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Evidence-Based Management Of Metabolic Emergencies In The Pediatric Emergency Department

A previously healthy 18-month-old girl presented to the emergency department with a 1-day history of poor feeding. On the morning of presentation, she was unarousable, so her parents called EMS. Paramedics arrived to find a somnolent child who was warm and well perfused, with a blood glucose level that was undetectable on a portable glucometer. She was given an infusion of glucose and transported to the ED, where she became somewhat more interactive. Blood and urine samples showed a normal blood sugar level and no ketonuria. The patient was continued on intravenous (IV) fluids containing dextrose and admitted to the hospital for observation. Her clinical course was unremarkable until that night, when she was weaned from IV fluids. At 4 am, her blood glucose level measured 47 mg/dL, and she was unarousable. As glucose was given, a more extensive laboratory panel was drawn, and her urine was collected a second time. The patient's diagnosis was made on the basis of these samples.

The management of metabolic emergencies in the pediatric population is challenging for the emergency clinician because it requires in-depth knowledge of a broad range of conditions. Some children may present with a metabolic complication resulting from a serious illness such as sepsis. Another group of patients may present with complications of chronic diseases like diabetes mellitus or with life-threatening symptoms from a previously undiagnosed inborn error of metabolism (IEM). The incidence of IEM may be as high as 1

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CME Objectives

Upon completion of this article, you should be able to:
1. Recognize the manifestations of metabolic disease.
2. Develop a diagnostic testing regimen for pediatric patients with a suspected metabolic disorder.
3. Develop a plan of care for the pediatric patient with a metabolic disorder, known or unknown.
4. Recognize common metabolic derangements in pediatric patients with a critical illness.
5. Develop a plan of care for pediatric patients with type 1 diabetes mellitus and hyperglycemia.

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in every 5000 live births.[1,2] This estimate may be revised as newborn screening for metabolic disorders is expanded. The American Academy of Pediatrics (AAP) and the American College of Medical Genetics have endorsed a plan to enact testing for more than 50 such disorders, 29 of which are amenable to treatment.[3] This issue of *Pediatric Emergency Medicine Practice* examines approaches to the pediatric patient who presents to the ED with a metabolic emergency and identifies areas where diagnostic and therapeutic strategies fall short from an evidence-based perspective.

The topic of metabolic emergencies is a broad one, even when the least inclusive definition is used. For the sake of this discussion, a *metabolic disorder* is defined as a disease process that results from an error in the metabolism of carbohydrates, fats, amino acids, or cholesterol. This definition overlaps with that of disorders that are endocrine in nature, including diabetes mellitus and adrenal insufficiency (AI).

Abbreviations Used In This Article

AAP: American Academy of Pediatrics
Acetyl-CoA: acetyl coenzyme A
ACTH: adrenocorticotropic hormone
AI: adrenal insufficiency
ATP: adenosine triphosphate
CAH: congenital adrenal hyperplasia
CNS: central nervous system
CT: computed tomography
DKA: diabetic ketoacidosis
ECG: electrocardiogram
GABA: gamma-aminobutyric acid
HHS: hyperosmolar hyperglycemic state
ICU: intensive care unit
IEM : inborn error of metabolism
IM: intramuscularly
IV: intravenously
MRI: magnetic resonance image
NAD: nicotinamide adenine dinucleotide
PKU: phenylketonuria

Evidence

Metabolic emergencies are challenging to study in a controlled fashion. Inborn errors of metabolism occur so rarely that it is difficult to construct a trial with a meaningful number of patients, even at a preeminent specialty center with a large number of patients. As a result, evidence addressing the diagnosis of patients with an unknown or suspected metabolic disorder is limited. Rather, the data address metabolic disorders from the larger perspectives of public health and epidemiology or are used as guidelines for the bedside care of patients with a known disorder. An abundance of case reports and cohort studies describe the presentation of individual disorders and the results of long-term care. This article will focus on the clinical management of the patient with a previously unrecognized metabolic derangement who presents to the ED. Emphasis will be placed on diagnostic clues and specific management strategies that are available to the clinician.

Demographics, Epidemiology, And Pathophysiology

Many metabolic disorders lead to repeated hospital visits during acute illnesses; a subset is associated with high morbidity and mortality. Because IEMs represent only a small proportion of the disease processes that lead to metabolic emergencies, calculating their overall impact on emergency services and on the medical system as a whole is difficult. Metabolic errors can be divided into 4 major subgroups according to the nature of the defect.[4] In the first subgroup, the transport protein or protein complex that allows passage of a substance across a membrane is missing or ineffective. For example, the presence of insulin is required for glucose to be transported into the cells; diabetes mellitus results from a lack of or resistance to insulin. In the second category, the enzyme responsible for catalyzing the reaction of a precursor into a physiologically necessary product is lacking. In patients with phenylketonuria (PKU), for example, the enzyme that converts phenylalanine to tyrosine is deficient, causing an accumulation of phenylalanine that is toxic to the central nervous system (CNS). The third type of error occurs when a primary metabolic pathway is blocked, necessitating the use of an alternative pathway that produces a toxic metabolite. For example, in some cases of congenital adrenal insufficiency (AI), patients may become virilized because of the overproduction of androgenic hormones after blockages in the glucocorticoid and mineralocorticoid pathways. In the fourth subgroup, the cofactor essential for a metabolic reaction is deficient. For example, a deficiency in pyridoxine, the original vitamin B6, inactivates the biosynthesis of the inhibitory neurotransmitter γ-aminobutyric acid (GABA), causing intractable neonatal seizures.

Energy metabolism is a complicated process; nevertheless, it is important to understand how nutrients are converted into energy for use by the cell. Essentially all nutrients, carbohydrates, proteins, and fats are metabolized to acetyl coenzyme A (acetyl-CoA), which is then fed into the Krebs cycle to produce reduced, or hydrogenated, nicotinamide adenine dinucleotide (NAD). This product is transported to the mitochondria, where it is involved in oxidative phosphorylation to create adenosine triphosphate (ATP), the main energy currency of the cell. The schematic diagram in **Figure 1** demonstrates this process.

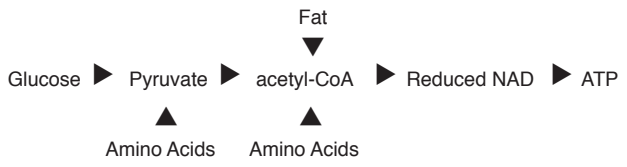
Carbohydrate metabolism is the primary and preferred source of energy for the body. Dietary sources of carbohydrates include simple sugars such as sucrose, lactose, and galactose as well as complex carbohydrates such as starches. The sugars must be broken down into glucose for the generation of energy; incomplete metabolism to glucose can lead to disorders such as hereditary fructose intolerance or galactosemia. Glycogen stores represent another form of complex carbohydrates and serve as the body's rapidly accessible energy reserve. Glycogen is produced when glucose is in abundance and is stored in the liver and muscles. Glycogen can be mobilized during times of stress or when glucose concentrations are low. An inability to break down glycogen to glucose leads to a variety of glycogen storage disorders, often called the mucopolysaccharidoses.

When glucose is in short supply or when glucose metabolism has failed, the body uses energy from fats and proteins. Dehydrogenases reduce suitable fatty acid chains by 2 carbon atoms, which are then converted to acetyl-CoA or ketones. Neonates are particularly vulnerable when glucose is unavailable because mechanisms that stimulate fat metabolism are immature or inefficient; as a result, neonates are slow to produce ketones. Some experts emphasize that significant ketosis in an infant is always abnormal and therefore strongly suggestive of a defect in glucose metabolism.[5]

Amino acid metabolism is somewhat more complex. It may be helpful to think of it as catabolism in order to differentiate this process from the use of amino acids as building blocks for proteins in the anabolic state. Amino acids are catabolized as either organic acids or amino groups. The organic acids are metabolized to energy-building blocks such as acetyl-CoA and ketones. The failure of this pathway results in toxic metabolites that produce the organic acidemias. The amino groups are detoxified through the urea cycle so that the byproducts can be excreted from the body. A faulty enzyme in this cycle also leads to the accumulation of toxic metabolites that characterizes the urea cycle disorders. A notable exception is PKU. As discussed earlier, this disease is characterized by an error in the metabolism of phenylalanine to tyrosine, resulting in a deficiency of tyrosine and the accumulation of phenylalanine. Because tyrosine is not present in adequate amounts in the diet, it must be derived from phenylalanine, whether the body is in an anabolic or catabolic state.

A final metabolic pathway of interest to the emergency clinician is the breakdown of cholesterol to steroids. Problems with steroid metabolism can lead to familiar disorders such as congenital adrenal hyperplasia (CAH), Cushing disease, and Addison disease. The absence or reduced functioning of enzymes during cholesterol metabolism can also lead to clinically significant deficiencies in the hormones cortisol and aldosterone as well as the sex hormones. When one hormone is deficient, excessive amounts of other hormone products can accumulate, often producing findings on physical examination that can aid in diagnosis. For example, female neonates with CAH may be virilized as a result of the overproduction of androgenic steroids.

Figure 1. Generalized Metabolic Pathway



Abbreviations: acetyl-CoA - Acetyl Coenzyme A; NAD - Nicotamide adenine dinucleotide; ATP - Adenosine Triphosphate

When Should The Emergency Clinician Consider A Metabolic Emergency?

Metabolic emergencies are heterogeneous in nature; accordingly, their presentations are diverse. Nevertheless, some common patterns emerge, and these are emphasized in the IEMs. Waber analyzed pediatric patients with IEMs and found that more than 90% had either neurologic features or vomiting on presentation.[6] It should be noted that many of the IEMs present in infants. As always, the emergency clinician should approach this population with great care and caution. As stated by Saudubray et al., "The neonate has a limited repertoire of responses to severe illness." [7] Therefore, a broad differential diagnosis is appropriate including sepsis/infection, nonaccidental trauma and asphyxia, intracranial injury, electrolyte abnormalities, and metabolic diseases. The signs and symptoms detailed in **Table 1 (page 4)** should alert the emergency clinician to the possibility of a metabolic disorder.

Symptoms And Signs Of Metabolic Disorders

The most distressing symptom of a metabolic disorder in pediatric patients is altered mental status, which has a variety of manifestations. For example, the symptoms of neuroglycopenia in both the acute and subacute phases have been well described.[8] The acute phase is characterized by autonomic nervous system activation through circulating catecholamines. Symptoms include tachycardia, tachypnea, vomiting, pallor, and diaphoresis. Early intervention with glucose supplementation can avoid the progression to the subacute phase, when poor feeding, lethargy, seizures, jitteriness, and exaggerated primitive reflexes can occur. Patients are also at risk for cardiac dysfunction and hypothermia.

Specific metabolic disorders to be considered in a patient with seizures are pyridoxine deficiency, maple syrup urine disease, nonketotic hyperglycinemia, and molybdenum cofactor deficiency. Prolonged neuroglycopenia can lead to the necrosis of neurons and permanent neurologic sequelae.

When neuroglycopenia occurs with hypoglycemia, the differential diagnosis is quite broad. A few should be emphasized in the ED, including AI, IEMs, infection, ingestions, and (in infants) hyperinsulinism. Mental status changes may occur during hyperglycemic episodes as well, although the observed changes may not be due directly to an excess of glucose. Rather, changes may occur as a result of the brain switching to ketone metabolism in the absence of intracellular glucose. Cushing triad and herniation syndromes may herald the onset of cerebral edema if the patient is untreated.

Encephalopathy is acute CNS dysfunction in the absence of localizing features. This profound mental status change can be acute or chronic depending on the nature of the underlying disorder. Encephalopathy results from the accumulation of toxic metabolites such as ammonia in the brain. Decreased sensorium may be accompanied by a relative hypertonicity rather than flaccidity.[7] Symptoms may progress to coma with seizures, cerebral edema, and death if untreated. Organic acidurias, urea cycle defects, and amino acid metabolism disorders must be considered in the differential diagnosis. Specific disorders include maple syrup urine disease, congenital lactic acidosis, and glutaric acidemia type I, which has also been associated with retinal and subdural hemorrhages.[5]

Ammonia levels should be measured in all infants with encephalopathy or with signs of hepatic dysfunction or protein intolerance. An elevated ammonia level should alert the practitioner to a urea cycle defect, although an organic acid defect and some benign entities should also be considered. One such entity is transient hyperammonemia of the newborn. This disease process may be limited to the neonatal intensive care unit (ICU), as affected infants are typically premature and large for gestational age and may require ventilatory support and other modalities for treatment. Two other diseases that may present at or shortly after birth are glutaric acidemia type II and pyruvate decarboxylase deficiency. Beyond the neonate's first day of life, a test for orotic acid in the urine may be helpful in the setting of hyperammonemia. An elevated orotic acid level is seen in ornithine transcarbamylase deficiency, one of the few X-linked urea cycle defects. A low level of orotic acid suggests carbamoyl phosphate synthetase deficiency.

Infants and toddlers who develop hyperammonemia in the setting of hypoglycemia without ketosis may have a fatty acid oxidation disorder. Broad differential diagnostic considerations are liver dysfunction, sepsis, herpes simplex virus infection, asphyxia, malignant disease, toxin exposure, *Proteus* infection, and intraperitoneal abscess.

Vomiting is sign of intolerance to a toxic metabolite, although the problem may be confused with more common diagnoses such as gastroenteritis and formula intolerance. Some authors include multiple formula changes as a red flag for a metabolic condition.[5] In fact, infants with recurrent vomiting and a negative workup for pyloric stenosis have occasionally been diagnosed with metabolic disorders. Harris and Perkin noted that vomiting can result when the accumulation of toxic metabolites affects the CNS or when toxic metabolites directly affect the pyloric sphincter, causing pylorospasm.[5]

Anion gap metabolic acidosis may be the presenting feature during a metabolic emergency. Patients may present with tachypnea that shows the body's attempt at respiratory compensation. This tachypnea may be accompanied by significant ketosis in infants. Patients with anion gap metabolic acidosis in the absence of a readily identifiable source may have an organic acidemia that produces acid byproducts detectable in the blood or urine. Methylmalonic, propionic, and isovaleric acidemias should be considered. Interestingly, both methylmalonic and propionic acidemias may present with choreoathetoid movements related to basal ganglia infarcts. Maple syrup urine disease is also a consideration. The differential diagnosis is summarized in **Table 2**.

Dysmorphism alone may be a sign of a metabolic disorder, although the dimorphic features are rarely the only abnormality. The phenotypes of these disorders will not be discussed at great length; however, **Table 3** presents a summary of dysmorphic diseases in which prominent features are linked to a metabolic disorder.

An unusual odor is commonly recognized as a

Table 1. Common Signs And Symptoms Of Metabolic Disorders

Suspect A Metabolic Disorder In The Following Situations:

- Symptoms emerge or worsen with a normally self-limited illness.
- There is recurrent vomiting despite multiple formula changes.
- Symptoms begin after a switch from human milk to formula.
- Symptoms occur abruptly after a new food is introduced to the diet.
- Symptoms begin after a long period of fasting.
- There is a family history of a metabolic disease.
- There is a history of unexplained infant death.
- There is a history of consanguinity.

Helpful Findings On Physical Examination:

- Pulmonary – hyperpnea, effortless tachypnea without lung disease
- Cardiac – cardiomyopathy, dysrhythmias, conduction defects
- Hepatic – hepatomegaly, liver failure, cholestasis
- Hepatic, splenic – organomegaly
- Neurologic – abnormal tone, altered mental status
- Hematologic – neutropenia, thrombocytopenia
- General – cataracts, abnormal hair, unusual rashes

sign of a metabolic disorder, more so perhaps because of questions on board examinations than due to the *piss prophets* of medieval times. Those practitioners recognized the distinctly sweet-smelling urine of patients with maple syrup urine disease. Another distinguishable odor is musty or sweaty foot, which has been recognized as a feature of both isovaleric acidemia and glutaric acidemia type II.

How Is The Suspicion Of A Metabolic Disorder Confirmed?

The evaluation of the patient with a suspected metabolic emergency can begin with point-of-care testing at the bedside. **(See Table 4.)** Handheld equipment such as a blood gas analyzer and a glucometer can help to identify a correctable problem such as hypoglycemia at the initiation of the diagnostic workup. Analysis of the urine for ketones and examination of the stool for reducing substances provides rapid, useful information. Results from secondary tests may not be immediately available but are still important because information from definitive tests (eg, urine organic acids, acylcarnitine profile) may not be available for days. **Table 5** lists suggested laboratory tests for patients with a suspected but undifferentiated metabolic disorder. Primary tests refer to initial screening measurements taken when signs and symptoms suggest a metabolic problem. Secondary tests are studies that may be ordered to further clarify management options when primary tests results are abnormal. Tertiary tests define the precise metabolic derangement.

When caring for the critically ill neonate, the emergency clinician may find that results from the newborn screening tests are helpful. Individual tests included in the screen vary from state to state, but tests for hypothyroidism and PKU are available across the United States. Results from newborn screening tests may confirm a suspected diagnosis and increase the therapeutic options available in the ED. Guthrie cards, which are used to collect blood from newborns via a heel stick, may also provide a snapshot of the blood at the time of presentation and can be saved for analysis at a later date. The absorbent cards are often stocked in newborn nurseries or primary pediatric clinics. The comprehensive newborn screen, which uses tandem mass spectroscopy to diagnose as many as 40 disorders, may also be of use, especially in states where the standard newborn panel is narrow.

When an infant in the ED has a suspected metabolic disease, radiographs are often obtained to assess the need for intervention or rule out other diagnoses. No specific radiologic studies are needed on an emergent basis to help confirm a diagnosis; however, subtle findings consistent with metabolic disease may be useful in an emergency. Glutaric acidemia type II is associated with subdural and retinal hemorrhages that may be identified with computed

Table 2. Differential Diagnosis For Anion Gap Metabolic Acidosis[9]

- Diarrheal dehydration
- Diabetic ketoacidosis
- Renal failure
- Inborn error of metabolism
- Poisoning or toxic ingestion
- Congenital/idiopathic metabolic acidosis including lactic acidemia

Table 3. Dysmorphic Syndromes Associated With Metabolic Disorders

- Mucolipidosis II – lysosomal disorders
- Pyruvate dehydrogenase deficiency – disorders of energy production
- Rhizomelic chondroplasia punctata – peroxisomal disorders
- Sialic acid storage disorder – lysosomal disorders
- Smith-Lemli-Opitz syndrome – cholesterol biosynthesis defects
- Zellweger syndrome – peroxisomal disorders

Table 4. Clinical Patterns Suggestive Of A Metabolic Emergency

- Hypovolemia, hyponatremia, hyperkalemia: Consider adrenal insufficiency
- Metabolic acidosis, hyperammonemia, ketotic hypoglycemia: Consider an organic acid defect
- Encephalopathy, respiratory alkalosis, hyperammonemia: Consider a urea cycle disorder

Table 5. Diagnostic Tests For Patients With A Suspected Metabolic Disorder

Primary Tests
- Capillary blood glucose
- Arterial or venous blood gas
- Electrolytes
- Serum urea nitrogen and creatinine
- Urine dipstick

Secondary Tests
- General – complete blood cell count with differential count
- Hypoglycemia – insulin, cortisol, corticotropin, β-hydroxybutryate
- Encephalopathy – ammonia, aspartate aminotransferase, alanine aminotransferase, bilirubin
- Suspected galactosemia – urine-reducing substances

Tertiary Tests
- Quantitative plasma organic acids
- Quantitative urine organic acids
- Plasma acylcarnitine
- Tandem mass spectroscopy for disorders of fatty acid oxidation
- Amino acids in the blood, urine, and cerebrospinal fluid
- Orotic acid in the urine
- Comprehensive newborn screen with tandem mass spectroscopy

tomography (CT). Magnetic resonance imaging (MRI) may demonstrate basal ganglia infarcts, a component of both methylmalonic and propionic acidemias that may lead to the clinical presentation of choreoathetoid movements, as noted previously. Bedside cranial ultrasound is an option for imaging a child with suspected metabolic disease when an experienced ultrasonographer is available for the study and its interpretation.[11]

When a child has a high probability of metabolic disease, certain fluid and tissue samples may provide the family with helpful information. Harris recommends that urine and plasma be obtained and kept in cold storage and that a sterile skin sample be stored at 37°C (98.6°F) in tissue culture media or sterile saline.[5] These samples may not help with initial diagnosis in the event of death, but they may provide more information than tissues that have degraded prior to autopsy. The results could also help the family with future genetic counseling and childbearing decisions.

What Emergency Therapies Should Be Considered For Suspected And Known Inborn Errors Of Metabolism?

Suspected Inborn Errors Of Metabolism

When an infant has a suspected IEM, a few therapeutic options available in the ED can reduce the risk of adverse sequelae. Information from the primary laboratory screen is paramount so that care may proceed in a sequential fashion. The provision of basic and advanced life support is the foundation of this care and includes the immediate correction of any hypoglycemia. Although administration of an ampule of dextrose 25% or dextrose 50% may be appropriate when no other options are available, low osmolarity solutions are preferred.[12] Glucose will not only correct hypoglycemia, but it will also help to move the patient from a catabolic to an anabolic metabolic state. Burton advocates the use of lipids to supplement caloric needs in infants provided there is no derangement in fatty acid metabolism.[13] Patients with acidosis benefit from alkali therapy, but caution is necessary to ensure that the patient can tolerate a potential decrease in respiratory drive. Alkali therapy remains a stopgap measure, and in some cases, removal of the offending anion can be achieved with hemodialysis.

Hemodialysis is also the preferred method for the removal of ammonia in patients with profound hyperammonemia or in critically ill infants with more modest ammonia levels.[28] This process is preferred over peritoneal dialysis, exchange transfusion, and hemofiltration. However, there are pharmaceutical options; drugs and dosages are provided in **Table 6**.

Administration of 3 cofactors should be considered, but only in very specific circumstances. L-carnitine can be used to treat presumed fatty acid oxidation disorders and allow the mitochondria to clear toxic acyl-CoA intermediates.[7] The L-carnitine dosage should begin at 100 to 200 mg/kg per day IV under the direction of a metabolic specialist. Pyridoxine can be given empirically to an infant with recalcitrant seizures when there is a presumptive diagnosis of pyridoxine deficiency (1 mg intramuscularly [IM]). Neonates with this disorder develop seizures shortly after birth and may not respond to typical antiepileptic drugs such as benzodiazepines or phenobarbital. A single IM injection of pyridoxine may be therapeutic and diagnostic with concurrent electroencephalographic (EEG) monitoring. A final adjunct is biotin, which can be used to treat some forms of organic acid defects at a dose of 10 mg via nasogastric tube.

Known Inborn Errors Of Metabolism

Children with a known metabolic disorder still present a significant challenge to the emergency clinician. Family members or other caregivers may have difficulty communicating the name or type of disorder, and the child may not appear to be gravely ill upon initial evaluation. Fortunately, anticipatory guidance from the child's pediatrician and metabolic specialist can help when emergency care is needed. Caregivers often have a letter from the treating physician that clearly delineates the child's diagnosis and a plan that serves to guide initial management and disposition. Medical alert bracelets and emergency care plans can also provide medical personnel with important information about a patient's underlying condition. The emergency care form advocated by the AAP and the American College of Emergency Physicians (ACEP) is available online at http://www.aap.org/advocacy/blankform.pdf.

Table 6. Drug Therapy For Hyperammonemia[4]

Drug	Dosage	Indication
Sodium phenylacetate	250 mg/kg IV bolus,* followed by a continuous infusion of 250 mg/kg per day	
Sodium benzoate	250 mg/kg IV bolus,* followed by a continuous infusion of 250 mg/kg per day	
Arginine	200-600 mg/kg IV bolus,* followed by 200-600 mg/kg per day	Indication: urea cycle defects when no acidosis is present

* Bolus doses are given over 120 minutes.

Clinical Pathway For Emergency Care Of Patients With A Metabolic Disorder

Perform ABCDEs

A – Airway - Evaluate and protect airway as needed.

B – Breathing - Ensure adequate ventilation

- Non-invasive ventilatory support may be considered where appropriate.
- Aggressive hyperventilation for cerebral edema should be avoided.

C – Circulation - Volume expansion should be provided when there is evidence of dehydration or volume depletion.

D – Disability - Bedside blood glucose testing:

- If below 60 mg/dL, obtain critical sample, IV access and provide glucose orally or via IV
- Low osmolarity glucose solutions (D5W, D10W) are preferred where available
- Critical sample: serum glucose, insulin, cortisol, and growth hormone

E – Exposure - Evaluate for exposure to infectious organisms, drugs, toxic substances, or new foods

Consider Additional Laboratory Testing

Primary: (most can be obtained with point of care testing devices)

- Arterial or venous blood gas
- Electrolytes
- Serum urea nitrogen and creatinine
- Urine dipstick

Secondary:

- General – complete blood cell count with differential count
- Hypoglycemia – insulin, cortisol, corticotropin, β-hydroxybutryate
- Encephalopathy – ammonia, aspartate aminotransferase, alanine aminotransferase, bilirubin
- Suspected galactosemia – urine-reducing substances

Tertiary:

- Quantitative plasma organic acids
- Quantitative urine organic acids
- Plasma acylcarnitine
- Tandem mass spectroscopy for disorders of fatty acid oxidation
- Amino acids in the blood, urine, and cerebrospinal fluid
- Orotic acid in the urine
- Comprehensive newborn screen with tandem mass spectroscopy

Treatment

If the child has a diagnosed metabolic disorder, follow instructions provided by their Metabolic specialist.

Hydration – D10 1/2 NS at 1.5 times maintenance until needs for fluid, glucose, and electrolyte replacement have been determined.

Glucose

Medications (as directed by Metabolic specialist, except as noted)

- Fatty acid oxidation disorders – L-carnitine
- Hyperammonenia – sodium phenylacetate, sodium benzoate, arginine
- Neonatal seizures – pyridoxine (may be given empirically with concurrent EEG monitoring as available)
- Organic acid defects – biotin

Consider Consultations Or Referrals To:

- Critical Care
- Genetics/Metabolism
- Nephrology– as indicated for renal replacement therapy for hyperammonemia

In pediatric patients with a known metabolic condition who present with an acute illness, the administration of dextrose and fluids is a priority. Proper management should address acute symptoms such as hypoglycemia while shifting the body away from protein and fat catabolism, which may exacerbate the underlying condition. A good rule of thumb is to initiate IV fluids with dextrose 10% in 1/2 normal saline at 1.5 times maintenance until laboratory results are available.

A few pharmaceutical agents are available for the treatment of patients who have specific disease processes. Often these patients will present with a care plan, but it is useful to review their indications and pharmacology to enhance one's knowledge about metabolic disorders as a whole. Drugs used in the ED for management of patients with IEMs are L-carnitine, L-arginine, and sodium benzoate.

As addressed previously, a fault in amino acid metabolism can result in an organic acid defect, a urea cycle defect, or PKU. The family of organic acid defects results from errors in the metabolism of amino acids while the body is in a catabolic state. When glucose levels are insufficient, the body begins using amino acids as fuel rather than as building blocks for proteins. The amino acids are initially broken down into their component parts, an amino group and an organic acid. The organic acid defect occurs when an enzymatic error allows the accumulation of a toxic metabolite. Common examples of organic acid defects are type I glutaric, methylmalonic, and propionic acidemias. The symptoms of organic acid defects are mixed, reflecting both the toxic and acidic effects of the metabolite. Patients can have vomiting and symptoms of encephalopathy with metabolic acidosis and with ketotic hypoglycemia. Specific therapy for isovaleric acidemia is glycine that will complex with isovaleric acid into a water-soluble compound amenable to renal excretion.[7] Also, multiple carboxylase deficiency may be responsive to the cofactor biotin.[7]

Urea cycle defects (eg, carbamoyl phosphate synthetase deficiency, ornithine transcarbamylase deficiency) are the result of errors during the breakdown of amino acids to urea. The defects typically lead to the accumulation of ammonia and symptoms of protein intolerance and encephalopathy. L-arginine can be used in conjunction with protein restriction and glucose delivery to treat the symptoms of urea cycle disorders.

Amino acid disorders such as PKU and maple syrup urine disease are grouped together because enzymatic defects lead to the accumulation of toxic intermediates. However, the disorders have very different clinical presentations depending on the nature of the metabolites that accumulate. Protein restriction is the cornerstone of therapy for long-term management on an outpatient basis, although this is not possible in all conditions, namely nonketotic hyperglycinemia. Unfortunately, there are no specific therapies available for the aminoacidopathies in the ED.

Disorders of carbohydrate metabolism involve either sugar intolerance or a glycogen storage disease. Sugar intolerance occurs with an error in the breakdown of sugars into glucose. For example, lactose is a disaccharide that is metabolized to glucose and galactose. When the body is unable to metabolize galactose because of a deficiency in the enzyme galactose-1-phosphate uridyl transferase, galactosemia results. Galactosemia is characterized by vomiting, diarrhea, poor weight gain, and cataracts. Galactose-1-phosphate accumulation may lead to hemolysis as well as jaundice, liver dysfunction, and CNS toxicity. Galactosemia is often associated with *Escherichia coli* sepsis in neonates. The condition is managed by eliminating galactose and its precursors from the diet. Other examples of sugar intolerance are galactokinase deficiency and hereditary fructose intolerance.

Glycogen storage diseases result from the inability to break down glycogen, which is the stored form of glucose. Glycogen typically builds up in the liver, causing hepatomegaly. Hypoglycemia results when glucose is not mobilized from the glycogen store. Patients may develop lactic acidosis, which reflects the lack of glucose available to the cells. Patients with glycogen storage disease type II, also known as Pompe disease or maltase deficiency, may not have hepatomegaly. Rather, glycogen accumulates in the cardiac tissues, causing cardiomegaly that leads to congestive heart failure. These patients may also have macroglossia and hypotonia, resulting in upper airway obstruction. Great caution should be used when these patients require an artificial airway because intubation may be very difficult due to redundant and stiff pharyngeal tissues.

Fatty acid oxidation defects lead to nonketotic hypoglycemia during times of fasting or acute illness, when glucose intake cannot be maintained. Once glucose becomes unavailable, the body tries to mobilize the energy stored in fats through oxidation. When there is a defect in fatty acid oxidation, the body cannot generate ketones for conversion into energy. Some patients may present with hyperammonemia, elevated liver transaminases, and metabolic acidosis, a picture that resembles Reye syndrome. Others may have an acute life-threatening event or arrhythmias due to cardiomegaly. Diagnostic testing includes urine organic acids and serum carnitine levels and a plasma acylcarnitine profile. Patients may have a secondary carnitine deficiency that can be treated with carnitine supplementation. Patients should avoid fasting and observe a diet that allows for adequate glucose intake and reduced dietary fats.

Other Than IEMs, What Metabolic Emergencies Can Present To The Pediatric Emergency Department?

Inborn errors of metabolism are not the only sources of metabolic emergencies. Adrenal insufficiency, diabetes mellitus, and electrolyte disorders can also cause life-threatening illnesses. As with IEMs, these disease processes should be considered early in the course of a patient's care because prompt therapy will reduce morbidity and mortality.

Adrenal Insufficiency

Adrenal insufficiency refers to a spectrum of disorders that occur when adrenal production of glucocorticoid and/or mineralocorticoid hormones is compromised. AI is classified as either primary or secondary. Congenital adrenal hyperplasia (CAH) is the most recognized form of primary AI in children, perhaps because it is a component of many newborn screening programs. Most commonly, it is associated with the absence of 21-hydroxylase, an enzyme in the cholesterol metabolism cascade, and results in virilization of females, salt-wasting crisis in newborns, and hyperpigmentation. Other congenital forms of primary AI are Addison disease and metabolic disorders such as adrenoleukodystrophy and mitochondrial disorders. Acquired primary AI can occur with adrenal destruction (eg, autoimmune disease, infection), infiltration (eg, infection, neoplasm), or infarction/hemorrhage (eg, trauma, Waterhouse-Friderichsen syndrome) or as a drug effect.[14]

Secondary AI has many etiologies, although the most common is the discontinuation of corticosteroids after a long treatment course. Acquired secondary AI can also occur after damage to the hypothalamic axis as a result of direct tissue damage (eg, trauma, surgery, radiation), inflammatory processes, or tumors and infiltrative processes. Congenital secondary AI occurs in disorders of the hypothalamic-pituitary axis such as septo-optic dysplasia.

Adrenal insufficiency can present with a variety of symptoms, although dehydration, hypotension, hypoglycemia, and altered mental status are most common. Patients with primary AI may have nonspecific symptoms such as fatigue, nausea, vomiting, weight loss, and abdominal pain that mimic other conditions such as chronic regional abdominal pain or neuropsychiatric disorders including depression. Hyperpigmentation and salt cravings may also be features of primary AI. The patient's hands, areolae, genitalia, and any scars or moles should be examined for hyperpigmentation; comparison with family members is helpful to determine if the patient's hyperpigmentation is familial. Except when caused by the cessation of corticosteroid medications, secondary AI is usually accompanied by other pituitary disorders.

The triad of hyponatremia, hyperkalemia, and hypoglycemia should alert the emergency clinician to the possibility of AI; this constellation of findings is more likely due to primary than secondary etiologies. In addition to electrolyte and glucose levels, adrenocorticotropic hormone (ACTH) and cortisol values should be obtained. With infants in whom CAH is likely, it is prudent to test for 17-hydroxyprogesterone, dehydroepiandrosterone, and testosterone. An ACTH stimulation test, detailed in **Table 7**, may be helpful to confirm the diagnosis, but this should only be performed in conjunction with an endocrinologist or intensivist.[15] One exception to this rule is the patient being resuscitated because of presumed septic shock. When patients do not improve after 60 cc/kg of crystalloid resuscitation, a diagnosis of AI should be entertained.[16] Hydrocortisone may be given empirically, but performing an ACTH stimulation test may help to determine a therapeutic endpoint once steroids have been supplemented. Some experts prefer the stress dosing of dexamethasone in normotensive patients because it does not interfere with the ACTH stimulation test.[8]

Ongoing debate surrounds the use of etomidate as an induction agent prior to intubation of the patient with severe sepsis or shock. A single dose of etomidate has been associated with AI in this setting, although the drug may not be the only contributing factor.[18] Strategies to combat this effect include the use of other induction agents such as ketamine or avoidance of induction or sedative agents. Testing for AI with the ACTH stimulation test in this patient population is a rational clinical decision, especially if stress dose hydrocortisone is used.

Table 7. Stress Dose Steroids And ACTH Stimulation Test For Adrenal Insufficiency[16]

Stress Dose Steroids

- Hydrocortisone: 25-75 mg/m2 IV or IM (approximately 2 mg/kg, to a maximum of 100 mg) then 50-75 mg/m2 IV divided into 4 doses daily
- Alternatives to hydrocortisone (with significantly less mineralocorticoid effect)
  - Methylprednisolone: 10-15 mg/m^2 IV
  - Dexamethasone: 1.5-2.0 mg/m^2 IV
- Fludrocortisone: 0.1-0.2 mg orally daily

ACTH Stimulation Test

- Draw cortisol level
- Administer ACTH
  - 2 years and younger: 15 mcgm/kg or 125 mcmg IV
  - Older than 2 years: 250 mcgm IV
  - Alternative low-dose stimulation test: 1 mcgm IV[17]
- Redraw cortisol level. Peak cortisol values less than 18 mcgm/dL indicates adrenal insufficiency.

Abbreviations: ACTH, adrenocorticotropic hormone; IM, intramuscularly; IV, intravenously.

Hyperglycemia And Diabetes Mellitus

Hyperglycemia may be the most common laboratory abnormality suggestive of a metabolic emergency. Although isolated hyperglycemia may be seen with stress, in the presence of ketonuria and acidosis, the disorder may progress to diabetic ketoacidosis (DKA) and death if left untreated.

Hyperglycemic stress response is a somewhat nebulous topic. A patient with an elevated blood glucose level after trauma is clearly different from a patient with sepsis whose blood glucose level rises beyond the normal range in the ICU. The former patient may be postprandial but could also have previously unrecognized insulin insensitivity. Screening tests such as a urinalysis and serum β-hydroxybutyrate and hemoglobin A_{1c} measurements may help to clarify whether the hyperglycemia is an episodic or long-term problem. The latter patient has an increased risk of morbidity because of hyperglycemia. Some efforts have been made to address this situation with insulin supplementation, either subcutaneously or IV.[19] Normoglycemia can be achieved, but at what cost? Mechanisms for the delivery of insulin that include frequent blood glucose monitoring to detect hypoglycemic complications have proven cumbersome, even in the relatively controlled environment of the ICU.[20] Intensive insulin therapy should be considered but may not be a priority. Discussion of patient management with the accepting intensive care physician may be helpful when intensive insulin therapy is being considered.

Presentation of type 1 diabetes mellitus can vary between patients who are diagnosed with diabetes mellitus by screening and symptom history and those who arrive at the ED with life-threatening cerebral edema from DKA. Interestingly, other than research identifying the risk factors for cerebral edema, little has been published about the acute complications of type 1 diabetes mellitus that affect the emergency clinician. The current recommendations for the emergent care of the patient with DKA are presented in **Table 8**. The Lawson Wilkins Pediatric Endocrine Society concedes that few of the recommendations are derived from high-quality research protocols. Instead, many are constructed from smaller studies and expert opinion.

Type 2 diabetes mellitus is a syndrome of insulin resistance that was previously thought to be a problem only in adults. The recent epidemic of obesity in children and adolescents has been accompanied by an increase in the incidence of type 2 diabetes in this group, more so in nonwhite populations with high adult rates of type 2 diabetes mellitus. According to the Centers for Disease Control and Prevention, 8% to 46% of cases of new-onset diabetes mellitus referred to pediatric centers are type 2 disease; 15- to 19-year-old Pima Indians from Arizona have the highest incidence at 50.9 per 1000 (the incidence is 4.5 per 1000 for all American Indian populations).[22] For comparison, the national incidence of type 1 diabetes in people 19 years and younger is 1.7 per 1000.[22] Currently, the emergency clinician has a limited role in the care of these patients, although they may present with a clinical picture consistent with DKA.

Clinicians should also be aware of the hyperosmolar hyperglycemic state (HHS), even though it is

Table 8. Guidelines For The Diagnosis And Treatment Of Diabetic Ketoacidosis [21]

Water And Salt Replacement

- Water and salt deficits must be replaced, taking into account fluids given prior to assessment (eg, a bolus given during emergency medical services transport).
- Isotonic crystalloid solutions (ie, 0.9% saline or balanced salt solutions) are preferred.
- Volume expansion with 10-20 mL/kg of an isotonic solution should be given over 1 to 2 hours and can be repeated as necessary.
- Subsequent fluid management should be accomplished with a solution containing a tonicity of ≥ 0.45% saline and calculated to replace fluids over at least 48 hours.
- Ongoing clinical assessments and calculation of effective osmolality should guide fluid and electrolyte therapy.
- Fluid infusion should not exceed 1.5 to 2 times maintenance requirements. Urinary losses should not be added to the calculation of replacement fluids.

Insulin/Glucose Therapy

- Insulin deficiency should be corrected with insulin 0.1 U/kg per hour IV.
- Insulin infusion should continue until the following values are reached:
  - Resolution of ketoacidosis (pH > 7.3)
  - Bicarbonate level > 5 mmol/L
  - And/or closure of the anion gap
- Glucose infusion should be started when blood glucose levels fall to ~14-17 mmol/L (250-300 mg/dL).
- Poor response to therapy may be a result of the following conditions:
  - Hypovolemia and hypoperfusion
  - Errors in insulin dosage or delivery
  - Occult infection
- Bolus doses of IV insulin are not necessary, but may be an option if insulin therapy is delayed. Intramuscular or subcutaneous routes may be used if IV access cannot be obtained.

Potassium, Phosphate, And Bicarbonate

- Potassium replacement should be based on serum potassium measurements and the patient's urine output. Replacement fluids should include 40 mmol/L potassium.
- There is no evidence that phosphate replacement has clinical benefit in the absence of hypophosphatemia; furthermore, phosphate supplementation may induce hypocalcemia.
  - Potassium phosphate salts may be used as an alternative to or combined with potassium chloride and potassium acetate.
- Data show that treatment with bicarbonate confers no clinical benefit. Fluid and insulin replacement without bicarbonate administration corrects ketoacidosis.
  - Bicarbonate administration should be reserved for situations when there is "profound" acidosis and when it is "likely to affect the action of adrenaline/epinephrine during resuscitation."

exceedingly rare in children and adolescents. Patients with HHS present with coma, hyperglycemia, and hyperosmolarity in the absence of acidosis or ketosis. This condition is poorly understood but is estimated to have a mortality rate of up to 15%. [23]Therapy with IV rehydration, continuous insulin infusion, and electrolyte replacement is similar to that recommended for DKA. Patients require frequent monitoring until their osmolality level returns to the reference range; mental status should improve as the serum osmolality value falls to 315 mOsm/kg.[24]

Hypoglycemia

The threshold blood glucose level for the diagnosis of hypoglycemia is subject to debate. The current trend is to increase the lower limits of acceptable blood glucose levels, reflecting data that show poor intellectual function and abnormal neuroimaging studies in neonatal intensive care patients who were not treated for hypoglycemia at levels previously thought to be safe.[24] In the same text, Marcus recommends that blood glucose levels less than 45 mg/dL should not be tolerated in an infant, regardless of whether the patient is symptomatic.[24] The Pediatric Advanced Life Support algorithm recommends treatment of hypoglycemia below the threshold of 60 mg/dL in children beyond infancy.[16] The clinical presentation of hypoglycemia is described in the previous discussion of IEMs.

The emergency clinician faced with hypoglycemia in a child is challenged to balance the need to deliver timely therapy with the need to obtain the appropriate diagnostic tests. Rather than considering the broad differential diagnoses of hypoglycemia, it is prudent to "shoot first and ask questions later" by obtaining the critical sample (ie, insulin, cortisol, and growth hormone levels) before glucose is delivered; serum and urine samples for ketones should also be obtained.

The differential diagnoses for hypoglycemia, which can be reduced to ketotic and nonketotic processes, are presented in **Table 9**. Glucagon delivery will stimulate the patient to metabolize glycogen to glucose and can help with diagnosis. Patients who are responsive to glucagon likely have a nonketotic form of hypoglycemia. Patients in the ketotic group are likely to have depleted or unavailable glycogen stores.

Bedside testing of glucose levels should be confirmed by a glucose level performed in the laboratory. Further testing should be driven by information obtained from the patient history and physical examination. Diagnostic tests should be selected from the secondary and tertiary groups in **Table 5 (page 5)**.

The primary treatment for hypoglycemia is glucose supplementation at a dosage of 0.5 to 1.0 g/kg IV. Dextrose 10% in water is preferred in neonates and infants to protect their delicate vasculature, but dextrose 25% can be used for children in older age groups. Oral glucose should be considered for patients with hypoglycemia who are capable of protecting their airway. Patients with continued glucose requirements should be treated at an IV rate of 6 to 10 mg/kg per minute. If a patient is unresponsive to glucose, administration of glucagon may help to mobilize glycogen stores. Patients with suspected hyperinsulinism may benefit from therapy with diazoxide (10 mg/kg per day divided into 3 oral doses) or octreotide (2-10 mcg/kg divided into 2 doses given IV or subcutaneously).

Hypernatremia

Increased serum sodium levels result in increased deep tendon reflexes, tetany or rigidity, tremulousness, and a high-pitched cry. Progressive hypernatremia can lead to seizures and altered mental status. Intracranial hemorrhage and venous sinus thrombosis due to hypernatremia have been reported. Etiologies are presented in **Table 10**, but the

Ten Risk Management Pitfalls For Metabolic Emergencies

1. Waiting for laboratory test results before treating hypoglycemia.
2. Waiting for laboratory test results before treating suspected or symptomatic AI with stress dose steroids.
3. Not ordering the appropriate tests (ie, the critical sample in a patient with hypoglycemia) while the patient is symptomatic.
4. Not consulting a metabolic specialist when planning the care of a severely ill child with a suspected metabolic disease.
5. Not involving a metabolic specialist in disposition decisions.
6. Failing to recognize that ketonuria is abnormal in the early neonatal period.
7. Obtaining diagnostic imaging prior to treating symptomatic cerebral edema in a patient with DKA.
8. Failing to provide pyridoxine to a neonate with intractable seizures.
9. Providing only medical therapy for a critically ill infant with hyperammonemia when dialysis is available.
10. Assuming that hyperkalemia results from a hemolyzed blood sample.

most common cause of hypernatremia is the loss of free water from diarrhea. The suspicion of hypernatremia can be confirmed by measuring electrolyte levels. Serum urea nitrogen, creatinine, liver function, and glucose levels should be measured in addition to a urinalysis.

Management of hypernatremia depends on the underlying cause. Volume depletion should be addressed with normal saline or another isotonic solution. Thereafter, careful free water replacement over 48 to 72 hours is the mainstay of therapy. Free water (4 cc/kg) should be given for every milliequivalent of sodium over 145 mEq/L. Free water should be given orally whenever possible or slowly and cautiously as a component of IV hypotonic saline solution. Patients with a history of diabetes insipidus should also be prescribed desmopressin when they present with hypernatremia.

Hyponatremia

After febrile seizures, hyponatremia is the second most common cause of first-time seizures in children younger than 2 years.[25] Acute gastrointestinal losses and improper mixing of formula leading to water intoxication are the most common causes of hyponatremia. Early symptoms of anorexia, agitation, disorientation, and apathy often go unrecognized until more serious symptoms appear. Late symptoms include lethargy, decreased reflexes, vomiting, decreased respiratory drive, and seizures. If the common diagnoses mentioned above do not seem likely from the given history, serious conditions such as syndrome of inappropriate antidiuretic hormone and CAH should be considered. Active seizures should be treated with 3% normal saline, with a target sodium level of 125 mEq/L. Dosage can be estimated at 5 to 12 mL/kg or calculated using the following formula, which estimates the extracellular fluid compartment at 60%:

10 mEq/L × body weight (kg) × 0.6 L/kg = volume of 3% normal saline to be delivered

A quick estimation may also be achieved by subtracting the measured sodium level from 125 mEq/L and multiplying the result by 1 mL/kg of 3% normal saline. For example, a seizing child who weighs 20 kg and has a serum sodium level of 117 mEq/L requires 160 mL of 3% normal saline.

Patients with water intoxication should be managed with fluid restriction. In contrast, hyponatremic dehydration should be treated with fluid resuscitation. Correction of hyponatremia should be slow (conducted over 24 hours) as long as the patient does not have life-threatening symptoms such as seizures. Correction at 0.5 mEq/L per hour should be slow enough to prevent central pontine myelinolysis.

Hypocalcemia, Hypomagnesemia

Hypocalcemia and hypomagnesemia should be considered together as they have similar presentations: jitteriness, seizures, irritability, lethargy, poor feeding, or vomiting. Symptomatic early-onset hypocalcemia is a risk for infants of mothers with diabetes mellitus, premature infants, and infants who have suffered an anoxic/ischemic event. A cow's milk diet, rich in phosphate, can lead to delayed neonatal hypocalcemia. Rickets may also be seen, especially in premature infants. However, rickets should also be considered in later onset childhood hypocalcemia, especially in breastfed African American infants. DiGeorge syndrome should be considered in a child with abnormal results on cardiac examination and the characteristic dysmorphic facies. Hypocalcemia may also occur as a result of hypercalciuria, which leads to nephrolithiasis; a family history of this disorder may help with the diagnosis. Hypomagnesemia occurs in infants of mothers with diabetes mellitus and in patients with increased losses

Cost- And Time-Effective Strategies

1. Institutions that treat high volumes of children with metabolic disorders should consider developing a database of these patients that contains specific treatment information.
2. Emergency clinicians should partner with parents, teachers, primary care providers, metabolic specialists, and emergency medical systems personnel to develop a unified plan of care for patients with known metabolic disorders. The form developed by the AAP and the ACEP for children with special health care needs may serve as a useful template **(see page 8)**.
3. When contacting a state laboratory for newborn screening results, it is useful to have the patient's date of birth, the mother's full name (including maiden name when applicable), the name of the primary care physician, and the name of the hospital where the child was born.
4. When there is doubt about the appropriate diagnostic tests, 3 to 5 mL of blood collected in a red top tube and blood spots collected on a Guthrie card can be set aside until diagnostic decision making is complete.
5. Institutions with large volumes of patients with diabetes mellitus may benefit from protocol-driven management of DKA, especially when it is designed in conjunction with consulting endocrinologists.

from the gastrointestinal and renal tracts.

Symptoms and signs should prompt a laboratory workup that includes the standard electrolyte values as well as ionized calcium, magnesium, and phosphorous levels. A handheld blood gas analyzer is preferred for obtaining the ionized calcium level in a rapid fashion. Secondary tests include parathyroid hormone and vitamin D metabolite measurements, as well as urine levels of calcium, phosphate, and creatinine. An electrocardiogram (ECG) should also be obtained, with ongoing cardiac monitoring available during calcium replacement. The ECG may reveal QT prolongation, and dysrhythmias have been reported. Calcium gluconate is the replacement therapy of choice for hypocalcemia because it is gentler than calcium chloride on the veins; 200 to 500 mg of calcium gluconate may be given either as an infusion or in 4 divided doses. Hypomagnesemia can be treated with IV replacement at 25 to 50 mg/kg.

Table 9. Differential Diagnosis For Hypoglycemia

Ketotic Processes

- Fasting
- Malabsorption, gastroenteritis
- Galactosemia
- Hereditary fructose intolerance
- Glycogen storage disease type I
- Idiopathic ketotic hypoglycemia

Nonketotic Processes

- Hyperinsulinism
- Infants of diabetic mothers
- Congenital panhypopituitarism
- Adrenal insufficiency
- Fatty acid oxidation defects
- Beckwith-Wiedemann syndrome

Other Diagnoses

- Sepsis
- Ingestion, poisoning
- Liver failure

Table 10. Etiologies Of Hypernatremia

Hypovolemic Causes

- Vomiting and/or diarrhea
- Inappropriately concentrated formula
- Insensible losses
- Diuretic use
- Diabetes insipidus

Euvolemic Causes

- Iatrogenic diseases
- Inappropriately concentrated formula

Hypervolemic Cause

- Hyperaldosteronism

Hypercalcemia

Hypercalcemia deserves mention because of the rare but severe disorder known as neonatal hyperparathyroidism, an autosomal recessive condition resulting in life-threatening calcium levels. Signs of elevated calcium levels include dehydration due to calciuria, failure to thrive, constipation, hypotonicity, weakness, and irritability. Patients can be hypertensive and are at risk for nephrocalcinosis. Studies should include measurements of electrolytes along with ionized calcium, serum urea nitrogen, creatinine, and parathyroid hormone levels. An ECG will show a shortened QT interval and perhaps a U wave; severe hypercalcemia increases the PR and QRS intervals. An elevated parathyroid hormone level despite hypercalcemia necessitates surgical consultation for parathyroidectomy, although some patients may respond to bisphosphonates.

Hyperkalemia

Hyperkalemia is another medical emergency that can cause weakness and paralysis and, more important, cardiac conduction disturbances including arrhythmias and cardiac arrest. Any patient with hyperkalemia should be placed on a cardiac monitor and the tracing for peaked T waves evaluated. More severe hyperkalemia may cause widening of the QRS segment, an increasing PR interval, a sine wave rhythm, and eventually cardiac arrest. In the absence of peaked T waves, hyperkalemia may be considered factitious as a result of hemolysis of the original sample. Hyperkalemia can result from CAH, oliguric renal failure, or extensive tissue damage due to burns or crush injuries. In addition to the ECG, electrolytes (including urine electrolyte), serum urea nitrogen, and creatinine should be measured and a urinalysis obtained.

Therapy should be rapidly initiated with calcium gluconate to provide cardioprotection. Sodium bicarbonate 1 mEq/kg IV will force potassium into the intracellular space and may be used in conjunction with insulin and glucose at 1 U of insulin per 5 to 6 g of carbohydrate. Polystyrene resin may also be used to help eliminate potassium through the gut; 1 g/kg per dose may be given orally or rectally. Nebulized albuterol can be used to drive potassium into the intracellular compartment. Patients with a history of oliguric renal failure may respond to dialysis.

Hypokalemia

Hypokalemia is a common finding in patients with protracted vomiting. Causes include pyloric stenosis, Bartter syndrome, renal tubular acidosis, cystic fibrosis, aminoglycoside exposure, and hypokalemic familial periodic paralysis.[27] The presentation may include weakness, polyuria, ileus, tetany, diminished reflexes, and paralysis leading to respiratory failure. An ECG will show a U wave. Prolonged episodes

can lead to myoglobinuria and renal failure. The treatment for hypokalemia is potassium replacement. When there is severe hypokalemia, oral replacement should be prescribed whenever possible to reduce the possibility of a catastrophic medical error in IV potassium dosage. Extreme caution is advised to ensure that IV potassium is given at the correct dose and over the appropriate time frame.

Disposition

Planning for the disposition of the patient with a metabolic emergency can be difficult. All patients with significantly altered mental status, encephalopathy, or profound hyperammonemia should be admitted to an ICU. Patients with hyperammonemia are best served at a center offering hemodialysis. Patients with suspected but undifferentiated IEMs should be admitted for further workup, even if their symptoms seem mild at the time of presentation. A patient with a known metabolic disorder who presents for an acute illness can be discharged from the ED, but specifics of the case should be discussed with the patient's treating physician or a metabolic specialist familiar with his or her care. It is critical to consider the home environment and to ascertain whether the caregivers are capable of tending to and monitoring the patient during the recovery period. Specific discharge instructions and early follow-up with the primary physician or metabolic specialist are essential.

Summary

Metabolic emergencies are a complex family of disorders that can be perplexing to the emergency clinician. Recognition of historical and clinical information that may suggest an IEM is critical in order to trigger the appropriate workup. Knowledge of basic diagnostic and therapeutic strategies can be helpful in treating pediatric patients with both known and undifferentiated metabolic disorders. Specific treatments should be discussed with a metabolic specialist when available; management includes drug regimens and dialysis, which can affect disposition decisions. More commonplace metabolic emergencies such as diabetes mellitus and electrolyte disorders also affect the ED.

Case Conclusion

On tandem mass spectroscopy, the patient's blood work revealed a pattern diagnostic of a medium chain CoA deficiency. The child was started on a regimen of "midnight snacks" with complex carbohydrates to limit times of fasting. With the parents' careful use of a glucometer, she has remained asymptomatic. Now under the care of a metabolic specialist, the patient has required no further ED visits.

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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 estimated incidence of IEMs?
a. 1 in 5 live births
b. 1 in 50 live births
c. 1 in 500 live births
d. 1 in 5000 live births
e. 1 in 50,000 live births

2. A urea cycle disorder is suspected, and the metabolic specialist recommends obtaining an orotic acid level, which is subsequently elevated. Which urea cycle defect does this patient most likely have?
a. Argininosuccinic aciduria
b. Carbamoyl phosphate synthetase deficiency
c. Citrullinemia
d. Ornithine transcarbamylase deficiency

3. Which disorder is NOT associated with an unusual odor?
a. Glutaric acidemia type II
b. Glycogen storage disease type II
c. Isovaleric acidemia
d. Maple syrup urine disease

4. Which modality is preferred for dialyzing a patient with profound hyperammonemia?
a. Exchange transfusion
b. Hemodialysis
c. Hemofiltration
d. Peritoneal dialysis

5. A 16-year-old patient with diabetes mellitus and a history of vomiting and diarrhea arrives in the ED. He has been unable to control his blood sugar level with his sliding scale insulin regimen, and his urine is strongly positive for ketones. The nurse is starting an IV. Which intervention should be done first?
a. A bolus dose of insulin
b. A bolus of isotonic crystalloid
c. A CT scan of the head
d. An endocrinology consult
e. A urine toxicology screen

6. Which therapy is NOT a critical intervention for a patient with DKA?
a. Electrolyte replacement
b. Fluid resuscitation and rehydration
c. Insulin replacement
d. Replacement of urinary losses

7. Which sample is NOT part of the critical sample that should be obtained in a patient with hypoglycemia?
a. ACTH
b. Cortisol
c. Insulin
d. Vasopressin

8. **What is the most appropriate concentration of dextrose to deliver to a neonate or infant with hypoglycemia?**
   a. Dextrose 5% in water
   b. Dextrose 10% in water
   c. Dextrose 25% in water
   d. Dextrose 50% in water

9. **After febrile seizures, which electrolyte disorder is the most frequent cause of first-time seizures in children younger than 2 years?**
   a. Hypocalcemia
   b. Hypokalemia
   c. Hypomagnesemia
   d. Hyponatremia
   e. Hypernatremia

10. **Which medication can be used to treat hyponatremic seizures?**
    a. Benzodiazepines
    b. Phenobarbital
    c. 3% normal saline
    d. b and c
    e. None of the above

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Target Audience: This enduring material is designed for emergency medicine physicians, physician assistants, nurse practitioners, and residents.

Goals & Objectives: Upon reading *Pediatric Emergency Medicine Practice,* you should be able to: (1) demonstrate medical decision-making based on the strongest clinical evidence; (2) cost-effectively diagnose and treat the most critical ED presentations; and (3) describe the most common medicolegal pitfalls for each topic covered.

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Evidence-Based Management Of Metabolic Emergencies In The Pediatric Emergency Department

Ewing P, Wiebe R. October 2009; Volume 6 Number 10

This issue of *Pediatric Emergency Medicine Practice* examines approaches to the pediatric patient who presents to the ED with a metabolic emergency and identifies areas where diagnostic and therapeutic strategies fall short from an evidence-based perspective. For a more detailed and systematic look at the latest evidence on managing metabolic emergencies in the pediatric ED as well as other considerations such as clinical pathways and other laboratory tests not noted here, see the full text article at www.ebmedicine.net.

Key Points	Comments
Metabolic emergencies are heterogeneous in nature; accordingly, their presentations are diverse. Nevertheless, some common patterns emerge, and these are emphasized in the inborn errors of metabolism (IEMs). Waber analyzed pediatric patients with IEMs and found that more than 90% had either neurologic features or vomiting on presentation.[6] It should be noted that many of the IEMs present in infants.	As always, the emergency clinician should approach this population with great care and caution. As stated by Saudubray et al., "The neonate has a limited repertoire of responses to severe illness." [7] A broad differential diagnosis is appropriate including sepsis/infection, nonaccidental trauma and asphyxia, intracranial injury, electrolyte abnormalities, and metabolic diseases.
The most distressing symptom of a metabolic disorder in pediatric patients is altered mental status, which has a variety of manifestations.	Symptoms of neuroglycopenia in both the acute and subacute phases have been well described.[8] The acute phase is characterized by autonomic nervous system activation through circulating catecholamines. Symptoms include tachycardia, tachypnea, vomiting, pallor, and diaphoresis. Early intervention with glucose supplementation can avoid the progression to the subacute phase, when poor feeding, lethargy, seizures, jitteriness, and exaggerated primitive reflexes can occur.
The evaluation of the patient with a suspected metabolic emergency can begin with point-of-care testing at the bedside.	• Hypovolemia, hyponatremia, hyperkalemia: Consider adrenal insufficiency. • Metabolic acidosis, hyperammonemia, ketotic hypoglycemia: Consider an organic acid defect. • Encephalopathy, respiratory alkalosis, hyperammonemia: Consider a urea cycle disorder.
Inborn errors of metabolism are not the only sources of metabolic emergencies. Adrenal insufficiency, diabetes mellitus, and electrolyte disorders can also cause life-threatening illnesses.	As with IEMs, these disease processes should be considered early in the course of a patient's care because prompt therapy will reduce morbidity and mortality.
For infants with suspected IEMs, a few therapeutic options are available in the ED to reduce the risk of adverse sequelae. Information from the primary laboratory screen is paramount so that care may proceed in a sequential fashion.	Basic and advanced life support is the foundation of caring for a patient with a suspected IEM and includes the immediate correction of any hypoglycemia. Although administration of an ampule of dextrose 25% or dextrose 50% may be appropriate when no other options are available, low osmolarity solutions are preferred.[12] Glucose will not only correct hypoglycemia, but it will also help to move the patient from a catabolic to an anabolic metabolic state. Burton advocates the use of lipids to supplement caloric needs in infants provided there is no derangement in fatty acid metabolism.[13]
Children with a known metabolic disorder still present a significant challenge to the emergency clinician. Anticipatory guidance from the child's pediatrician and metabolic specialist can help when emergency care is needed.	In pediatric patients with a known metabolic condition who present with an acute illness, the administration of dextrose and fluids is a priority. A good rule of thumb is to initiate IV fluids with dextrose 10% in 1/2 normal saline at 1.5 times maintenance until laboratory results are available.

See reverse side for reference citations.

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