

Critical DecisionsTM in Emergency Medicine

Volume 26 • Number 11

In This Issue

- Lesson 21 Adrenal Insufficiency Page 2**
Adrenal insufficiency, although rare, is a potentially life-threatening disorder. Nonspecific symptoms and subtle signs frequently make this disease difficult to diagnosis in the emergency department. Emergency physicians must be able to recognize acute adrenal insufficiency because delays in diagnosis and treatment can lead to significant morbidity and mortality.
- Lesson 22 Pediatric Seizures Page 12**
Pediatric seizures are common and can represent benign or malignant pathologies. Emergency physicians must be able to distinguish the two and, through a structured approach, quickly and safely stabilize the child in status epilepticus.

2012

July

Also in This Issue

- The LLSA Literature Review / Page 10
- The Critical Image / Page 11
- The Critical ECG / Page 21
- CME Questions / Page 22
- The Drug Box / Page 24

Next Month

- Variceal Bleeding
- Emergencies in Head and Neck Cancer Patients

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Commercial Support. There was no commercial support for this CME activity.

Target Audience. This educational activity has been developed for emergency physicians.

Lesson 21

Adrenal Insufficiency

Brian E. Burgess, MD, FACEP, and P. Justin Roe, MD

■ Objectives

On completion of this lesson, you should be able to:

1. Describe the pathophysiology of primary, secondary, and tertiary adrenal insufficiency.
2. Explain the clinical manifestations of adrenal insufficiency.
3. List risk factors for developing adrenal insufficiency.
4. Discuss emergency management of patients with adrenal insufficiency.
5. Describe the clinical presentation of patients with adrenal crisis.
6. List risk factors for the development of adrenal hemorrhage or infarction.
7. Explain how failed diagnosis or delay in treatment can lead to significant morbidity and mortality in patients with chronic adrenocortical insufficiency (Addison disease).

■ From the EM Model

5.0 Endocrine, Metabolic, and Nutritional Disorders

5.2 Adrenal Disease

Adrenal insufficiency encompasses a group of disorders in which the adrenal cortex fails to secrete sufficient amounts of glucocorticoids to maintain physiologic homeostasis. The most common cause of acute adrenal insufficiency in North America is the rapid withdrawal of exogenous steroids in patients who are on long-term glucocorticoid therapy.¹

Adrenal crisis refers to a life-threatening exacerbation of adrenal insufficiency which is caused by either an acute deficiency of glucocorticoids (ie, withdrawal of exogenous steroids) or an increased demand for glucocorticoids for which the diseased adrenal system cannot appropriately compensate. The latter is often triggered by a significant stressor such as infection, trauma, or surgery. Patients with adrenal crisis classically present with rapid and inappropriate hemodynamic decompensation in the presence of a stressor.¹

Adrenal insufficiency is a relatively rare diagnosis in the Western population with a prevalence of 5 per 10,000 people.² The onset of adrenal insufficiency occurs when approximately 90% of the adrenal glands are affected. Symptom onset is often gradual such that adrenal insufficiency may remain undiagnosed until an illness or stressor precipitates an acute adrenal crisis. Since the consequences of a missed diagnosis and delay in treatment of adrenal crisis can be life-threatening, it is imperative that

emergency physicians be cognizant of the subtle clinical presentation that should suggest underlying adrenal insufficiency. Early recognition of the illness and empiric treatment are critical to improved patient outcomes.

Case Presentations

■ Case One

A 10-year-old boy presents with a 2-day history of sore throat, fever, and odynophagia. He denies cough, rhinorrhea, hoarseness, stridor, drooling, shortness of breath, and vomiting. His medical history is significant for congenital adrenal hyperplasia, and his medications include hydrocortisone and fludrocortisone. Vital signs are blood pressure 110/64, pulse rate 105, respiratory rate 16, temperature 38.2°C (100.8°F), and oxygen saturation 100% on room air. He appears in no acute distress. The physical examination reveals tonsillar hypertrophy with exudates, soft palate petechiae, and anterior cervical lymphadenopathy. He has no stridor, and lung sounds are clear. A rapid pharyngeal swab is positive for group A β -hemolytic streptococcus.

■ Case Two

A 6-year-old boy presents with a 4-day history of nausea, vomiting, decreased oral intake, and lethargy. He complains of abdominal pain, but no diarrhea, dysuria, fever, cough, or shortness of breath. The patient has no known medical conditions. Initial vital signs are blood pressure 82/54, pulse rate 132, respiratory rate

Critical Decisions

- When managing a patient with low blood pressure, what clues should alert emergency physicians to consider acute adrenal insufficiency (adrenal crisis)?
- What are the treatment priorities when managing patients with acute adrenal crisis, and which medications should be administered?
- What patient characteristics and laboratory results should alert emergency physicians to the possibility of an underlying adrenal insufficiency?
- What are some of the important underlying etiologies to consider when diagnosing adrenal insufficiency?
- What laboratory tests should be ordered prior to initiating treatment in patients with acute adrenal crisis?
- What important management issues should emergency physicians consider when treating patients with concomitant endocrine disorders and acute adrenal crisis?
- When should emergency physicians recommend stress-dose steroids at the time of discharge for patients with chronic adrenocortical insufficiency?

24, temperature 38.5°C (101.3°F), and room air oxygen saturation 99%. He is lethargic, arouses briefly to sternal rub, and is able to answer a few questions. His lungs are clear, and his heart is tachycardic without murmurs, rubs, or gallops. His abdomen is soft with mild diffuse tenderness but no guarding or rebound, and his neurologic examination is nonfocal. Laboratory studies are as follows: sodium 115 mm/L, potassium 6.5 mm/L, chloride 91 mm/L, bicarbonate 16 mm/L, BUN 26 mg/dL, creatinine 1.2 mg/dL, and glucose 42 mg/dL.

■ Case Three

A 43-year-old woman with a history of hypertension presents with a severe headache that began suddenly about 3 hours prior to her arrival. She has had recurrent frontal headaches for the past 2 weeks and was seen in a medical aid unit and treated for a migraine. Today the headache became much worse, and the patient experienced blurry vision, diplopia, nausea, vomiting, and confusion. She has no history of chronic headaches. Vital signs are blood pressure 98/50, heart rate 120, respiratory rate 24, temperature 36.8°C (98.2°F), and oxygen saturation 98% on room air. She appears in acute distress. She is somnolent but arouses to voice, following commands and protecting her airway. The neurologic examination reveals a dilated,

minimally-reactive left pupil, a globe that is deviated inferiorly and laterally, and bitemporal hemianopsia. Laboratory results reveal only a mild hyponatremia of 130. She is sent for a stat computed tomography (CT) scan of the brain.

Pathophysiology of Adrenal Insufficiency

The adrenal gland is divided into the cortex and medulla. The medulla secretes endogenous catecholamines in response to sympathetic stimulation, and the cortex secretes glucocorticoids (cortisol), mineralocorticoids (aldosterone, 11-deoxycorticosterone), and gonadocorticoids (dehydroepiandrosterone). Although the cortex is responsible for the synthesis of multiple steroids, aldosterone and cortisol are by far the most abundant and physiologically active.³

The secretion of adrenal hormones is regulated by the hypothalamic-pituitary-adrenal (HPA) axis. The hypothalamus secretes corticotropin-releasing hormone (CRH), which stimulates the anterior pituitary to secrete adrenocorticotrophic hormone (ACTH), which subsequently stimulates the adrenal cortex to secrete cortisol. Elevated levels of cortisol inhibit release of CRH and ACTH through a negative feedback mechanism (Figure 1).

Cortisol is vital in the maintenance of physiologic homeostasis in

the human body and has a broad range of effects on all body tissues. Primarily, it promotes catabolism through protein and lipid breakdown, decreased insulin secretion, stimulation of gluconeogenesis, and decreased glucose utilization by skeletal muscle. The overall effect is to increase glucose availability to vital tissues during stress. Additionally, cortisol promotes sodium and water retention, stimulates angiotensinogen release by the liver, increases vascular reactivity to vasopressors, and acts as a cofactor in the conversion of norepinephrine to epinephrine in the adrenal medulla. This ultimately helps to maintain a perfusing blood pressure during stressful times. Finally, its anti-inflammatory properties include decreasing capillary permeability and inhibiting production of vasodilatory kinins, prostaglandins, and nitrous oxide. These properties are crucial in preventing widespread capillary leak and hemodynamic collapse in critical illness. In the absence of cortisol, acute stress results in hypotension, shock, and death.^{4,5}

Aldosterone, the primary mineralocorticoid, is responsible for regulating fluid and electrolyte balance as well as maintaining an adequate blood volume and pressure. Regulation is controlled by the renin-angiotensin system in response to volume, posture, and sodium intake. Hyperkalemia also stimulates aldosterone release. Aldosterone

recalled rule of thumb is the “3 × 3” rule which recommends three times the usual dose for 3 days followed by normal dosing on subsequent days. Any patient with an acute stressor who has not increased the home dose of steroids is at high risk for developing adrenal crisis. In patients with chronic adrenocortical insufficiency, the incidence of adrenal crisis is conservatively estimated at 8% per year.⁶ The greatest risk factor for adrenal crisis in these patients is gastrointestinal illness with nausea and diarrhea, which is causative in more than 50% of cases. Other common triggers are flu-like illnesses (17%), surgery (6%), and trauma (4%).

For patients without a known history of adrenal insufficiency, the diagnosis is often difficult. Importantly, up to 50% of patients with adrenal insufficiency will not be diagnosed until they experience an episode of adrenal crisis, and most patients will see more than three doctors before the diagnosis is made.² The most common symptoms are nausea and vomiting with a history of weight loss and anorexia. Occasionally, patients will present with generalized abdominal pain that can mimic an acute abdomen. Emergency physicians should look for evidence of chronic adrenal insufficiency such as hyper-pigmentation, vitiligo, and a thin body habitus. Unexplained hypoglycemia should raise suspicion for possible underlying adrenal insufficiency. Laboratory clues include hyponatremia, hyperkalemia, acidosis, azotemia, hypercalcemia, and eosinophilia. Risk factors for developing adrenal crisis include autoimmune disease, HIV, head trauma, and a history of brain tumors or surgery. Many patients with adrenal insufficiency wear a medical information bracelet or carry a steroid-adjustment card in their wallet that can provide valuable information for health care workers in the event that a history cannot be obtained. Finally, consider adrenal crisis in any patient with shock that is refractory

to fluid and pressor administration or in any patient with an undetermined etiology of shock after the initial workup is complete.

CRITICAL DECISION

What are the treatment priorities when managing patients with acute adrenal crisis, and which medications should be administered?

The resuscitation of a patient in adrenal crisis should be managed in a manner similar to resuscitation in other critically ill patients. Ensure an adequate airway with ventilation and oxygenation. If the patient requires intubation, consider avoiding the use of etomidate as an induction agent during rapid sequence intubation as adrenal suppression can occur.⁷ Although these adrenal-suppression effects may be transient and well tolerated in other patient populations, any additional adrenal suppression in a patient with adrenal crisis could be life-threatening.

Hypotension should be treated initially with intravenous crystalloid boluses. Children should be given a 20 mL/kg isotonic saline bolus, up to three, as needed. Vasopressors may be necessary if the patient remains hypotensive after adequate fluid resuscitation. Hydrocortisone is the steroid of choice in an acutely ill patient presenting with acute adrenal crisis because it provides both glucocorticoid and mineralocorticoid effects. In the adult patient, hydrocortisone, 100 mg IV, should be given in the emergency department. Children should receive hydrocortisone, 1 to 3 mg/kg IV.⁸ Clinical improvement is often seen within a few hours of steroid administration. Traditional teaching has been to use dexamethasone (4-mg IV bolus) initially as it does not interfere with the ACTH stimulation test or cortisol assays. Dexamethasone can be used in the non-critically ill patient who may need an ACTH stimulation test in the hospital; however, dexamethasone has no mineralocorticoid properties and

thus should be avoided in patients who are severely hypotensive. Pure mineralocorticoids are rarely given in the emergency department and are not necessary if the patient is receiving more than 50 mg of hydrocortisone in 24 hours.⁹ Adrenal androgen replacement therapy is not necessary.

Underlying electrolyte abnormalities should be corrected as necessary. Hypoglycemia is more common in secondary adrenal insufficiency and should be corrected quickly with 5 mL/kg of a 10% dextrose solution (D10) in infants, 2 mL/kg of a 25% dextrose solution (D25) in toddlers, 1 mL/kg of a 50% dextrose solution (D50) in older children, and 50 mL of a 50% dextrose solution (D50) in adults. Finally, emergency physicians should treat the underlying illness that precipitated adrenal crisis.

CRITICAL DECISION

What patient characteristics and laboratory results should alert emergency physicians to the possibility of an underlying adrenal insufficiency?

The characteristics of patients with chronic adrenal insufficiency are often vague and nonspecific. Generalized weakness, fatigue with exertion, weight loss, anorexia, nausea, vomiting, loss of libido, and diffuse myalgias and arthralgias are the most common clinical manifestations. Psychiatric symptoms can occur in longstanding cases and include memory impairment, depression, and psychosis. Patients may be inappropriately diagnosed with chronic fatigue syndrome or anorexia nervosa.

Primary and secondary adrenal insufficiencies have slightly different presentations secondary to differences in the underlying pathophysiology. Because of aldosterone depletion, patients with primary adrenal insufficiency might complain of salt craving and orthostasis. Moreover, laboratory values may reveal hyperkalemia,

hyponatremia, and a non-anion gap hyperchloremic acidosis. Patients may also display hyperpigmentation because the increased ACTH secretion stimulates melanin production. Hyperpigmentation is usually most pronounced in sun-exposed areas, as well as the axillae, nipples, palmar creases, and mucous membranes. In children with preexisting type I diabetes mellitus, recurrent bouts of hypoglycemia in the absence of recent insulin dosing changes should prompt suspicion for underlying autoimmune adrenal insufficiency.

Patients with secondary adrenal insufficiency will not display hyperkalemia or orthostasis because aldosterone levels remain normal. Hyperpigmentation is also absent in secondary adrenal insufficiency since ACTH levels are low. Patients may still develop hyponatremia because cortisol deficiency leads to an increase in antidiuretic hormone secretion. Hyponatremia is generally responsive to hydrocortisone administration. Hypoglycemia will likely be present and is often severe. Patients with hypopituitarism may have symptoms from the loss of luteinizing hormone (LH), follicle-stimulating hormone (FSH) (infertility, amenorrhea, poor libido), and thyroid-stimulating hormone (TSH) (weight gain, cold intolerance). Patients on chronic steroids may display cushingoid features such as truncal obesity, rounded facies, striae, a buffalo hump, and acne.

CRITICAL DECISION

What are some of the important underlying etiologies to consider when diagnosing adrenal insufficiency?

There are many underlying causes of adrenal insufficiency for emergency physicians to consider (Table 1). The most common cause of primary adrenal insufficiency in the United States is autoimmune adrenalitis. This may be an isolated deficiency or associated with polyglandular autoimmune (PGA) syndromes. PGA type-I is associated

with hypoparathyroidism, chronic mucocutaneous candidiasis, and vitiligo. PGA type-II (Schmidt syndrome) is associated with

hypothyroidism, type I diabetes mellitus, hypogonadism, celiac disease, pernicious anemia, and primary biliary cirrhosis. Worldwide,

Table 1.
Etiology of adrenal insufficiency

Primary: Chronic adrenocortical insufficiency
Adrenal Infiltration
Amyloidosis
Hemochromatosis
Metastasis
Sarcoidosis
Autoimmune
Isolated
Polyglandular autoimmune syndromes types I and II
Bilateral adrenalectomy
Bilateral adrenal hemorrhage
Antiphospholipid syndrome
Meningococcal sepsis (Waterhouse-Friderichsen syndrome)
Septic shock (<i>Pseudomonas</i> in children)
Trauma
Drug-induced
Etomidate
Ketoconazole
Methadone
Phenytoin
Rifampin
RU-486 (Mifepristone)
Genetic
Adrenoleukodystrophies
Congenital adrenal hyperplasia
Infectious
AIDS or severe immunosuppression
HIV, cytomegalovirus, cryptococcus, histoplasmosis, coccidioidomycosis
Tuberculosis
Secondary
Genetic
Infiltrative disease
Amyloidosis
Metastasis
Sarcoidosis
Wegener granulomatosis
Pituitary apoplexy
Pituitary irradiation and surgery
Pituitary tumors
Sheehan syndrome (postpartum pituitary infarction)
Traumatic brain injury
Withdrawal of exogenous steroids
Tertiary
Brain tumor
Corticotropin-releasing factor genetic defects
Hemochromatosis
Hemorrhage
Sarcoidosis
Surgery

the most common cause of primary adrenal insufficiency is glandular infiltration by tuberculosis. Other infectious causes include HIV, fungal, and cytomegalovirus infection. Medications including but not limited to ketoconazole, etomidate, rifampin, phenytoin, and methadone can occasionally cause adrenal insufficiency. Infiltrative diseases such as sarcoidosis, amyloidosis, metastatic cancer, and lymphoma may also cause primary adrenal insufficiency. Other rare causes include adrenal metastasis and bilateral hemorrhagic adrenal infarction in the Waterhouse-Friderichsen syndrome in meningococcal sepsis.³ Spontaneous hemorrhage in the anticoagulated patient during severe stress¹⁰ or trauma¹¹ can also lead to adrenal insufficiency. A CT scan often reveals enlarged adrenal glands when infarction, hemorrhage, or infiltrative diseases are considered as the cause of adrenal insufficiency.

In children, the most common cause of adrenal insufficiency is congenital adrenal hyperplasia (CAH), an inherited defect in cortisol synthesis. Most will be diagnosed on newborn screening. Unscreened females are often diagnosed at birth secondary to virilization of the genitalia. Unscreened males usually present with a salt wasting crisis at 2 to 3 weeks of age, although the diagnosis may not be made until school age or later.¹²

Secondary adrenal insufficiency is a far more common clinical problem. This is usually due to the sudden cessation of chronic exogenous steroid administration. Reduced responsiveness and adrenal atrophy

can occur whenever supraphysiologic doses of a glucocorticoid are taken for more than three weeks (hydrocortisone 30 mg, prednisone 7.5 mg, dexamethasone 0.75 mg).³⁻⁵ The severity of adrenal suppression is variable and depends on the dose potency and when the drug is taken (Table 2). More than once-a-day dosing and isolated evening doses have a greater suppressive effect on pituitary ACTH.³ Therefore, once-a-day dosing should be prescribed in the morning. Prolonged therapy can result in suppression for up to 6 to 9 months. Other causes of secondary adrenal insufficiency include Sheehan syndrome, pituitary apoplexy, brain tumors, pituitary surgery or irradiation, and infiltrative and infectious etiologies. Traumatic brain injury is also increasingly recognized as a cause of central secondary adrenal insufficiency and can be present in up to 25% of patients.^{13,14} The presentation may even be delayed up to 6 months after the injury, although the clinical significance of this is still unknown.¹⁵

CRITICAL DECISION

What laboratory tests should be ordered prior to initiating treatment in patients with acute adrenal crisis?

Patients with adrenal crisis require rapid resuscitation and empiric steroid replacement that should not be delayed for confirmatory testing. In the emergency department, drawing random serum cortisol, ACTH and renin levels, electrolytes, BUN and creatinine, and glucose is sufficient before treating with glucocorticoids. In an acutely ill patient, physiologic stress should result in an elevation

of serum cortisol regardless of the time of day, so a random level is usually adequate. A cortisol level below 15 mcg/dL is presumptive evidence of hypoadrenalism; a random level greater than 33 mcg/dL essentially excludes the diagnosis, and measurements between 15 and 33 mcg/dL are equivocal and these patients should be treated empirically.¹⁶

In the non-acutely ill patient, morning cortisol levels, ACTH levels, and ACTH stimulation tests are often obtained, although these tests are rarely required in the emergency department. Serum cortisol displays diurnal variation with a peak between 6 and 8 am and a nadir in the late evening. Therefore, cortisol levels should be measured in the morning near peak levels. The ACTH stimulation test is rarely necessary acutely but involves administration of a synthetic ACTH and subsequent cortisol measurements at 30 minutes and 1 hour. A subnormal peak of less than 18 mcg/dL after 60 minutes confirms adrenal insufficiency. Of note, the ACTH stimulation testing should not be used in the patient with acute central hypoadrenalism such as pituitary infarct or hemorrhage because depressed ACTH responsiveness may take weeks to develop.¹⁷

CRITICAL DECISION

What important management issues should emergency physicians consider when treating patients with concomitant endocrine disorders and acute adrenal crisis?

Patients with adrenal insufficiency often suffer from concomitant

Table 2.
Comparative steroid potencies

Steroid	Anti-inflammatory properties	HPA axis suppression	Salt retention
Hydrocortisone	1	1	1
Prednisolone	3	4	0.75
Methylprednisolone	6.2	4	0.5
Fludrocortisone	12	12	125
Dexamethasone	26	17	0

endocrine abnormalities. Patients with autoimmune adrenal insufficiency may have concomitant hypothyroidism, hypoparathyroidism, hypogonadism, and diabetes mellitus. Those with secondary adrenal insufficiency may suffer from panhypopituitarism. Corresponding endocrine deficiencies should be corrected as clinically necessary.

Although hypothyroidism is the most common concomitant endocrine disorder, it is important to recognize that an elevated TSH in the setting of acute adrenal

insufficiency does not necessarily imply hypothyroidism. Cortisol inhibits TSH secretion; thus, mildly to moderately elevated TSH is common in acute adrenal insufficiency. This does not, however, necessarily indicate coexisting hypothyroidism. In the absence of underlying thyroid pathology, TSH levels will normalize after glucocorticoid replacement. Initiating thyroxine therapy in the setting of acute adrenal insufficiency will instead increase cortisol metabolism, which can subsequently lead to worsening adrenal crisis and

circulatory collapse.⁸ Thus, emergency physicians should refrain from initiating thyroid replacement therapy in the setting of adrenal insufficiency unless the patient has confirmed concomitant hypothyroidism and has already received appropriate glucocorticoids. Similarly, patients with concomitant hyperthyroidism may require increased dosages of hydrocortisone. These changes should be discussed with the consulting endocrinologist.

CRITICAL DECISION

When should emergency physicians recommend stress-dose steroids at the time of discharge for patients with chronic adrenocortical insufficiency?

Patients with known adrenal insufficiency who present with mild to moderate illness with no clinical evidence of acute adrenal insufficiency may be managed in an outpatient setting if they can tolerate oral fluids and medications. Which patients require stress-dose steroids at the time of discharge is a source of debate. Mild, uncomplicated infections such as upper respiratory infections or pharyngitis without fever may not require an increase in steroids.⁸ However, the clinician should have a low threshold for giving stress-dose steroids in any patient with an acute febrile illness, including acute otitis media or streptococcal pharyngitis. The patient should be instructed to double or triple the daily dose of steroids until recovery.⁷ Patients with gastrointestinal infections deserve special attention as they are at higher risk for adrenal crisis. Intravenous fluid repletion and parenteral hydrocortisone may be necessary, and hospital admission should be strongly considered. Ideally, adjustments in steroid dosing should be discussed with the patient's endocrinologist.

If the patient meets discharge criteria, detailed discharge instructions are critical for prevention of adrenal crisis. Patients should return to the emergency department

Pearls

- Common clinical manifestations of adrenal insufficiency (fatigue, nausea, weight loss) are nonspecific and can lead to a delay in diagnosis.
- Consider adrenal crisis in any patient with shock that is refractory to fluid and pressor administration or after an undetermined etiology of shock following a complete workup.
- Enlarged adrenal glands by CT scan imaging can indicate that the cause of the adrenal insufficiency is adrenal infarction, infection, or infiltrative disease.
- Hydrocortisone is the steroid of choice in adrenal crisis.
- Waiting for diagnostic test results should never delay treatment in patients with suspected adrenal crisis.
- Stress-dose steroids should be considered in any patient with a history of adrenal insufficiency presenting with a febrile illness.
- Patients with underlying adrenal insufficiency who are discharged from the emergency department with an illness involving fevers or gastroenteritis should transiently increase their steroid dosage and be sent with a hydrocortisone emergency pack.

Pitfalls

- Initiating thyroxine therapy in acute adrenal insufficiency because TSH is elevated without confirming the diagnosis of hypothyroidism and having administered appropriate glucocorticoids.
- Failing to consider adrenal crisis in the patient in shock.
- Failing to give stress-dose steroids on discharge to patients with adrenal insufficiency who have a febrile illness or significant stressor.
- Waiting for confirmatory testing before initiating treatment in the patient with possible adrenal crisis.
- Failing to provide detailed discharge instructions for patients with adrenal insufficiency instructing them to return to the emergency department if they have signs and symptoms of dehydration and orthostasis, altered mental status, their clinical conditions worsens, or they are unable to tolerate oral steroids because of nausea and vomiting.

if they have signs and symptoms of dehydration and orthostasis, altered mental status, their clinical condition worsens, or if they are unable to tolerate oral steroids secondary to nausea and vomiting. They should avoid any major physical exercise or similar stressor while acutely ill. If they do not already have a “hydrocortisone emergency pack,” the emergency physician should provide a prescription for patients at risk. A typical pack contains a prefilled syringe and needle containing 100 mg hydrocortisone that may be given subcutaneously during episodes of vomiting or diarrhea when oral medication may not be absorbed.

Case Resolutions

■ Case One

The 10-year-old boy with a sore throat was diagnosed with streptococcal pharyngitis and prescribed penicillin, 50 mg/kg/day divided every 6 hours for 10 days. He showed no signs of dehydration and was able to tolerate oral medications. His endocrinologist was notified, and he was discharged home with a tripling of his daily doses of hydrocortisone for 3 days. He was prescribed an intramuscular hydrocortisone stress pack in case of emergency. Strict instructions were given to return for dehydration, inability to tolerate oral medications, or any signs of adrenal crisis. He was feeling much better by the third day, after which he resumed his normal doses of steroids and completed his 10-day course of penicillin.

■ Case Two

In the case of the 6-year-old boy with nausea, vomiting, and lethargy, intravenous access was established, and he was given a 20-mL/kg bolus of normal saline. Bedside glucose test results were 38 mg/dL. The patient was given a 2-mL/kg bolus of a D25 solution, and his mental status improved. Laboratory results revealed marked hyponatremia, hyperkalemia, and a non-anion gap

metabolic acidosis. An ECG revealed peaked T-waves, short QT, prolonged PR, and QRS intervals. The patient was treated for hyperkalemia with 1 gram of calcium gluconate (50 to 100 mg/kg with a maximum of 1 gram), 2 mL/kg IV bolus of D25, 0.1 units/kg of IV regular insulin, and sodium bicarbonate 1 to 2 mEq/kg IV. A presumed diagnosis of adrenal crisis was made. A random cortisol was added to the laboratory testing, and hydrocortisone was given as a 2-mg/kg IV bolus. Endocrinology and critical care consultations were obtained, and the patient was transferred to the pediatric ICU. The inpatient workup confirmed the diagnosis of autoimmune primary adrenal insufficiency. The patient improved and was discharged on chronic glucocorticoid and mineralocorticoid replacement.

■ Case Three

In the case of the woman with a history of hypertension who presented with a severe headache, her CT scan revealed an intrasellar mass with bony destruction, and she was given a tentative diagnosis of pituitary apoplexy. Neurosurgery was consulted, and a stat magnetic resonance imaging (MRI) of the brain was ordered. She remained hypotensive despite 2 liters of normal saline. A random cortisol was obtained, and the patient was treated empirically with 100 mg of intravenous hydrocortisone for presumed adrenal insufficiency from pituitary apoplexy. The random cortisol level of 8 mcg/dL confirmed the diagnosis. Her blood pressure stabilized after administration of the hydrocortisone. The MRI confirmed the diagnosis of pituitary apoplexy, and the patient was taken to the operating room for transsphenoidal surgical resection.

Summary

Adrenal insufficiency is a rare but potentially life-threatening disease with often subtle and nonspecific presentations. Emergency physicians must consider adrenal crisis in

any patient with shock. Initiation of early empiric treatment with hydrocortisone and appropriate fluids is necessary to prevent circulatory collapse and death. Recognition of the patient at risk for adrenal insufficiency and administration of appropriate adrenal replacement therapy are crucial for good patient outcomes.

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The LLSA Literature Review

"The LLSA Literature Review" summarizes articles from ABEM's "2013 Lifelong Learning and Self-Assessment Reading List." These articles are available online in the ACEP LLSA Resource Center (www.acep.org/llsa) and on the ABEM Web site.



Chest Compression-only CPR by Lay Rescuers and Survival from Out-of-Hospital Cardiac Arrest

Reviewed by Sarah Elisabeth Frasure, MD, and J. Stephen Bohan, MD, MS, FACEP; Harvard Affiliated Emergency Medicine Residency; Brigham and Women's Hospital

Bobrow BJ, Spaite DW, Berg RA, et al. Chest compression-only CPR by lay rescuers and survival from out-of-hospital cardiac arrest. *JAMA*. 2010;304(13):1447-1453.

Although more than 300,000 Americans suffer an out-of-hospital cardiac arrest each year, the survival-to-hospital-discharge rate remains dismal. The performance of bystander cardiopulmonary resuscitation (CPR) improves patient outcome but is carried out less than 30% of the time. Bystanders have voiced their reluctance to perform CPR because of fears about the acquisition of disease through mouth-to-mouth contact, the fear of harming the patient during the resuscitative act, and the perceived difficulty of the task itself. In recent years, however, animal studies have demonstrated that compression-only CPR (COCPR) is at least as effective as conventional CPR.

Bobrow et al conducted a prospective observational cohort study of survival in 4,415 adults with out-of-hospital cardiac arrest between 2005 and 2009. On arrival to the scene, EMS personnel recorded whether the patient had undergone conventional CPR, COCPR, or had received no CPR. If the bystander performing the resuscitation was a medical professional, or the cardiac arrest occurred in a hospital setting, the case was excluded from the study. Concurrently, the authors initiated a state-wide effort to educate people about COCPR. In conjunction with EMS agencies, they distributed training kits to schools, performed public service announcements, published newspaper articles, and taught classes about COCPR.

Over 5 years, bystander CPR increased from 28.2% to 39.9%, likely secondary to the comprehensive educational campaign. In addition, COCPR was associated with the highest rate of survival to hospital discharge (13.3%) when compared to conventional CPR (7.8%) and no CPR (5.2%).

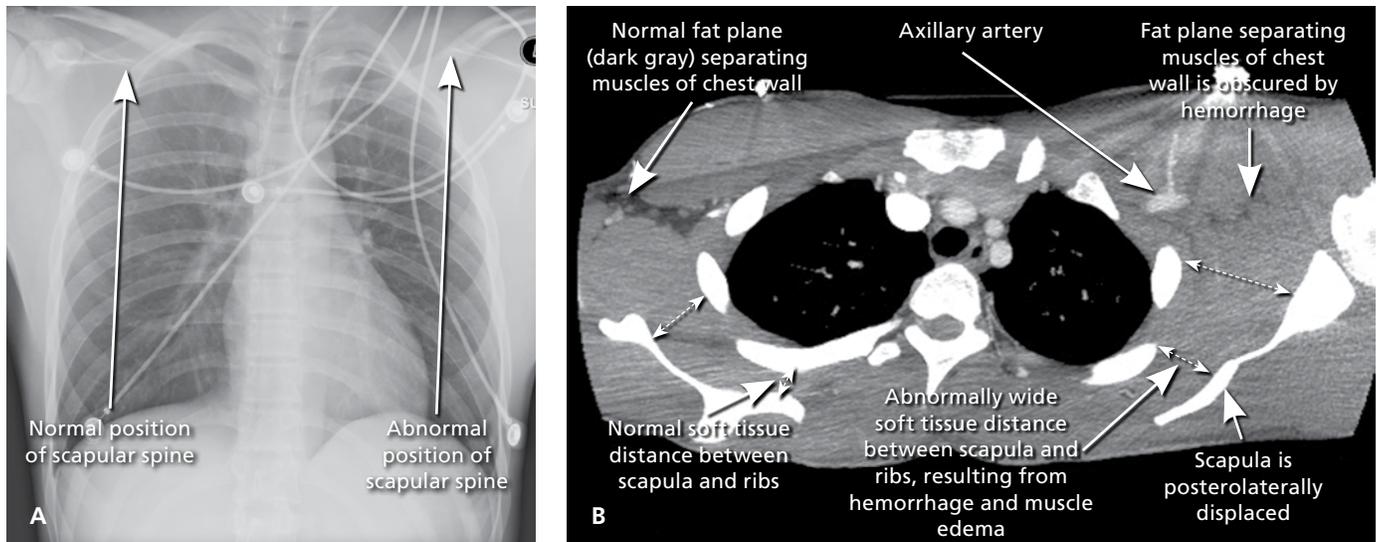
Minimizing interruptions in chest compressions is associated with a significant increase in survival. A well-designed campaign to disseminate this simple, yet vital, skill to the public not only increases the rate at which bystander COCPR is performed but also the likelihood of survival following out-of-hospital cardiac arrest.

Highlights

- COCPR is associated with fewer interruptions in chest compressions, which may prevent the otherwise rapid deterioration in cerebral and cardiac blood flow that occurs when chest compressions are alternated with mouth-to-mouth ventilation.
- COCPR improves the chance of survival to hospital discharge in cardiac arrest patients when compared to either traditional bystander CPR or no CPR.
- A multi-year widespread campaign to educate the public about COCPR significantly improved the incidence at which bystander resuscitation was performed in Arizona.
- A nationwide campaign would provide out-of-hospital cardiac arrest patients with the best possible chance at survival to hospital discharge.

The Critical Image

A 16-year-old boy brought in by EMS following an ATV collision at an estimated 45 mph. The patient complained of left upper extremity pain near the shoulder; there were no other apparent injuries. Vital signs were stable. The patient's left upper extremity appeared mottled, with no radial pulse and capillary refill time of more than 3 seconds. The patient was unable to move the hand, elbow, or shoulder and had no sensation in the left arm. The emergency physician suspected anterior shoulder dislocation and attempted immediate reduction. Following this intervention, the radial pulse remained absent and the neurologic deficits persisted. A radiograph was performed, followed by computed tomography (CT).



A. An AP chest radiograph demonstrates lateral displacement of the scapula, most conspicuous with attention to the scapular spine.

B. CT angiography shows soft tissue swelling and lateral displacement of the scapula. Not seen in this image but visible in other CT slices is axillary artery dissection.

Scapulothoracic dissociation is a rare but potentially devastating injury resulting from traction on the shoulder girdle. It may be radiographically subtle despite limb-threatening vascular and nerve injuries. When suspected, it can be further evaluated by CT angiography.

Because of its rarity, the "typical" radiographic appearance is poorly described. Lateral displacement of the scapula may be the only clue on an AP chest radiograph and can be mistaken for an artifact of patient positioning. Disruption of the acromioclavicular joint or distracted clavicle fractures can be seen.^{1,2}

Subclavian and axillary artery injury are common and can be visualized with CT or conventional angiography.³ Brachial plexus or cervical nerve root avulsion are also frequent with scapulothoracic dissociation. Complete brachial plexus injuries at presentation portend poor functional outcomes.⁴

The patient was managed nonoperatively because of spontaneously improving perfusion and neurologic examination results.

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Thanks to Mark Toyer, MD, for identifying this case.

Feature Editor: Joshua S. Broder, MD, FACEP. See also *Diagnostic Imaging for the Emergency Physician* (winner of the 2011 Prose Award in Clinical Medicine, the American Publishers Award for Professional and Scholarly Excellence) by Dr. Broder, available from the ACEP Bookstore, www.acep.org/bookstore.

Lesson 22

Pediatric Seizures

Kyle Drullinger MD, MPH, and N. Ewen Amieva-Wang, MD, FACEP

■ Objectives

On completion of this lesson, you should be able to:

1. List a broad but practical differential diagnosis for secondary causes of seizure based on patient age.
2. Explain when a neuroimaging study is necessary in the emergency department workup of a child with seizures.
3. Discuss when a lumbar puncture is indicated and when it should be avoided.
4. Describe a standard progression of therapies for, and the immediately reversible causes of, status epilepticus.
5. Elucidate a stepwise approach to seizure management in children, avoiding common pitfalls.

■ From the EM Model

12.0 Nervous System Disorders

12.9 Seizure Disorder

Up to 6% of children have at least one seizure in their childhood,¹ but seizures are a symptom of a wide range of pathophysiologic processes including toxic, metabolic, infectious, vascular, and traumatic disorders. The emergency physician's role in managing acute pediatric seizures is four-fold: 1) stabilize the patient; 2) stop ongoing seizures; 3) identify the cause of the seizure; and 4) determine the appropriate disposition and followup for the patient.

Seizures can be terrifying for the family, and although they can represent significant pathology, especially in younger patients, most of the time they are benign. The challenge for emergency physicians is to appropriately manage actively seizing patients and to differentiate between the dangerous and benign underlying pathophysiologic processes.

Case Presentations

■ Case One

A 24-day-old girl arrives by ambulance from home with reported seizure and fever. The child is a previously healthy term infant delivered by spontaneous vaginal delivery with no complications. At home she had been feeding and growing well, but her mother noted she felt warm when she went down for her nap. Shortly afterwards, the child became stiff and then began rhythmically shaking all four limbs; this lasted for about 2 minutes. On arrival of paramedics, the patient was crying and interactive. Vital signs in

the field were blood pressure 90/50, heart rate 165, respiratory rate 25, and oxygen saturation 99% on room air. In the emergency department, her rectal temperature is 38.7°C (101.7°F). On physical examination the child is alert, with an age-appropriate neurologic examination. Her examination is otherwise notable for rhinorrhea, clear lungs on auscultation, and no difficulty breathing. No cardiac murmur or rashes are noted, and the infant has a supple neck. Acetaminophen is given rectally.

■ Case Two

A 6-month-old boy is brought in after experiencing what the parents describe as "shaking fits." The mother noted that the patient had been doing well but had been a little more tired than usual, when, 45 minutes prior to arrival, his eyes seemed to roll back in his head and his whole body began to shake. The episode lasted from 1 to 3 minutes and then resolved. On evaluation, the boy is alert but appears tired. He is taking a bottle of formula and has normal vital signs, including temperature. The fontanelles are flat, the neurologic examination is nonfocal, and the remainder of the examination is unremarkable. The mother denies any history of sick contacts, fever, cough, any possible ingestion, or vomiting but has noticed some mildly loose stools.

■ Case Three

A 5-year-old boy is brought in by ambulance after having two

Critical Decisions

- What is the age-based differential diagnosis for seizures?
- What are some common mimics of seizure in children?
- What are the common infectious etiologies for fever and seizure?
- What is the recommended workup for first-time simple and complex febrile seizures in children?
- What is the role of neuroimaging in the emergency department for first-time pediatric seizures?
- What is the ideal algorithm for treating the pediatric patient in status epilepticus?
- When should intubation be considered in the seizing pediatric patient?

witnessed seizures. The parents reported that the patient was in his usual good health when, 1 hour prior to arrival, he became confused and then collapsed with shaking of all four extremities, which lasted for 30 seconds. His grandmother called paramedics, who found the child minimally responsive with stable vital signs and glucose of 118 mg/dL. En route to the emergency department, the child experienced another generalized seizure of similar duration and was given one dose of lorazepam, 2 mg IV. In the emergency department, the patient is somnolent and is placed in the left lateral decubitus position with supplemental oxygen and seizure precautions. All vital signs are within normal limits for the patient's age. On physical examination, the pupils are midrange and reactive. The child has a gag reflex but does not withdraw to painful stimuli. As the parents arrive, the patient has another seizure.

CRITICAL DECISION

What is the age-based differential diagnosis for seizures?

There is a broad differential for pediatric seizures (Table 1), which can be unwieldy when evaluating these patients in a busy emergency department. Fortunately, the age of the child can help focus the differential diagnosis and the necessary workup, with the more significant pathologies disproportionately affecting the youngest children.

Neonates (1 to 28 days old) with a seizure have the potential for the worst prognosis of all patients with seizures. In this age group, seizures almost invariably represent underlying pathology. Even without fever, neonates must be presumed to have a central nervous system (CNS) infection due to possible exposure to perinatal pathogens, their poorly developed immune system, and permeable blood-brain barrier. They are also at significant risk for intracranial hemorrhage, congenital

structural brain abnormalities, and metabolic disorders. Neonates can also experience withdrawal from in-utero exposure to alcohol, benzodiazepines, and opiates (Table 2). The prognosis in neonates with seizure is poor; the mortality rate is 24% to 30%, and 65% to 78% of infants who survive have a mental deficit later in life.² Accordingly, the workup in this age group should be aggressive, with all cases requiring neuroimaging, lumbar puncture, and empiric coverage for infectious etiologies.

Neonates also present the most dramatic departure from the adult population in terms of signs and symptoms of seizure. Although classic symptoms, including generalized or focal tonic-clonic motions, remain the most common presentation, subtle findings can be the only indicator of a neonatal seizure. These more subtle findings include a sucking or chewing motion, lip smacking, bicycling of legs, apnea, eyelid fluttering, eye deviation, laughter, or tonic posturing.³ Emergency physicians should note any of these activities in the history or examination notes and have a low threshold for admission for further testing if the diagnosis of seizure is in question.

Children 1 to 6 months old with a seizure are the most challenging for the emergency physician, as they represent the middle ground between the highest-risk neonatal population and older children who can typically be assessed on clinical grounds alone. Similar to neonates, children age 1 to 6 months remain at significant

Table 1.

General differential diagnosis of pediatric seizures (VITAMIN)

Vascular – Intracranial/intraventricular hemorrhage, subarachnoid hemorrhage, stroke, aneurysm, hypoxic event
Infectious – Meningitis, encephalitis, cysticercosis, <i>Shigella</i> , TORCH
Trauma – Closed head injury, nonaccidental trauma
Anatomic – Mass, metastases, hydrocephalus
Metabolic/endocrine – Glucose/electrolyte abnormalities, Addison disease, hyper/hypothyroidism, eclampsia
Ingestion – Isoniazid, tricyclics, EtOH withdrawal, organophosphates, lead, lidocaine, lithium, camphor, sympathomimetics
Neurologic/congenital – Intracranial malformations, primary seizure disorder

risk for CNS infection and may have seizure as the presenting symptom of a congenital metabolic or structural abnormality. They also remain at high risk for electrolyte and metabolic abnormalities such as hypoglycemia and hyponatremia. For these reasons, all children age 1 to 6 months require electrolyte (including calcium and magnesium) and glucose testing,⁴ and, if febrile, a full septic workup, including lumbar puncture, regardless of other symptoms.^{5,6}

Children age 6 months to 5 years require careful, thoughtful evaluation. Although CNS infection must be considered in this age group, it is less common and usually will occur with other signs/symptoms to guide further evaluation.⁷ These include severe headache, meningismus, altered mentation before the seizure, and an ill-appearing child. In this age group, it is critical to assess for ingestions, especially in toddlers, as well as trauma, be it accidental or nonaccidental. Febrile seizures, the most common seizure disorder in children, are by definition seen in this age range⁸ and are further discussed below. Consideration must also be given to metabolic derangement when the history is suggestive (eg, persistent diarrhea/vomiting or a lethargic child), but routine laboratory evaluation in this age group is not warranted.^{4,8}

Older children and adolescents have a differential diagnosis that starts to resemble that of adults. CNS infection must be considered, but, as in adults, this workup is based on history and classic physical examination findings for meningitis/encephalitis. There should always be a high clinical suspicion for ingestions. History should elicit alcohol withdrawal, tricyclic antidepressant overdose, jimson weed ingestion, and huffing; all are associated with seizures. In the appropriate clinical setting, rarer conditions should be considered, including thyrotoxicosis, neuroleptic malignant syndrome, serotonin syndrome, and eclampsia in girls of childbearing age.

In general, the most valuable data to guide the differential will come from the history. A birth history should be obtained for younger children, noting maternal infectious risks, antimicrobial treatment before or during delivery, and vaccine history. It is also important to evaluate travel history or time spent living abroad, which can raise the concern for acute CNS infection or more chronic infectious etiologies of pediatric seizures such as cysticercosis—the number one cause of acquired epilepsy worldwide.⁹ Trauma, both accidental and nonaccidental, should be considered in all children, as well as

any possibility of a toxic ingestion or exposure (Table 3).

CRITICAL DECISION

What are some common mimics of seizure in children?

It can be challenging to differentiate true seizure from several other medical conditions, both serious and benign. The most common of these are myoclonic jerks in the setting of syncope or hypoxic events, breath-holding spells, psychogenic seizure (usually in older teens and adults), apparent life-threatening

Table 2.

Most frequently occurring etiologies of neonatal seizures^{2,3}

In first 24 hours of life ^a
Hypoxic/ischemic encephalopathy
Intracranial hemorrhage (intraventricular versus epidural/subdural)
Infection (intrauterine transmission: meningitis, TORCH syndrome, sepsis)
Metabolic (hypocalcemia, hypoglycemia, hypomagnesemia)
Pyridoxine dependency/deficiency (in mother on INH)
After 24 hours ^a
Infection (intrapartum transmission: meningitis/encephalitis, HSV, sepsis)
Intracranial hemorrhage
Metabolic (inborn errors of metabolism, dietary hyponatremia/hypocalcemia)
Intracranial malformations
Drug withdrawal

^aListed in order of approximate frequency; most frequent listed first. Approximately 10% of cases are “unknown” etiology.

Table 3.

Age-based^a differential diagnosis of pediatric seizures¹⁰

Neonatal
Intracranial hemorrhage
Congenital brain abnormalities
Meningitis/encephalitis
Hypoglycemia/hypocalcemia/hypomagnesemia
Perinatal hypoxic brain injury
Inborn errors of metabolism
Nonaccidental head injury
Drug intoxication or withdrawal
Infants and Toddlers
Accidental/nonaccidental head injury
Brain tumor
Meningitis/encephalitis
Febrile seizure
Hyponatremia
Meningitis
<i>Shigella</i> gastroenteritis
Toxic ingestion
Children
Accidental head injury
Brain tumor
Toxic ingestion
Inborn errors of metabolism
Adolescents
Accidental head injury
Toxic ingestion
Brain tumor
Epilepsy
Eclampsia

^aNote that there is significant overlap among these groups

events (ALTEs), arrhythmias, and even gastroesophageal reflux (GERD).

As with most emergency department evaluations, a thorough history is the best way to differentiate these entities from true seizures. Important clues include events leading up to the seizure-like activity, any preceding aura, prior trauma, or recent illness. Additionally, a detailed description of the specific types of movement witnessed may be very helpful, with special attention to possible focality, loss of consciousness, incontinence, tongue biting, or color change, as well as duration of symptoms. Inquiring about the post "seizure" period is also helpful, noting if the patient is confused (postictal), sleepy, lethargic, or experienced focal neurologic deficits (Todd paralysis). Frequently seen seizure mimics are discussed below.¹

Syncope/myoclonic jerks. This is a transient loss of consciousness, with no postictal state. Movements are often brief and usually spasmodic without a regular rhythm, and there is rarely incontinence or tongue biting. Preceding lightheadedness or diaphoresis are consistent with this diagnosis.

Breath-holding spells. These typically occur in children between 6 and 18 months of age and are seen in up to 5% of children. The episodes are defined by the child holding his/her breath, often with resultant color change to pale or cyanotic. They can be confused with seizure, usually if the child has syncope as a result of the hypoxia and has myoclonic jerks as above. These episodes by definition last less than 1 minute and do not result in a postictal state

ALTEs. Now loosely defined as any event that frightens the child's caretakers or makes them think the child may die, these events can include color change, apnea, choking or gagging, and often a change in muscle tone (becoming rigid or flaccid), which may be confused with a seizure.

Arrhythmias. Nonperfusion or poor perfusion arrhythmias can lead

to hypoxic episodes associated with seizure-like movements.

Sandifer syndrome. This syndrome presents with dystonic posturing, usually torticollis or retrocollis, and back arching in response to GERD with no alteration in level of consciousness.

Recognizing the factors in the history that make these seizure mimics more likely can be critical in making the appropriate diagnosis and avoiding an extensive workup. In the absence of a truly convincing history, seizure must be presumed.

CRITICAL DECISION

What are the common infectious etiologies for fever and seizure?

Seizures in the setting of fever are the most common presentation of first-time seizures in children, primarily because of the prevalence of febrile seizures (3% to 5% of children have a febrile seizure).¹¹ The differential diagnosis and workup of fever and seizure vary by age group. Broadly, the differential diagnosis for seizure in a febrile child of any age must include consideration of CNS infection (meningitis/encephalitis), as well as the more benign simple and complex febrile seizures. The infectious etiologies that cause seizure vary by age, with neonates at risk for significantly different pathogens than older children.

Neonates (1 to 28 days). Neonates are at high risk of acquiring infections transmitted in utero or from the birth canal during delivery. These infections include group B streptococcus, herpes simplex virus (HSV), *Escherichia coli*, and *Listeria monocytogenes*. Antibiotic coverage in suspected or confirmed CNS infection in neonates necessarily covers these pathogens as well as the more common *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae*. Empiric antibiotic regimens typically consist of ampicillin (for *Listeria* and strep), gentamycin (*E. coli*), and acyclovir (HSV). Given the elevated risk of infection in the neonatal population, all neonates with seizure should be started

on this or an equivalent regimen. Importantly, although known maternal infection with group B streptococcus or herpes suggests these infections as the cause, the lack of such history should not preclude empiric treatment for these organisms. In utero infection with the classic TORCH pathogens (toxoplasmosis, others including syphilis and varicella zoster virus, rubella, cytomegalovirus, HSV/HIV) can also cause neonatal seizures, although these infections would not change emergency department management and are usually not discovered until later in the hospital stay.

Of the above pathogens, HSV meningoencephalitis is one of the most devastating CNS infections seen in the neonatal population. Although history can help if a clear exposure occurred, often no clear exposure is evident, and empiric therapy must be started. In general, HSV is transmitted to the neonate during vaginal delivery (85%), but it can be transmitted in utero (5%) or after birth, usually from oral lesions on a caregiver.¹² These children usually present in the second or third week, but this infection can occur any time during the first 6 weeks of life. The presence of herpetic skin lesions can be helpful in the diagnosis, but their absence is in no way reassuring; as many as 50% of neonates never manifest a rash.¹³

Age 1 to 6 months. Etiologic agents in this group trend away from perinatal infections and toward the standard adult meningitis-causing agents such as *S. pneumoniae*, *N. meningitidis*, and, in the under-immunized, *H. influenzae*. Empiric treatment usually consists of ceftriaxone with or without vancomycin with or without acyclovir. Children at the younger end of this age group (especially younger than 6 weeks) should, however, be treated similarly to neonates because the risk for perinatal infections remains. As mentioned above, clinical findings of CNS infection are often limited in patients younger than 6 months of age

and CNS infection must be ruled out by testing in these children.¹⁴

Age 6 months to 18 years. These children generally present with the same pathogens as adults and are treated similarly. Clinical examination and history will guide the diagnostic evaluation. Other non-CNS infections, while rare, can be associated with seizure, most notably *Shigella* gastroenteritis.

CRITICAL DECISION

What is the recommended workup for first-time simple and complex febrile seizures in children?

Most children presenting with seizure and a fever from the ages of 6 months to 5 years will be diagnosed with a febrile seizure.¹¹ These seizures are categorized as simple or complex and, by definition, only occur in this age group.

A simple febrile seizure is a seizure in the setting of fever (>100.4°F), generalized, and lasting less than 15 minutes, with return to baseline mental status and no recurrence of seizure in a 24-hour period. There must be no indication of CNS infection or prior epilepsy.

A complex febrile seizure is a seizure in setting of fever, plus any of the following: focal component, duration longer than 15 minutes, and more than one seizure within a 24-hour period. There must be no indication of CNS infection or prior epilepsy.

The workup for simple and, especially, complex febrile seizures is not standardized and varies widely among emergency practitioners.¹⁵ Current American Academy of Pediatrics (AAP) guidelines⁶ give a broad overview and address the issues of what laboratory and imaging studies should be considered, as well as the disposition of these patients.

In the setting of a *simple febrile seizure*, although these children should be evaluated for causes of fever including urinary tract infection when clinically applicable, there is no need for invasive investigations to rule out CNS pathology in a

well-appearing child with a normal neurologic examination. Evaluation with basic screening laboratory studies such as CBC, chemistry, or even inflammatory markers has been shown to be nonspecific and noncontributory.^{4,16,17} In the past, lumbar puncture was considered mandatory in first-time seizure in the setting of fever in all children between the age of 6 and 12 months; however, recent evidence shows that few practitioners were applying these guidelines regularly¹⁸ and that there was little or no use for routine lumbar puncture in these children despite concerns that classic signs and symptoms of meningitis may be lacking.⁷ AAP guidelines from 2009 reflect this, stating, “In any infant between 6 and 12 months of age who presents with a seizure and fever, a lumbar puncture is an option when the child is considered deficient in *H. influenzae* type b (Hib) or *S. pneumoniae* immunizations or when immunization status cannot be determined.”¹⁶ For those children less than 6 months of age, who by definition cannot have a febrile seizure, a lumbar puncture and basic laboratory studies including blood cultures, are recommended.

The picture in *complex febrile seizures* is much less clear. These seizures are generally considered more concerning for underlying pathology and are known to place the child at higher risk of developing epilepsy.¹⁹ In general, as in simple febrile seizures, the workup should be driven by clinical factors such as focal neurologic deficits, signs and symptoms of meningitis/encephalitis, or evidence of trauma. Those children who recover quickly and completely from a complex febrile seizure, have no indication of CNS infection or focal neurologic deficit, and are otherwise well appearing can generally be sent home with outpatient followup.¹ Although a more conservative approach, including laboratory studies, neuroimaging, and lumbar puncture, is often employed in these patients, there is

little evidence of benefit and large variation among practitioners. One study of 526 patients age 6 to 60 months with complex febrile seizures found that only 2 of these patients had positive lumbar punctures and they both had other signs of meningitis/encephalitis that would have guided the practitioner to obtain the test. The authors concluded that lumbar punctures should not be a routine consideration in patients with complex febrile seizures who are otherwise asymptomatic.⁷ A 2006 review of the literature on first-time complex febrile seizures concluded that computed tomography (CT) scans were not indicated in this setting; no patients in the seven studies reviewed were found to have an abnormality on CT that changed their treatment.²⁰

It is also critically important to discuss with the parents the rationale behind a workup, or lack thereof, and to give them a reasonable sense of what to expect going forward. For children with *simple febrile seizures* this means only a very slight risk of developing epilepsy,²¹ but a roughly 35% chance of recurrent febrile seizure, with estimates as high as 55% in those children with younger-onset febrile seizure.²²⁻²⁴ In *complex febrile seizures* these numbers are higher, with anywhere from 5% to 9% going on to develop nonfebrile seizures later in life.^{21,25} Providing parents with handouts explaining febrile seizures and answering some of the basic questions about prevention and return precautions can greatly reduce anxiety and facilitate appropriate care of these children at home.

CRITICAL DECISION

What is the role of neuroimaging in the emergency department for first-time pediatric seizures?

It is widely recognized that there is no role for emergent neuroimaging in the setting of a simple febrile seizure in a patient with a nonfocal neurologic examination, but opinions vary on the use of emergent CT neuroimaging in the setting of a first-time, nonfebrile and complex

febrile seizure. As with any seizure evaluation, clinical features such as a focal neurologic examination, concern for hydrocephalus, or a history of trauma should guide these decisions.

Imaging is often advocated in the following situations: suspected increased intracranial pressure; focal seizure; focal neurologic deficit; seizure following head trauma; the ill-appearing patient; prolonged seizure; or patients with HIV.^{26,27} More recent guidelines and literature are moving away from regular emergency department imaging in pediatric seizures for both clinical and cost-saving reasons. The latest practice guidelines (2006) from the American Epilepsy Society recommend emergent neuroimaging only for children with a postictal focal neurologic deficit, unless it is a rapidly resolving Todd paralysis, or for those who do not return to baseline mental status within a few hours.⁴ Similar recommendations are made in the American College of Radiology's guidelines from 2009.²⁸ These guidelines also note that magnetic resonance imaging (MRI) is the study of choice in children, not only because of the radiation exposure of CT scans, but also because MRI has much higher sensitivity for CNS lesions that can lead to seizures. There is no formal recommendation from the AAP for or against imaging in patients with focal seizures or complex febrile seizures. As noted, significant data refute the use of CT in the setting of complex febrile seizures.²⁰ The 2009 American Academy of Radiology guidelines for imaging infants and children with new-onset epilepsy report that only 2% to 4% of children with recurrent focal seizures were found to have MRI results that might change immediate management,²⁹ and a 2008 emergency department-based study concluded that inpatient MRI in the setting of new-onset afebrile seizures did not change care for patients and significantly increased cost compared to outpatient MRI.³⁰ Several other studies reiterate the need for judicious

use of emergency department CT and MRI in the setting of new-onset seizures without other concerning findings from the history or physical examination.^{29,31,32}

Although local guidelines vary, CT scans in children with new-onset seizures, even if focal, appear to be of little use unless there is a persistent alteration of consciousness, a persistent focal deficit, concern for hydrocephalus, or history of trauma. If neuroimaging is to be considered outside of this setting, then MRI is the study of choice, and obtaining the study as an outpatient should be considered.

CRITICAL DECISION

What is the ideal algorithm for treating the pediatric patient in status epilepticus?

Status epilepticus (SE) is a dangerous condition that can lead to permanent disability and death. Emergency treatment of SE focuses on stabilization (ABCs), termination of seizure activity, and determination of immediately reversible causes of seizure (Figure 1, Table 4). As therapies have evolved to manage SE in the emergency department, so too has the definition of SE. Historically, SE was defined as a seizure lasting 30 minutes or more or a recurrence of seizure activity without recovery of consciousness in between.⁸ As the evidence of the potential harm of extended seizure activity has grown and as it has been demonstrated that this morbidity begins as early as after 5 minutes of continuous seizure activity, many authors now argue that the definition of SE should be changed to seizure activity lasting more than 5 minutes.^{33,34} Additionally, duration of seizure activity is negatively correlated with self-termination and treatment effectiveness, making expeditious treatment of SE prior to arrival and in the emergency department key to the effective management of SE.^{35,36} For this reason, algorithms for treating SE have been developed to minimize delays and maximize effectiveness,

although the best overall algorithm has yet to be determined.³⁷ Becoming familiar with first- and second-line medications is crucial as nearly 60% of patients who present in SE fail to have their seizures terminated with first-line medications.³⁸ Below is an overview of one recommended course of intervention.

First line. It is widely accepted that first-line medication for the termination of SE is a benzodiazepine, with most authors suggesting the use of lorazepam if it is available.

A Cochrane Review from 2008³⁹ suggests that intravenous lorazepam is the superior first choice of benzodiazepine, with a wealth of literature indicating equal or superior effectiveness, less need for re-dosing, and fewer side effects, including decreased respiratory suppression, compared to diazepam.^{40,41} If these medications are not effective within 3 to 5 minutes, the dose may be repeated once, taking into account that the emergency department first dose may be the patient's second dose if prior EMS or home administration has taken place.^{42,43} At this time, prepare a second-line medication, and administer it concurrently with the benzodiazepine.

Note that neonatal SE is often difficult to treat given the generally severe underlying pathologic condition. By convention, neonatal seizures are often initially treated with phenobarbital or phenytoin/fosphenytoin, neither of which has been shown to be superior.^{44,45} Thus the first-line use of benzodiazepines is also accepted in this age group.^{8,46} Given the limited comparison data, it is reasonable to use the same algorithm as established for older children to avoid confusion and delays in treatment.

Second line. Most emergency department-based approaches now recommend the use of a fosphenytoin/phenytoin infusion if benzodiazepines fail. This can be administered after or concurrently with the second dose of benzodiazepine. Phenobarbital is another acceptable second-line

agent but causes more respiratory depression and increases the likelihood of respiratory failure.¹

Third line. Once first- and second-line agents have failed, the seizure is considered “refractory,”

regardless of its duration.⁸ At this point, most emergency physicians will progress to rapid sequence intubation (RSI) for airway protection and then start a more aggressive regimen while trying to get the

child rapidly to the pediatric ICU on constant electroencephalographic monitoring. Few guidelines exist to direct this next step, which should be performed in consultation with a pediatric neurologist. Several options

Figure 1.

Algorithm for management of the undifferentiated patient with SE.^{1,8,42} In all cases, immediately reversible causes must be considered early. The algorithm for treating SE must include early consideration of all the diagnoses listed in Table 4.

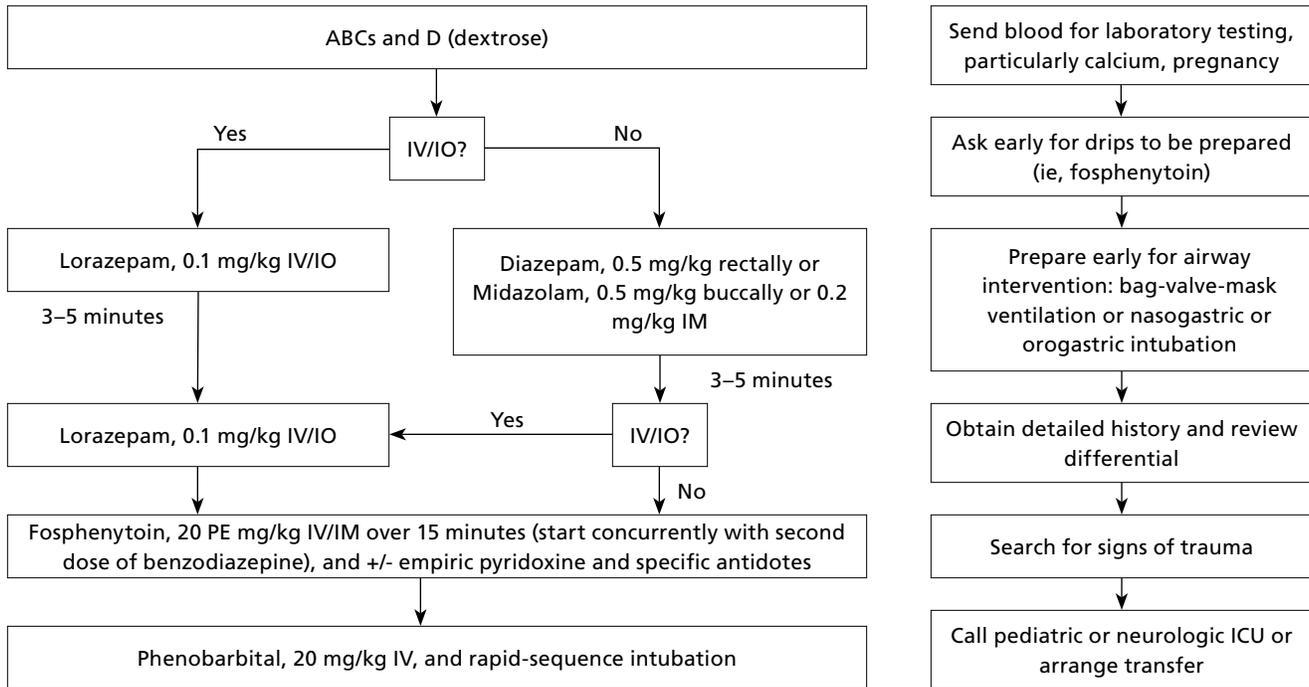


Table 4.

Immediately reversible causes of seizure/status epilepticus

Special case	Signs/symptoms	Treatment
Hypoglycemia	Lethargy, history of infection, sulfonylurea or insulin ingestion, gestational diabetes mellitus, high birth weight	4 to 6 mL/kg D10W IV bolus Consider octreotide in sulfonylurea overdose
Hyponatremia	Lethargy may or may not be present, history of free water/diluted formula intake, recurrent seizures	4 to 6 mEq/kg 3% normal saline (1 mEq/2 mL – 1 mEq/kg raises serum sodium by 1 mEq/L)
Hypocalcemia	Increased neuromuscular irritability, “jittery” infant	Calcium, 60 to 100 mg/kg IV/IO, must also replete magnesium, if low
Isoniazid ingestion	History, significant anion-gap acidosis, refractory status epilepticus	Pyridoxine (vitamin B ₆): —Known ingestion: 1 g IV/PO for each gram of isoniazid ingested —Unknown ingestion: 70 mg/kg IV (maximum 5 g/30 minutes)
Eclampsia	Third trimester to 6 weeks post partum	Magnesium, 4 to 6 g IV, then 2 g/hr gtt 5 g IM x 2
Alcohol withdrawal	History of maternal or child alcohol abuse	Lorazepam, 0.1 mg/kg IV

for continued sedation/seizure suppression are listed in Table 5, with some references supporting their use. Most of these medications will cause some degree of respiratory depression and hemodynamic instability, which should be managed with aggressive hydration and, rarely, vasopressors.

CRITICAL DECISION

When should intubation be considered in the seizing pediatric patient?

Whether or not to intubate a patient in SE or a patient whose seizure has been controlled through the above management techniques is a challenging decision for emergency physicians. As with any discussion of intubation, the decision is a clinical one and is based on two simple questions: 1) is the patient oxygenating and ventilating appropriately, and 2) is the patient protecting the airway. For children who are not adequately oxygenating or ventilating, either from the seizure or, more commonly, from the therapies used to treat the seizure, intubation should be undertaken using established RSI techniques. Continuous capnography can help with this determination in unclear cases and should be used when available. Children in the postictal state are often oxygenating and ventilating well, but their depressed mental status calls into question their ability to protect their airway. Many of these children will meet objective criteria (Glasgow Coma Scale score less than 8) for intubation for airway protection; however, because the

postictal state is self-limited, many of these children will make a full recovery without invasive airway management. There are no guidelines to help with this decision, but most often these children can be managed by placing them in lateral decubitus position and even placing an adjunct nasal or oropharyngeal airway, if tolerated. Prophylactic antiemetics should be given to all patients. If a patient is obtunded enough to tolerate an oropharyngeal airway or is going to be transferred to another facility, then the threshold for intubation should be lower.

Case Resolutions

■ Case One

This neonate, although well appearing, was at high risk for a CNS infection. Laboratory studies, including blood cultures and a lumbar puncture, were performed, and he was started on ampicillin, gentamycin, and acyclovir before lumbar puncture results returned. Further history from the mother on her arrival revealed no known infections and no antibiotics for her or her child at the time of delivery, but she did note a remote history of genital herpes that she thought had resolved. Cerebrospinal fluid evaluation was consistent with HSV encephalitis. The patient was continued on acyclovir and made a good recovery.

■ Case Two

Because the 6-month-old boy was tired but otherwise well appearing and had mild diarrhea, the emergency

physician decided to send basic laboratory studies and was debating whether or not to perform a lumbar puncture out of concern for a subclinical CNS infection when the child's sodium level returned at 114 mm/L. Glucose was noted to be 80 mg/dL on a bedside point-of-care test. On further questioning of the family, it was noted that the husband had recently lost his job, and in order to make the baby formula last longer the mother had been diluting it with water. The child was changed to regular formula, given a bolus of 20 mL/kg of normal saline, and admitted to the pediatric service for serial sodium checks and social work consultation.

■ Case Three

Because of persistent seizure activity in this 5-year-old boy, a nasal airway was placed, and he was given an additional dose of 2 mg of lorazepam, and a fosphenytoin loading dose of 20 mg/kg was called for. Laboratory studies were sent, including a CBC, blood cultures, and toxicology panel, and the blood glucose was rechecked and found to be 110 mg/dL. As the emergency physician considered advancing down the SE algorithm and intubating the patient, further history was obtained from the parents who had arrived. There was no report of trauma or recent illness, but the grandmother noted she was on pills for "TB" and could not find her pill bottle. Isoniazid toxicity was suspected, and because the total ingestion was unknown, the child was given a 70-mg/kg dose of pyridoxine with resolution of seizure activity.

Summary

Seizures in children are common in emergency medicine. Differentiating dangerous from benign causes requires a thorough history and physical examination and a good understanding of the age-based differential diagnosis. Ancillary testing, including basic laboratories, lumbar puncture, and possible neuroimaging, is needed in specific

Table 5.
Options for third-line anticonvulsant agents

Agent	Comments
Midazolam infusion ^{36,47}	
Pentobarbital	Induces coma
Propofol	
Valproic acid	Safe and effective, but slow onset ⁴⁸
Levetiracetam (Keppra)	Common adjunct with limited side effects
Ketamine	Only anticonvulsant to target NMDA and not GABA receptors ²⁷

cases but is often overused in the emergency department. Aggressively treating pediatric SE minimizes morbidity and should proceed through the use of predetermined algorithms and rapid evaluation for immediately reversible causes.

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Pearls

- The workup in neonates with a seizure should be aggressive, with all cases requiring neuroimaging, lumbar puncture, and empiric coverage for infectious etiologies.
- All children 1 to 6 months of age require electrolyte (including calcium and magnesium) and glucose testing and a full septic workup including lumbar puncture, regardless of other symptoms.
- Obtain a detailed history in all children with seizures to delineate risk factors.
- Consider observation instead of lumbar puncture if the patient is at low risk for meningitis and older than 6 months.
- Always check bedside glucose in the actively seizing or altered pediatric patient.
- Keep the differential broad initially and always consider nonaccidental trauma and ingestions.
- Febrile seizure is not the same as seizure in the setting of fever.

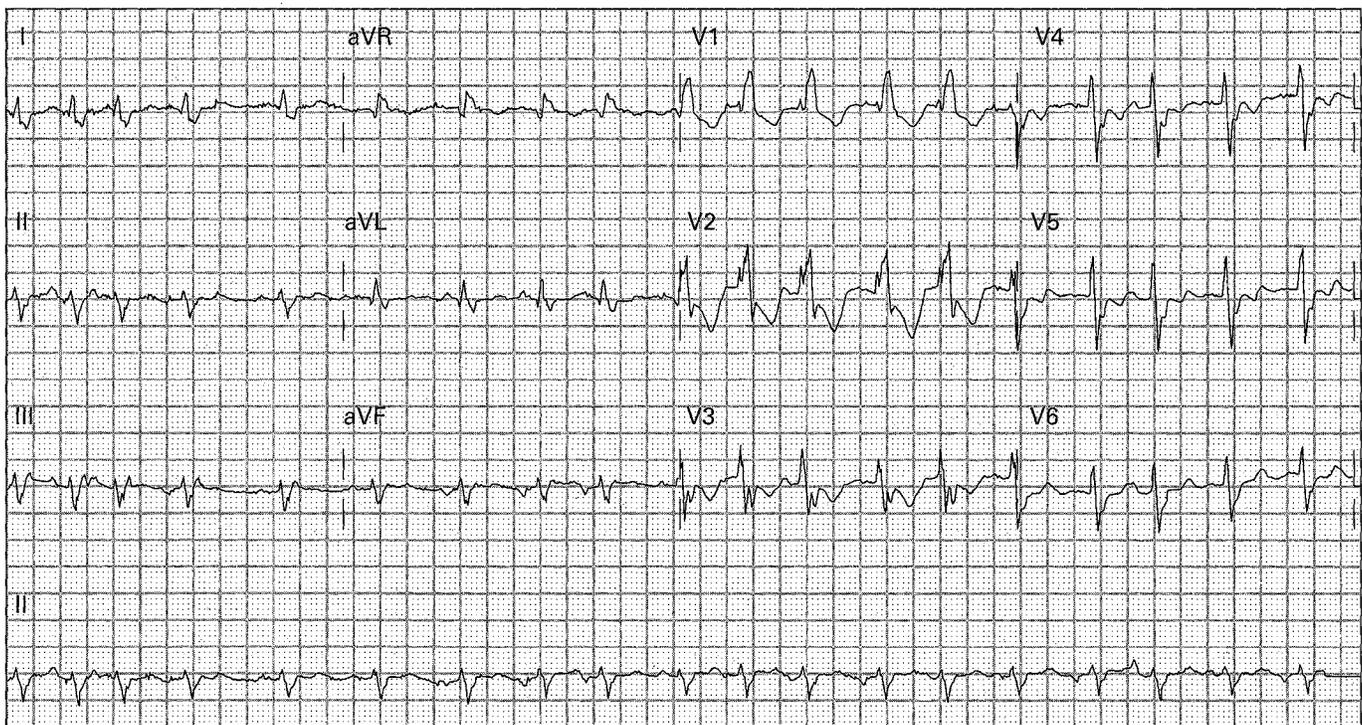
Pitfalls

- Failing to consider reversible causes of seizure early in the management of SE.
- Delaying advancing to second- and third-line drugs rapidly when SE does not resolve.
- Not taking into account the duration of the seizure prior to emergency department arrival and any EMS medication administration when considering advancing down the SE algorithm.
- Neglecting to consider infectious causes in infants younger than 6 months old even if no fever is present.
- Expecting a rash in neonates with herpes simplex encephalitis when half of these patients do not have a rash.
- Neglecting immunization history when deciding whether to perform a lumbar puncture in a child with seizure in the setting of fever.
- Being unprepared to manage the airway for all seizure patients.

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The Critical ECG

A 60-year-old man with history of chronic bronchitis presents with dyspnea and palpitations.



Multifocal atrial activity (MAT), rate 115, right bundle-branch block (RBBB). The main considerations with any wide-complex, irregular tachycardia include atrial fibrillation with aberrant conduction (for example bundle-branch block), atrial flutter with variable block and aberrant conduction, MAT with aberrant conduction, atrial fibrillation with Wolff-Parkinson-White syndrome, and polymorphic ventricular tachycardia. P waves are noted in the rhythm strip; they occur irregularly, are followed by QRS complexes without evidence of nonconducted beats, and are of various morphologies. These findings are typical of MAT. An RBBB is present, accounting for the wide QRS complexes.

Feature Editor: Amal Mattu, MD, FACEP

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CME Questions

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- In an acutely ill patient, which of the following is most suggestive of acute adrenal insufficiency?
 - AM cortisol >15 mcg/dL
 - PM cortisol level >15 mcg/dL
 - random cortisol <15 mcg/dL
 - random cortisol >15 mcg/dL
- In the patient with adrenal insufficiency, which of the following stressors mostly commonly precipitates adrenal crisis?
 - acute otitis media
 - gastrointestinal illness
 - myocardial infarction
 - trauma
- What laboratory abnormality is more commonly seen in primary rather than secondary adrenal insufficiency?
 - hyperkalemia
 - hyponatremia
 - hypoglycemia
 - hypokalemia
- What is the steroid of choice in the acutely ill and hypotensive patient with adrenal insufficiency?
 - dexamethasone
 - hydrocortisone
 - methylprednisolone
 - prednisolone
- Which of the following is the most common cause of secondary adrenal insufficiency?
 - pituitary apoplexy
 - Sheehan syndrome
 - traumatic brain injury
 - withdrawal of exogenous steroids
- The risk of hemodynamic collapse is greatest in which of the following causes of adrenal insufficiency?
 - chronic adrenocortical insufficiency
 - pituitary apoplexy
 - Sheehan syndrome
 - withdrawal of exogenous steroids
- A patient with a known history of adrenal insufficiency presents with an acute gastrointestinal illness and hypotension. Random cortisol is 10 mcg/dL, glucose is 62, and TSH is 6.2 mIU/L (mildly elevated). What is the appropriate treatment?
 - hydrocortisone
 - hydrocortisone and glucose
 - hydrocortisone and thyroid hormone
 - hydrocortisone, glucose, and thyroid hormone
- Which of the following combinations of laboratory abnormalities suggests underlying adrenal crisis in a patient with undifferentiated shock?
 - hyperkalemia, hyponatremia, metabolic acidosis
 - hyperkalemia, hyponatremia, metabolic acidosis
 - hypokalemia, hyponatremia, metabolic alkalosis
 - hypokalemia, hyponatremia, metabolic acidosis
- An 11-year-old boy with chronic adrenocortical insufficiency presents with acute otitis media. His vital signs are blood pressure 115/90, heart rate 80, respiratory rate 14, and temperature 38.3°C (101°F). Examination reveals a well-hydrated child in no acute distress. He is able to tolerate oral fluids and medications and has had no episodes of vomiting. What is the appropriate disposition for this patient?
 - admission to hospital with parenteral steroids
 - discharge home with doubling of his home steroid dose
 - discharge home with no change to steroid dosing
 - hospital observation with intravenous fluids and parenteral steroids
- A 25-year-old woman with a history of chronic adrenocortical insufficiency arrives in the trauma bay after a motor vehicle accident. Vital signs are blood pressure 75/30, heart rate 128, and respiratory rate 22. Her only injury is an open tibia-fibula fracture, and she is in severe pain. You irrigate the wound, reduce the fracture, update her tetanus, and administer prophylactic antibiotics. Regarding her adrenal disease you should:
 - give her double the usual home dose of steroids orally
 - give hydrocortisone, 100 mg IV, now
 - give only her home dose of steroids now
 - give steroids only if cortisol stimulation test results are abnormal
- Which of the following patients does not require neuroimaging in the emergency department?
 - a 3-year-old boy with persistent right arm weakness after a first-time seizure
 - a 4-year-old, well-appearing girl with her third complex febrile seizure in the past year
 - a 10-day-old neonate who had a 3-minute generalized seizure but is now alert and appropriate
 - a well-appearing 8-year-old boy who had a seizure and lost consciousness after falling from his bike

12. Which of the following patients should have a lumbar puncture?
- a 2-year-old boy with a simple febrile seizure
 - a 3-year-old girl with a complex febrile seizure, now back to baseline
 - a well-appearing 4-year-old girl with upper respiratory tract infection symptoms presenting with a 30-second generalized seizure and a fever to 39°C
 - a well-appearing 6½-year-old boy with upper respiratory tract infection symptoms presenting with a 90-second generalized new-onset seizure and a fever to 39°C
13. Which of the following is a common cause of seizures among neonates?
- acute renal failure
 - alcohol ingestion
 - congenital disorders
 - withdrawal from benzodiazepines
14. Which of the following is correct?
- all seizures in the presence of a fever require a lumbar puncture
 - neonatal seizures are always less worrisome than those in older children
 - prehospital doses of benzodiazepines should be considered the same as an emergency department dose when assessing how to advance down the treatment algorithm for status epilepticus
 - rectal diazepam is the most effective and recommended out-of-hospital treatment for seizures
15. What is the first action that should be taken with an actively seizing child in the emergency department?
- administer benzodiazepines
 - check a glucose
 - position patient to avoid aspiration, and provide supplemental oxygen
 - secure the airway via intubation
16. What must be checked immediately in all actively seizing children?
- bedside glucose
 - electrocardiogram
 - family history of seizures
 - vaccination history
17. Which of the following is the most common cause of seizure in the neonate?
- CNS infection
 - hypoglycemia
 - intracranial hemorrhage
 - nonaccidental trauma
18. Which of the following children is most likely to have a benign cause of their seizure?
- a 10-month-old infant with a dry cough and rhinorrhea, presenting with a 4-minute generalized seizure and noted to have a fever to 39.1°C
 - a 12-year-old boy who is alert and appropriate but who seized after being tackled on the playground at school
 - a well-appearing 23-day-old neonate without fever, presenting with a 2-minute generalized shaking episode
 - a well-appearing 8-month-old girl with a fever, presenting with a 2-minute seizure that began in her right arm and leg and then became generalized
19. Which of the following patients requires neuroimaging in the emergency department?
- an ill-appearing 8-year-old child with a fever but no stiff neck who had a brief generalized seizure but now has a nonfocal examination without signs of increased intracranial pressure
 - a well-appearing 8-day-old infant with a nonfocal neurologic examination, presenting with a first-time, 4-minute generalized seizure and normal laboratory results
 - a well-appearing 4-year-old boy with a first-time complex febrile seizure but normal neurologic examination
 - a well-appearing 7-year-old girl with no past medical history, normal vital signs, and a normal neurologic examination with a first-time generalized seizure lasting 2 minutes
20. Parents of a child presenting with a first-time febrile seizure should be told that:
- taking antipyretics can help prevent seizures
 - their child is likely to develop epilepsy
 - their child is likely to have another febrile seizure before the age of 5
 - their child should be evaluated by a pediatric neurologist

Answer key for June 2012, Volume 26, Number 10

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
D	D	B	B	A	B	C	D	C	A	A	A	C	C	C	D	D	C	C	B

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 **The Drug Box**

Phenobarbital

Josef Lowe, MD; Summa Health System Emergency Medicine Residency

Phenobarbital was the first barbiturate synthesized. It is a third-line drug for status epilepticus, but it is commonly used for neonatal seizures. It is also used as a maintenance drug for children with epilepsy. The drug has a narrow therapeutic window, therefore children and adults are subject to overdose at low ingestions of the drug.

Mechanism of Action	Barbituric acid derivative that is a nonselective CNS depressant. It binds to GABA receptors, modifying chloride currents through the channels. It also inhibits glutamate-induced depolarizations.
Indications	May be used to treat or prevent seizures; short-term treatment of insomnia. May be used as a sedative. Also has use in treatment for withdrawal from alcohol or benzodiazepines.
Dosing—Adult	Seizure disorder: 60 mg PO twice or three times daily Status epilepticus: 10 to 20 mg/kg IV x 1, may be repeated if necessary Sedation: 10 to 40 mg PO/IM/IV three times daily
Dosing—Child	Seizure disorder: 3 to 8 mg/kg PO/IV daily or twice daily Status epilepticus: 10 to 20 mg/kg IV x 1, then 5 to 10 mg/kg every 15 to 30 minutes
Side Effects	Drowsiness, headache, dizziness, hyperactivity, nausea, vomiting, difficulty or slowed breathing, swelling of the eyes, lips, or cheeks, rash, blistering of the skin, fever, confusion
Estimated Cost to Hospital and Patient	Tablets—\$0.08–\$0.36 IV—\$1.63–\$4.32
Contraindication/Precautions	History of porphyria, severe liver disease, history of addiction to barbiturates or sedatives, severe asthma or COPD Pregnancy Class D

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