Severe anemia**
- **Gastrointestinal disorders**
 - Gastroenteritis with dehydration
 - Pyloric stenosis
 - Intussusception
- **Neurologic disease**
 - Infantile botulism
 - Child abuse (eg, intracranial trauma)

ptosis, although this is typically not as pronounced as it is in adults.^{99,102}

Unlike other manifestations of hyperthyroidism, thyroid storm is not a subtle clinical entity. Its defining features include fever as well as dysfunction of the cardiovascular, gastrointestinal, and central nervous systems.¹¹³ The temperature typically exceeds 38.9°C (102°F), and the pulse is usually above 140 beats/min, often with atrial fibrillation. Signs of congestive heart failure may be present. Vomiting and diarrhea are frequent symptoms, and the patient may be jaundiced. Signs of CNS dysfunction range from agitation to delirium and even coma. Some patients with thyroid storm may present with a seizure of new onset.

Diagnostic Studies

Laboratory Testing

The laboratory abnormalities associated with severe, long-standing hypothyroidism include anemia, hyponatremia, hypercholesterolemia, and rarely

Table 20. Clinical Characteristic Of Hypothyroidism

Congenital Hypothyroidism	Acquired Hypothyroidism
<p>Findings in the first month:</p> <ul style="list-style-type: none"> • Prolonged neonatal jaundice • Edema of the eyelids, hands, and feet • Poor feeding • Hypothermia • Large anterior and posterior fontanelles • Decreased muscle tone <p>Findings beyond the first month:</p> <ul style="list-style-type: none"> • Infrequent and hard stools • Failure to gain weight • Lethargy • Dry skin • Large tongue • Hoarse cry • Umbilical hernia 	<p>Findings between 6 months and 3 years:</p> <ul style="list-style-type: none"> • Coarse facial features • Dry skin • Deceleration in linear growth • Hoarse cry • Large tongue <p>Findings during childhood:</p> <ul style="list-style-type: none"> • Deceleration in linear growth • Delay in eruption of teeth and in shedding of primary teeth • Fatigue • Weight gain • Constipation • Dry skin • Generalized swelling • Precocious sexual development without pubic hair <p>Findings during adolescence:</p> <ul style="list-style-type: none"> • Delayed onset of puberty • Deceleration in linear growth • Constipation • Dry skin • Galactorrhea in girls • Generalized swelling • Bradycardia • Enlarged thyroid gland • Cold intolerance • Irregular, often heavy periods

hypoglycemia. The ideal screening tests for children with suspected hypothyroidism are TSH and free thyroxine (T₄) levels.^{95,96} This combination allows for the identification of primary, secondary, and tertiary causes of hypothyroidism. Since the total T₄ level can be altered by the availability of binding proteins in the serum, it is not as reliable as the free T₄ level. Similarly, triiodothyronine (T₃) is an unreliable indicator of hypothyroidism.

Measuring TSH is the single best screening test for hyperthyroidism, since this hormone will be undetectable in the vast majority of pediatric cases.¹¹⁴ Most authors also recommend obtaining a free T₄ level and, if possible, a total or free T₃ level.^{96,99,114-117} In a small minority of cases of hyperthyroidism, T₃ will be elevated and free T₄ will be normal. If a free T₄ level cannot be obtained, a total T₄ level can be used, even though it is not as reliable as free T₄, as noted previously.

In those rare children in whom thyroid storm is suspected, additional testing will be required to detect multiorgan dysfunction. Electrolytes, serum glucose levels, and calcium levels should be measured, since these children will often have metabolic evidence of dehydration, hyperglycemia, and hypercalcemia owing to their hypermetabolic state. One should also rule out hepatic dysfunction, as indicated by elevations in liver transaminases, alkaline phosphatase, and bilirubin. An electrocardiogram is indicated to distinguish sinus tachycardia from other arrhythmias, most notably atrial fibrillation. Finally, some authors advocate urinalysis and a chest radiograph as a way of screening for a precipitating infection.¹¹⁸

Table 21. Clinical Characteristics Of Hyperthyroidism

Congenital Hyperthyroidism	Acquired Hyperthyroidism	
Symptoms	Symptoms	Prevalence
Hyperexcitability Poor weight gain Poor feeding	Restlessness and irritability Increased sweating Weight loss Palpitations Diarrhea Reduced school performance	60%-83% 41%-99% 39%-86% 34%-59% 27%-86% 32%-34%
Signs	Signs	Prevalence
Tachycardia Goiter Hepatomegaly/splenomegaly Abnormal stare Gynecomastia Congestive heart failure	Goiter Tachycardia Proptosis Systolic hypertension Tremor Thyroid bruit Hyperreflexia	95%-99% 83%-95% 46%-66% 68% 30%-69% 25%-84% 16%

Treatment

The ultimate goal of treatment in pediatric hypothyroidism is to restore the euthyroid state as rapidly as possible. This is especially true for children under 2 years of age, in whom any delay in treatment will likely result in permanent neurologic deficits. On the rare occasion that pediatric hypothyroidism can be diagnosed and confirmed in the ED, treatment should begin immediately — ideally after consultation with a pediatric endocrinologist. A more likely scenario would be close follow-up with a pediatric endocrinologist or primary care physician to review screening results and initiate therapy. Treatment consists of daily oral levothyroxine and is easy and inexpensive. The recommended starting doses are based on age and are listed in **Table 22**.^{90,95}

In pediatric hyperthyroidism, treatment must be individualized and should ideally be discussed with a pediatric endocrinologist. Other than in cases of suspected thyroid storm, specific treatment should be delayed until hyperthyroidism can be confirmed by the necessary laboratory tests (a rare occurrence in most EDs). Radioactive iodine therapy, thyroidectomy, and antithyroid drug therapy (ie, propylthiouracil [PTU] and methimazole [MMI] in the United States) are the main treatment modalities, with antithyroid drugs being the initial treatment of choice.^{115, 117,119,120} Because of the recently recognized increase

Table 22. Recommended Doses Of Levothyroxine By Age

Age	Dosage
0-3 months	10-15 mcg/kg
3-6 months	8-10 mcg/kg
6-12 months	5-8 mcg/kg
1-3 years	4-6 mcg/kg
3-10 years	3-5 mcg/kg
10-18 years	2-4 mcg/kg

in the incidence of PTU-induced hepatotoxicity in children, MMI is now the antithyroid drug of choice for pediatric hyperthyroidism.¹²¹⁻¹²³

The medications used in the treatment of pediatric hyperthyroidism are listed in **Table 23**. In those few children with symptomatic and confirmed hyperthyroidism, begin treatment with an antithyroid drug. These drugs block the synthesis of thyroid hormones but do not suppress the release of pre-existing hormones stored in the thyroid. To achieve the latter goal, an iodine-containing solution can be added to the treatment regimen; however, do not begin treatment with an iodine-containing solution until approximately 2 hours after the first dose of an antithyroid drug. This delay is necessary to assure that thyroid hormone synthesis is adequately blocked so that iodine cannot exert a potentially stimulating effect on hormone production. Iodine is usually reserved for the treatment of neonatal hyperthyroidism and thyroid storm. A beta-blocking agent can help to control tremors and tachycardia in those patients with more pronounced symptoms.

Continued on page 22

Table 23. Medications Used For Hyperthyroidism

Medication	Dosage
Antithyroid drugs	
Propylthiouracil (PTU) PO (not recommended in children)	5-10 mg/kg/day in 3 divided doses
Methimazole (MMI) PO	0.5-1 mg/kg/day in 3 divided doses
Iodine solutions	
Saturated potassium iodine (SSKI) (48 mg iodine/drop) PO	1 drop daily
Lugol's solution (8 mg iodine/drop) PO	1-3 drops daily
Sodium iodide IV	1-2 g daily
Beta-adrenergic blockers	
Propranolol PO	2 mg/kg/day in 3 divided doses
Propranolol IV	0.01-0.1 mg/kg/dose
Glucocorticoids	
Dexamethasone IV	1-2 mg every 6 hr
Prednisone PO	2 mg/kg/day

Cost- And Time-Effective Strategies

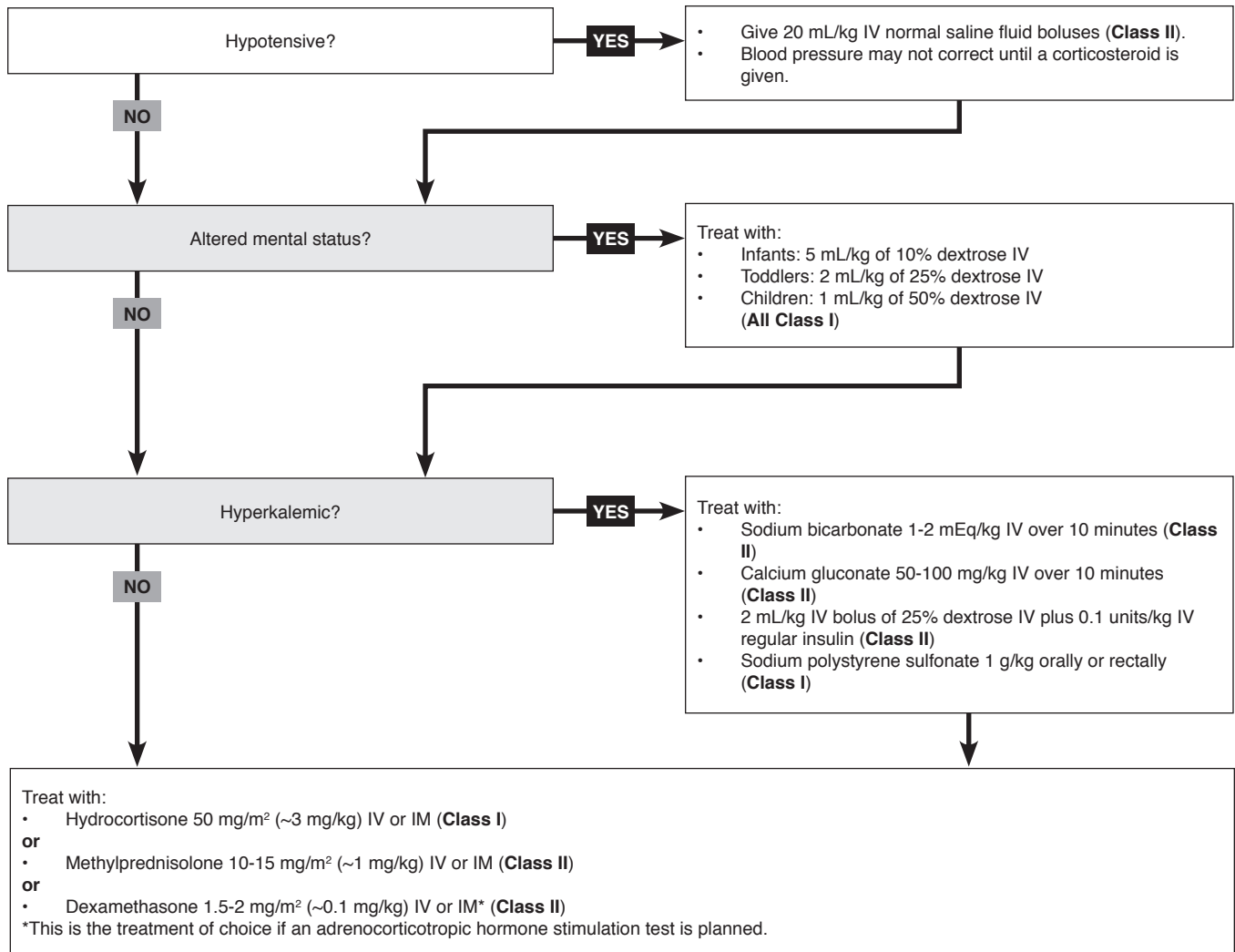
A rapid bedside glucose determination in children with polydipsia, polyuria, and clinical signs of dehydration quickly rules in or out diabetes mellitus as the cause.

Risk Management Caveat: Finger-stick serum glucose measurements are not infallible and can be influenced by technique and user experience. This is another reason to order a chemistry panel in such cases in addition to evaluating serum electrolytes.

The dipstick urine specific gravity is a useful bedside test when one suspects diabetes insipidus (inappropriately dilute urine) or SIADH (inappropriately concentrated urine).

Risk Management Caveat: Infants' kidneys cannot concentrate urine as well as older children's kidneys. Therefore, although specific gravity is a convenient early indicator of these conditions, it is neither 100% sensitive nor specific for them.

Clinical Pathway For Assessment And Management Of A Child With Suspected Adrenal Insufficiency



Class Of Evidence Definitions

Each action in the clinical pathways section of *Pediatric Emergency Medicine Practice* receives a score based on the following definitions.

Class I

- Always acceptable, safe
- Definitely useful
- Proven in both efficacy and effectiveness

Level of Evidence:

- One or more large prospective studies are present (with rare exceptions)
- High-quality meta-analyses
- Study results consistently positive and compelling

Class II

- Safe, acceptable
- Probably useful

Level of Evidence:

- Generally higher levels of evidence
- Non-randomized or retrospective studies: historic, cohort, or case control studies
- Less robust RCTs
- Results consistently positive

Class III

- May be acceptable
- Possibly useful
- Considered optional or alternative treatments

Level of Evidence:

- Generally lower or intermediate levels of evidence
- Case series, animal studies, consensus panels
- Occasionally positive results

Indeterminate

- Continuing area of research
- No recommendations until further research

Level of Evidence:

- Evidence not available
- Higher studies in progress
- Results inconsistent, contradictory
- Results not compelling

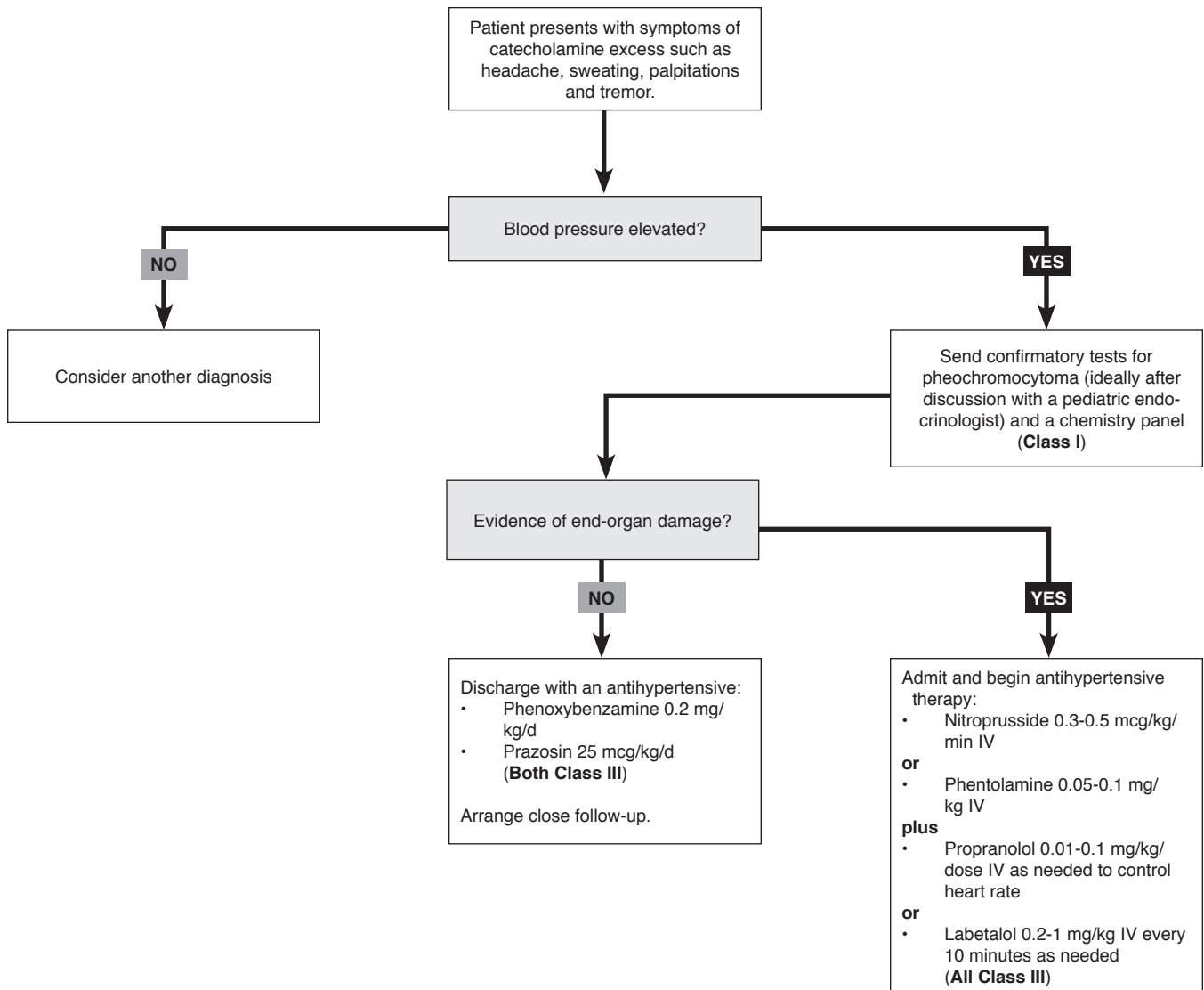
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Clinical Pathway For Assessment And Management Of A Child With Suspected Pheochromocytoma



Class Of Evidence Definitions

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Class I

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Level of Evidence:

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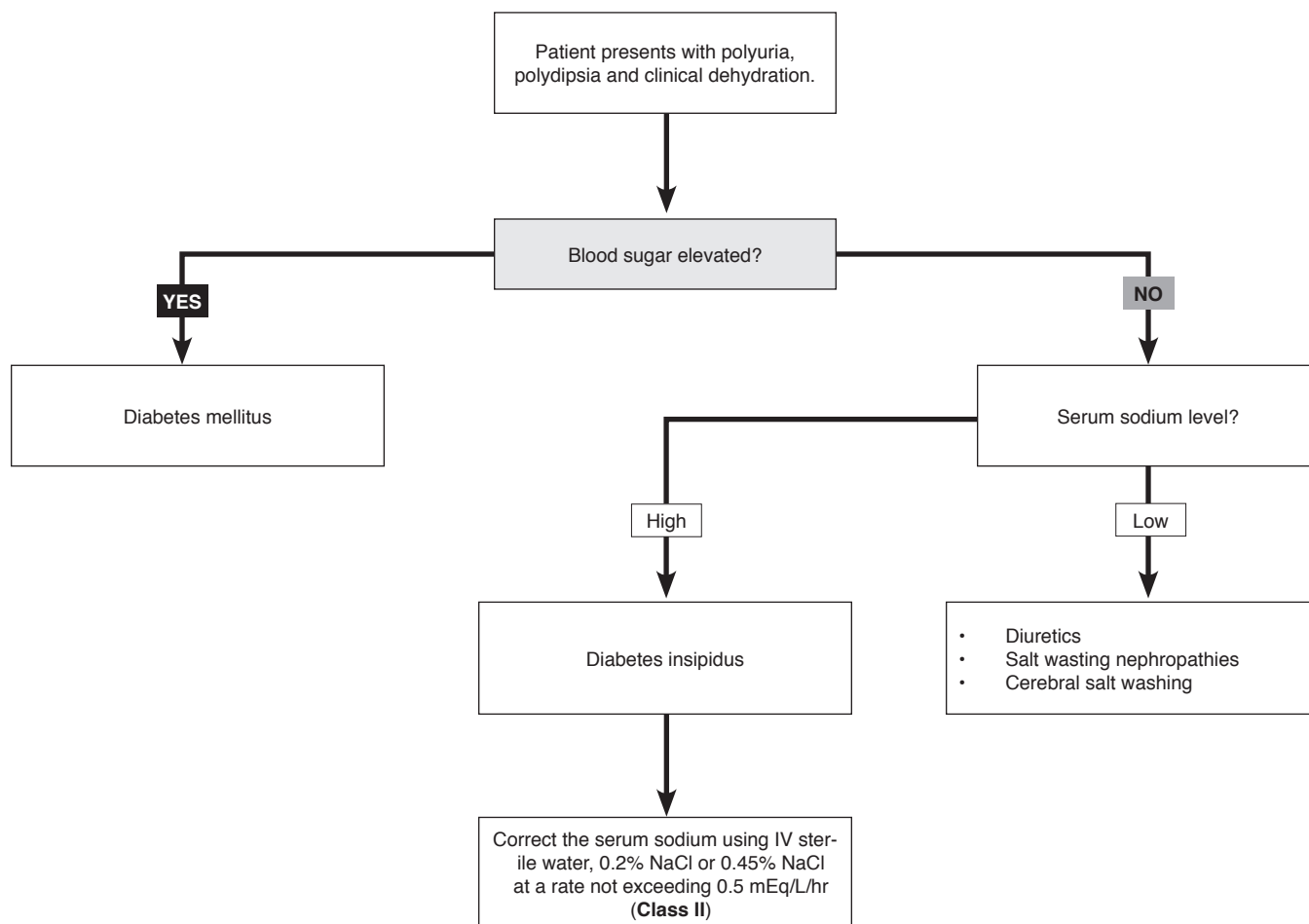
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Clinical Pathway For Assessment And Management Of A Child With Suspected Diabetes Insipidus



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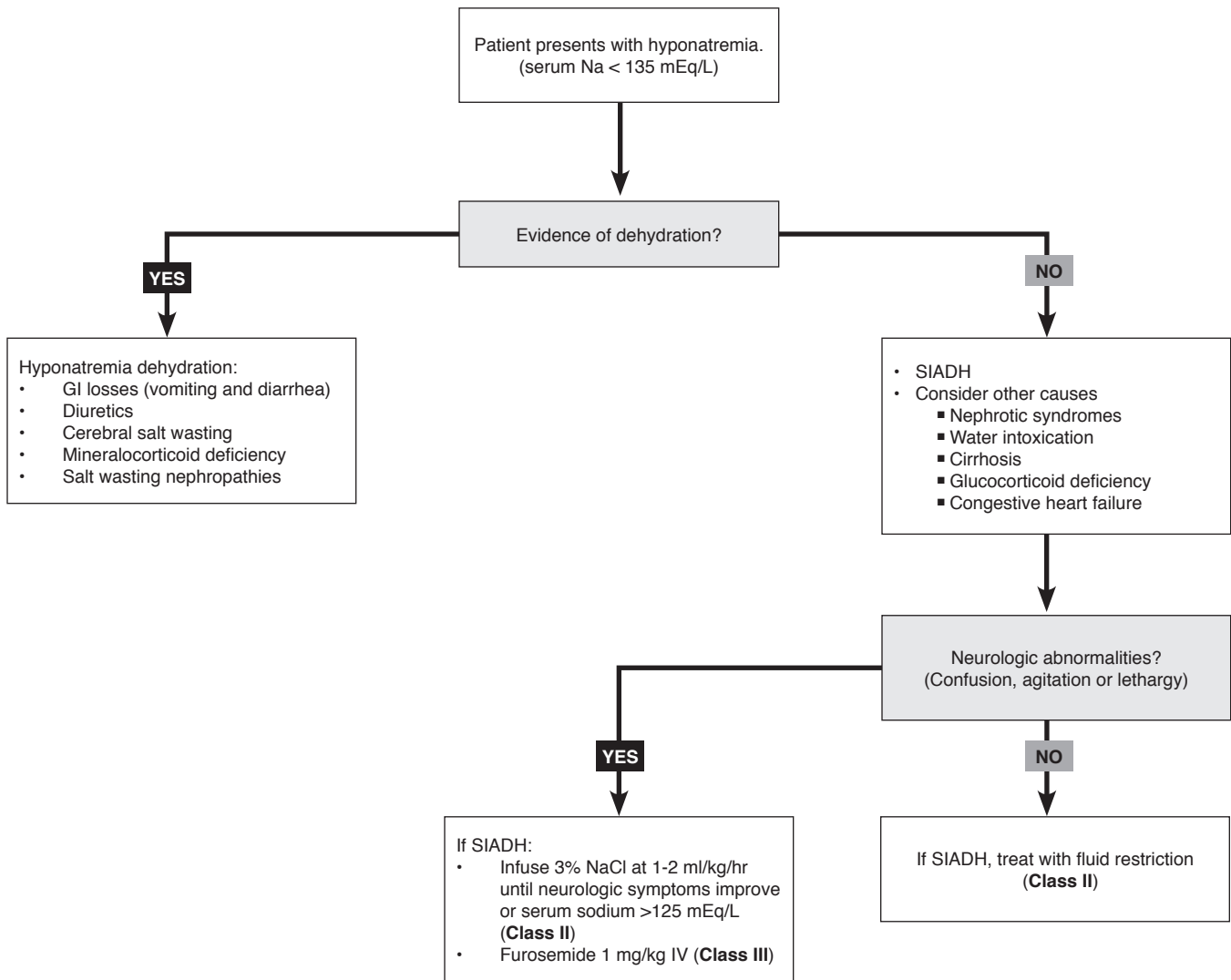
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Clinical Pathway For The Assessment And Management Of A Child With Suspected SIADH



Abbreviation: GI, gastrointestinal; SIADH, syndrome of inappropriate antidiuretic hormone

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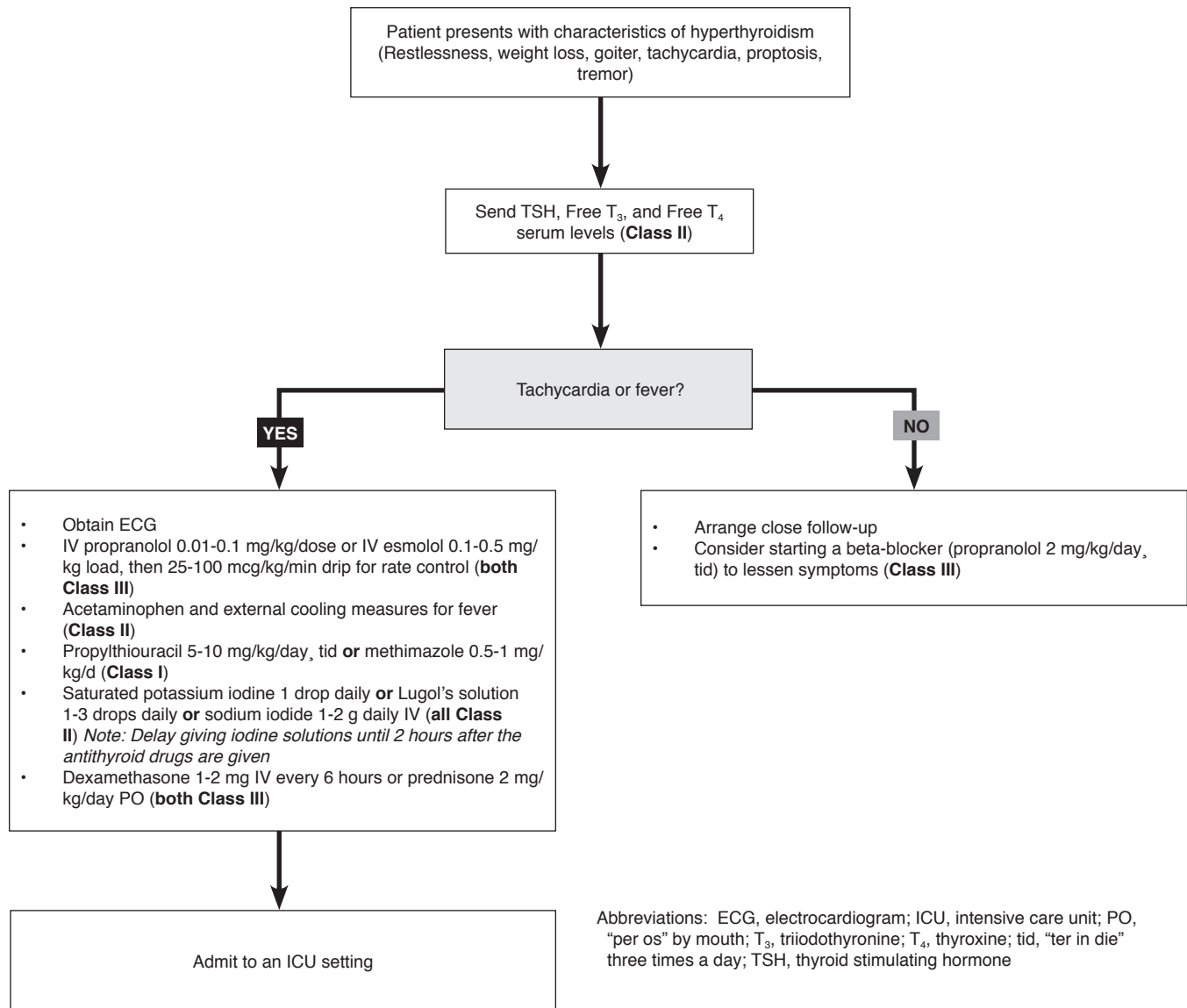
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Clinical Pathway For Assessment And Management Of Child With Suspected Hyperthyroidism



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Risk Management Pitfalls To Avoid In Endocrine Emergencies

1. **"I forgot to give 'stress-dose' corticosteroids to my critically ill patient on chronic corticosteroid therapy."**

Failure to give hydrocortisone 100 mg/m²/d (approximately 7 mg/kg) IV or IM to these children may result in refractory hypotension or worse. Even children with simple febrile illnesses such as streptococcal pharyngitis should take double or triple their usual daily dose for the duration of the illness.

2. **"My patient just has a headache. She's a child, I don't need to check her blood pressure."**

This step is automatic for most emergency clinicians when caring for adults with this complaint, but in children it is often overlooked. Although pheochromocytomas are rare in children, headache is their most common chief complaint.

3. **"We don't have time to get the blood and urine for adrenal insufficiency testing. Just give the steroids now and they can do confirmatory testing later."**

These tests will be of little value if they are carried out after treatment has begun.

4. **"The child has classic symptoms of new-onset diabetes."**

Her blood sugar is probably in the normal range right now because she hasn't eaten recently. Although the vast majority of children with polydipsia and polyuria will indeed be found to have diabetes mellitus of new onset, a significant minority will have diabetes insipidus — and you're not going to make that diagnosis until you check their electrolytes.

5. **"His sodium is 172. We should give boluses of quarter normal saline until we at least get that down below 150."**

Lowering the serum sodium faster than 0.5 mEq/L/hr in these children can cause cerebral edema, resulting in seizures, coma, permanent neurologic injury, and death. A steady, controlled lowering of serum sodium levels can be achieved with any hypotonic fluid, and the de-

tails for accomplishing this should be discussed with a pediatric intensivist.

6. **"His sodium is 118. We should give a bolus of 3% sodium chloride to get that serum level up before he seizes."**

Only those children with signs of cerebral edema (ie, altered mental status or seizures) require 3% sodium chloride. In these symptomatic children, serum sodium levels should be raised at a rate no faster than 2 mEq/L/hr. Correcting these levels too rapidly can cause cerebral osmotic demyelination, resulting in permanent neurologic disabilities and death.

7. **"I don't know why he's so hyponatremic. He's not on any meds that would cause that."**

Plenty of children are taking desmopressin for either hemophilia or bed wetting. Perhaps because this drug is given intranasally many parents won't list this as a "medication."

8. **"She has pretty nonspecific complaints; the physical exam probably won't reveal much."**

The majority of children with either hypothyroidism or hyperthyroidism will have an enlarged thyroid. This may be your only diagnostic clue in these children who otherwise often have nondiagnostic findings on history and physical examination.

9. **"With such nonspecific symptoms, screening tests are of little value."**

As with a goiter, the majority of children with either hypothyroidism or hyperthyroidism will have an abnormal TSH level. This is a nice screening tool for such illnesses, in which symptoms are notoriously vague.

10. **"As sick as she is, we should start both the methimazole and Lugol's solutions now."**

While iodine solutions are key to prevent the release of preformed thyroid hormones, they also will increase the production of new hormone unless the antithyroid drugs have had adequate time to halt this process.

Beta-blockers are typically required for only the first few weeks until thyroid hormone levels decline as a result of antithyroid medication.

Children believed to have thyroid storm will require treatment with an antithyroid drug, an iodine solution, a beta-blocker, and possibly a glucocorticoid. Glucocorticoids inhibit the conversion of T₄ to T₃ and will treat the relative adrenal suppression that is frequently present with thyroid storm.

Disposition

Few, if any, children will require admission for the treatment of hypothyroidism, although close follow-up (ie, the next day) must be assured.

Since there are no guidelines regarding the treatment of pediatric hyperthyroidism, it would be wise to discuss the disposition of these children with their primary care physician or, ideally, a pediatric endocrinologist. Those children with mild symptoms and no tachycardia or fever may be discharged with close follow-up. Admit any child with suspected hyperthyroidism who has abnormal vital signs. Children with suspected thyroid storm are better managed in an intensive care setting.

Summary

Although endocrine emergencies other than DKA are uncommon in children, they are potentially life-threatening. These children typically present with nonspecific symptoms and many are critically ill. Attention to key findings on the history and physical examination can give the astute emergency clinician clues to the presence of these illnesses. Treatment of these children should ideally be coordinated with the appropriate pediatric subspecialist.

Case Conclusion

The septic-appearing 2-year-old did indeed have a left lower lobe pneumonia on chest x-ray and showed little improvement in her circulatory status after being given a 20 mL/kg bolus dose of normal saline. Finger-stick testing revealed a serum glucose of 52. Having recognized the picture of possible adrenal insufficiency in the face of sepsis, you drew and saved extra serum for confirmatory testing and gave a 2 mL/kg bolus of D25, 25 mg of IV hydrocortisone, another 20 mL/kg bolus of normal saline, and IV antibiotics. You discussed the case with the pediatric intensivist at the children's hospital on the other side of town and arranged for a transfer. The child's condition had improved significantly by the time the transport team arrived.

References

Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study, such as the type of study and the number of patients in the study, will be included in bold type following the reference, where available. In addition, the most informative references cited in this paper, as determined by the authors, will be noted by an asterisk (*) next to the number of the reference.

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1. **What is the most common cause of acute adrenal insufficiency in North America?**
 - a. Congenital adrenal hyperplasia
 - b. Adrenal hemorrhage
 - c. Withdrawal after prolonged glucocorticoid therapy
 - d. Primary adrenal insufficiency (Addison disease)
2. **Which of the following are characteristic laboratory findings with chronic adrenal insufficiency?**
 - a. Hyponatremia, hyperkalemia, hypoglycemia
 - b. Hyponatremia, hypokalemia, hypoglycemia
 - c. Hyponatremia, hyperkalemia, hyperglycemia
 - d. Hyponatremia, hypokalemia, hyperglycemia
3. **A 16-year-old boy on daily prednisone therapy for congenital adrenal hyperplasia is diagnosed with appendicitis. What would be an appropriate "stress dose" of IV hydrocortisone to be given prior to his going to the operating room?**
 - a. 25 mg
 - b. 100 mg
 - c. 250 mg
 - d. 500 mg
4. **Which are the most common presenting symptoms in children with a pheochromocytoma?**
 - a. Blurry vision and dizziness
 - b. Headache and inappropriate sweating
 - c. Anorexia and constipation
 - d. Palpitations and tremors
5. **Which is the most consistent physical finding in children with pheochromocytoma?**
 - a. Tachycardia
 - b. Hypertension
 - c. Hyperthermia
 - d. Dilated pupils

6. **What are the most common symptoms of children with diabetes insipidus?**
 - a. Polyuria and polydipsia
 - b. Headache
 - c. Vomiting and anorexia
 - d. Seizure
7. **What is/are the most common symptom(s) of children with SIADH?**
 - a. Nocturia
 - b. Intense thirst
 - c. Increased skin pigmentation
 - d. Anorexia, lethargy, and weakness
8. **Which of the following would be the most appropriate initial treatment of an obtunded child with presumed SIADH and a serum sodium of 110 mEq/L?**
 - a. Fluid restriction
 - b. A 20 mL/kg bolus of 0.9% sodium chloride
 - c. A 20 mL/kg bolus of 3% sodium chloride
 - d. A 2 mL/kg/hr infusion of 3% sodium chloride
9. **The correction of symptomatic hypernatremia in a child with presumed diabetes insipidus should not exceed what rate?**
 - a. 5 mEq/L/hr
 - b. 2 mEq/L/hr
 - c. 0.5 mEq/L/hr
 - d. 10 mEq/L/hr
10. **Which of the following statements is true regarding urine specific gravity and disorders involving antidiuretic hormone (vasopressin)?**
 - a. Urine is typically dilute in diabetes insipidus (specific gravity < 1.005 mOsm/kg) and is typically concentrated in SIADH (specific gravity > 1.030 mOsm/kg)
 - b. Urine is typically concentrated in diabetes insipidus (specific gravity > 1.030 mOsm/kg) and is typically dilute in SIADH (specific gravity < 1.005 mOsm/kg)
 - c. Both diabetes insipidus and SIADH typically present with concentrated urine (specific gravity > 1.030 mOsm/kg)
 - d. Both diabetes insipidus and SIADH typically present with dilute urine (specific gravity < 1.005 mOsm/kg)
11. **Which of the following is the main cause of acquired hypothyroidism in children in the United States?**
 - a. Graves' disease
 - b. Thyroid dysgenesis
 - c. Iodine deficiency
 - d. Autoimmune (Hashimoto) thyroiditis
12. **Which is the most common physical finding in children with acquired hyperthyroidism?**
 - a. Tremor
 - b. Systolic hypertension
 - c. Goiter
 - d. Proptosis
13. **What are the best screening labs for pediatric hypothyroidism?**
 - a. TSH and free T₃
 - b. Free T₃ and free T₄
 - c. TSH and free T₄
 - d. TSH and total T₄
14. **Which of the following is the single best screening test for pediatric hyperthyroidism?**
 - a. Free T₃
 - b. Free T₄
 - c. Total T₄
 - d. TSH
15. **Which class of drugs is preferred for treating the tachycardia and tremors associated with pediatric hyperthyroidism?**
 - a. Calcium-channel blockers
 - b. Benzodiazepines
 - c. Beta-blockers
 - d. Cardiac glycosides (digoxin)
16. **Which of the following is true concerning the treatment of pediatric thyrotoxicosis?**
 - a. Iodine solutions should not be given until at least 2 hours after the first dose of antithyroid drugs
 - b. Antithyroid drugs should not be given until at least 2 hours after the first dose of iodine solutions
 - c. Antithyroid drugs should not be given until at least 2 hours after the first dose of beta-blockers
 - d. Glucocorticoids inhibit the release of thyroid hormone

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