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Metabolic Emergencies

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Children with metabolic disturbances frequently present with symptoms similar to those with other emergencies, particularly in the newborn period and early infancy. Initial consideration of a metabolic disease in the differential diagnosis is important, especially in previously healthy neonates with acute deterioration. Metabolic disorders, either acquired or congenital, comprise a variety of entities which cause derangement in normal physiology and metabolism. These disorders may include diseases related to electrolyte imbalances, endocrine dysfunction, or inborn errors of metabolism. Although some use the term metabolic disorder only in relation to inherited inborn errors as first described by Garrod in 1902, this article focuses on pediatric metabolic disorders in the general sense.

Metabolic diseases can vary as much in clinical presentation as they can in classification. Because the symptomatology of these disorders is also associated with a variety of non-metabolic diseases, many metabolic conditions are missed in the emergency department. A definitive diagnosis is frequently not possible or necessary during the emergency department course, but proper initial management based on the probable diagnosis can be life-saving or reduce neurologic sequelae. Disorders which are responsive to emergency department treatment are highlighted herein.

Infants with metabolic disorders frequently present with nonspecific symptoms similarly seen in other infectious, neurologic, and toxicologic emergencies. Differences in presentation can be subtle, especially in the neonatal period. Vomiting, alterations in neurologic status, and feeding difficulties are perhaps the most prominent features of metabolic diseases.

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Characteristic clinical manifestations of specific disorders are discussed in the following sections.

Hypoglycemia

Hypoglycemia is one of the most commonly encountered metabolic problems, especially in the neonatal period. The definition of hypoglycemia is somewhat controversial and age dependent. In children, infants, and term neonates older than 1 to 2 days of life, hypoglycemia is usually defined as a serum glucose concentration less than 40 to 45 mg/dL [1,2]. In term and premature neonates within 1 day of life, levels as low as 30 mg/dL are considered by some to be normal. The laboratory value should be interpreted in the context of the clinical presentation, because symptoms may occur within a continuum of low glucose levels. Glucose levels of 50 to 60 mg/dL with symptoms of hypoglycemia may warrant treatment.

Glucose is the main energy substrate for the brain, and its levels represent a balance between exogenous supply and endogenous gluconeogenesis and glycogenolysis. Mobilization and use of glucose is mediated by hormones, primarily insulin. Insulin stimulates glucose uptake in cells and glycogen synthesis, and its actions are opposed by epinephrine, glucagon, cortisol, and growth hormone. Hypoglycemia can occur when imbalances exist between exogenous and endogenous substrate supply which may involve these hormonal abnormalities. Causes of hypoglycemia in the pediatric population are listed in Box 1. Important etiologies in the emergency department include infection, adrenal insufficiency, inborn errors, and medication-induced causes. Hyperinsulinemia, particularly persistent hyperinsulinemic hypoglycemia of infancy, should be considered as a potential cause of intractable hypoglycemia from the newborn period to 6 months of age.

Symptoms of hypoglycemia generally fall into two categories: (1) those associated with activation of the autonomic nervous system (adrenergic), and (2) those associated with decreased cerebral glucose use (neuroglycopenic). Adrenergic symptoms are usually seen early with a rapid decline in blood glucose and include tachycardia, tachypnea, vomiting, and diaphoresis. Because most of these patients are hypoglycemic before arrival to the emergency department, these symptoms are frequently absent. More familiar are the neuroglycopenic symptoms, which are usually associated with slower or prolonged hypoglycemia. These symptoms include poor feeding, altered mental status, lethargy, and seizures. These classic symptoms are usually evident in older children and adults; in infants, the presentation may be subtle and include only hypotonia, hypothermia, jitteriness, exaggerated primitive reflexes, or feeding difficulties.

Early detection of hypoglycemia is critical because permanent brain damage may begin shortly after symptoms develop, particularly in newborns and infants. Bedside glucose testing should be performed on all

Box 1. Causes of hypoglycemia

Decreased production/availability of glucose
Low glycogen stores
  Small for gestational age, prematurity
Malnutrition/fasting
Malabsorption/diarrhea

Increased use of glucose
Hyperinsulinemic states
  Infant of diabetic mother
  Persistent hyperinsulinemic hypoglycemia of infancy
    Nesidioblastosis
    Islet cell adenoma/hyperplasia
  Beckwith-Wiedemann syndrome
Stress
  Infection/sepsis

Combined or other mechanism
Inborn errors of metabolism
Hormone deficiency
  Adrenal (glucocorticoid) insufficiency
  Growth hormone deficiency
  Glucagon deficiency
Iatrogenic
  Insulin/oral hypoglycemic therapy
  Poisoning (ethanol, propanolol, salicylates)
  Reye's syndrome

pediatric patients who appear seriously ill or altered. Hypoglycemia occurring in children requiring resuscitation care is associated with increased mortality [3].

Acute treatment for hypoglycemia begins with intravenous glucose bolus replacement. The recommended dose ranges from 0.2 to 1 g/kg; a midlevel range of 0.4 to 0.5 g/kg glucose translates to approximately 4 mL/kg of 10% dextrose or 2 mL/kg of 25% dextrose. Some advocate a smaller bolus of 0.2 g/kg (2 mL/kg of 10% dextrose) to minimize hyperglycemia and resultant insulin secretion and possible prolonged hypoglycemia [4]. Generally, a 10% solution is used in neonates and infants, whereas a 25% solution is used in toddlers and children. More dilute solutions are used in younger patients to minimize vascular injury caused by more concentrated fluids. Continuous glucose infusion should follow bolus administration to maintain normal glucose homeostasis, especially in neonates. The normal glucose

requirement in a neonate is 6 to 10 mg/kg/min, which is roughly equivalent to an infusion of 10% dextrose-containing solution at 1.5 times the maintenance rate. Glucose levels should be rechecked frequently (every 1–2 hours) and the infusion rate adjusted accordingly.

If hypoglycemia persists despite boluses and infusions, a hyperinsulinemic state should be considered. Glucagon, 0.1 to 0.2 mg/kg (up to 1 mg) parenterally, can be given to infants for refractory hypoglycemia. Because it can be given intramuscularly, glucagon can be particularly helpful when intravenous access is difficult or delayed. Glucagon will not be effective in patients lacking adequate glycogen stores, such as those with inherited storage diseases [5]. Hydrocortisone, 2 to 3 mg/kg or 25 to 50 mg/m^2, can also be considered for refractory hypoglycemia [6].

Hyperglycemia and diabetic ketoacidosis

Hyperglycemia is typically defined as a glucose concentration of greater than 125 to 150 mg/dL. It is often seen in critically ill, non-diabetic patients of all ages and can signify increased mortality. Hyperglycemia is frequently seen in the first week of life and is inversely correlated to gestational age, with up to 18 times greater occurrence in neonates with birth weights less than 1000 g [7,8]. It is also seen in infants who are acutely stressed or septic, receiving high rates of glucose infusion, or being treated with corticosteroids or other drugs. In non-iatrogenic conditions, hyperglycemia is a consequence of physiologic stress and increased levels of counterregulatory hormones including glucagon, catecholamines, cortisol, and growth hormones. Mechanisms of hyperglycemia include immaturity in the neonatal period, absolute or relative insulin insufficiency, and hepatic and peripheral insulin resistance. Owing to their small mass of insulin-dependent tissue, namely, muscle and fat, infants have limited glucose use when compared with larger children and adults [7,8]. The greatest risk of hyperglycemia is dehydration secondary to the resulting urinary loss of glucose and osmotic diuresis. The hyperosmolarity and osmotic shifts that occur can increase the risk of cerebral bleeding due to brain cell dehydration, dilation of capillaries, and an inability to autoregulate cerebral blood pressure. It is unknown whether infants with stress-induced hyperglycemia are at risk for later development of diabetes mellitus [9,10].

Insulin-dependent diabetes mellitus (IDDM) diagnosed in the newborn or during the first 6 months of life is extremely rare, affecting approximately 1 in 500,000 births [7,8]. More common is a temporary form called transient neonatal diabetes mellitus. It resembles permanent diabetes mellitus but resolves within several weeks or months. Patients affected with the transient form during infancy may have diabetes mellitus recur later in life [8]. The ultimate cause of neonatal diabetes remains unclear; however, many theories have related to immature metabolic pathways. Most children studied do

have a low birth weight for gestational age, with some full-term infants weighing less than 1500 g. Other possible associations include short-term maternal enterovirus infection, autoimmune enterocolitis, congenital absence of the islet of Langerhans, rare genetic disorders, and pancreatic agenesis [7–9]. Patients in whom IDDM develops after the first 180 days of life have genetic profiles and a clinical course similar to patients in whom IDDM develops later in life [8].

Diagnosing IDDM in the young infant can be difficult for obvious reasons. Polydipsia cannot be communicated by the nonverbal infant, new absorbent diapers may mask polyuria, and oral rehydration may conceal acute weight loss. Recurrent cutaneous candidiasis, although common in infants, can be considered an indication for the clinician to check blood glucose levels [9–11]. Infants are often misdiagnosed with pneumonia, asthma, or bronchiolitis and undergo treatment with corticosteroids that will only aggravate the metabolic derangements of IDDM. These difficulties help explain why the younger the patient presents with IDDM, the more likely they will present with severe decompensation, including acidosis, obtundation, and possibly cerebral edema [9].

Diabetic ketoacidosis (DKA) is defined as a glucose level greater than 200 mg/dL with either a bicarbonate level less than 15 mEq/L or a venous pH less than 7.3. It is more difficult to recognize and treat in younger patients for several reasons. The higher basal metabolic rate and larger surface area to body mass ratio in infants require stricter amounts of fluid and electrolyte repletion. The smaller patient is also at greater risk for cerebral edema owing to the immaturity of autoregulatory mechanisms. Cerebral edema is thought to occur in about 0.5% to 1% of all children with DKA and is the most likely cause of morbidity, with death in 20% to 25% of these patients and pituitary insufficiency in 10% to 25% of survivors [9,11–13]. Other causes of mortality in infants with DKA include concomitant pneumonia, sepsis, pulmonary edema, and cardiac arrhythmias associated with electrolyte imbalances.

The pathophysiology of DKA can be condensed to a blend of insulin deficiency and antagonism during physiologic stress with the actions of counterregulatory hormones. Increased glucose production from glycogenolysis and gluconeogenesis coupled with the incapacity to use glucose lead to hyperglycemia, osmotic diuresis, loss of electrolytes, hyperosmolarity, and dehydration. This vicious cycle occurs concurrently with lipolysis as the body senses a starvation mode and enters oxidative metabolism with resultant ketone (beta-hydroxybutyrate) formation and metabolic acidosis. Lactic acid also contributes to the acidosis as tissues undergo anaerobic metabolism with inadequate perfusion. Clinically, the infant will most likely present with vomiting, lethargy or frank coma, polyuria, deep Kussmaul's respirations, and severe dehydration. DKA can be categorized as mild with a venous pH of 7.2 to 7.3, moderate with a venous pH of 7.1 to 7.2, and severe with a venous pH less than 7.1.

Assessment starts with the suspicion of DKA if the young infant did not previously carry the diagnosis of diabetes. Clinical examination should focus on volume status as well as a search for a source of infection, although this may not be the precipitating cause in first time presentations. The patient should be carefully weighed and measured for accurate fluid therapy calculations. Previously known weights should not be used because the patient may have sustained an unnoticed amount of weight loss. Airway protection with intubation may be necessary in the unresponsive infant or with impending respiratory failure. Care must be taken to set the respiratory rate on the ventilator to match the infant's previous natural rate to compensate for the metabolic acidosis; however, aggressive hyperventilation (to $P_{CO2} < 22$) is associated with poorer neurologic outcomes and is not recommended [9,11,12]. Initial diagnostic tests should include blood draws for serum electrolyte levels, glucose, osmolality, pH, complete blood count, beta-hydroxybutyrate and acetone levels, and blood cultures. Blood gases from venous or capillary origin are generally regarded as acceptable in non-intubated and well-perfused infants [14,15]. Catheterized urinalysis and culture should also be performed. An electrocardiogram can be obtained as a rapid way to assess the potassium level. Pseudohyponatremia is usually seen from the dilutional effect of hyperglycemia. Leukocytosis may be from a stress response rather than an underlying infection.

Initial management should focus on rapid expansion of the intravascular volume and improvement of acidosis, the two life-threatening circumstances; however, rapid fluid administration to improve glomerular filtration must be carefully monitored to avoid excessive hydration and augmenting the possibility of cerebral edema. Approximately, a 10% fluid deficit in infants with DKA can be assumed. Isotonic solutions of 0.9% saline or Ringer's lactate can be used with a volume of 10 to 20 mL/kg over 1 to 2 hours. If the infant remains severely dehydrated or hypotensive, this volume can be repeated. Once adequate intravascular volume is obtained, the remaining fluid deficit can be restored over the next 24 to 48 hours depending on the degree of initial hyperosmolality. The first 4 to 6 hours of replacing fluid deficit can be done with 0.9% normal saline or Ringer's lactate. Subsequent volumes should be replaced with a fluid of tonicity greater than 0.45% saline and added potassium or phosphate, provided that urine output is adequate [9].

Insulin therapy is key to resolving DKA and halting lipolysis and ketone generation. Insulin infusion should begin after the initial fluid bolus, about 1 to 2 hours after the start of resuscitation. Only intravenous routes should be considered, because subcutaneous and intramuscular absorption is irregular or inadequate in the dehydrated patient. Insulin bolus is not recommended in the pediatric population, because extensive evidence demonstrates this may exacerbate the risk of cerebral edema by dropping blood glucose levels too quickly. The dose of insulin should be 0.1 U/kg/h (or as low as 0.05 U/kg/h in some infants) with the rate of infusion adjusted to achieve

a fall in blood glucose of about 50 to 90 mg/dL per hour. Once the blood glucose level falls to about 300 mg/dL, glucose should be added to the intravenous solution. As long as acidosis is present, insulin infusion should continue with the amount of added glucose adjusted to maintain levels between 150 and 200 mg/dL. Once acidosis has resolved and the patient can tolerate oral intake, subcutaneous insulin can be initiated, usually 1 to 2 hours before insulin infusion is discontinued. The dose for subcutaneous insulin is 0.25 U/kg [9,10].

DKA patients generally experience a potassium deficit of about 3 to 6 mEq/kg. Most of the potassium deficit is intracellular as the acidosis, lipolysis, hypertonicity, and glycogenolysis promote a general efflux of potassium out of cells. Extracorporeal losses through vomiting and urinary diuresis also contribute to total body potassium deficit. At presentation of DKA, the extracellular potassium level that is measured may be decreased, normal, or increased. Once insulin therapy is begun and acidosis is improved, potassium is forced back into cells, which may cause a precipitous drop in potassium levels and lead to cardiac arrhythmias. As a general guideline, potassium replacement is necessary early in treatment. If the potassium level is greater than 4 mEq/L, 40 mEq/L of potassium is added to the intravenous fluids after vascular competency and urine output are restored. If the initial potassium level is less than 4 mEq/L, replacement should be started after the fluid bolus and before insulin therapy. Should laboratory values be delayed, the electrocardiogram and cardiac monitor can serve as a way to estimate potassium levels. Potassium phosphate combined with potassium chloride or acetate can be used with the maximum infusion rate at 0.5 mEq/kg/h.

Phosphate depletion due to osmotic diuresis can also be expected in DKA patients, but the benefit of phosphate replacement is unclear. Although a few studies have not demonstrated a clinical benefit to phosphate repletion, severe hypophosphatemia exhibited by muscle weakness can be treated through supplementation. Calcium levels may decline, and phosphate infusion should be terminated if hypocalcemia occurs. Potassium phosphate has been shown to be safe for use with close observation of calcium levels [9].

Bicarbonate therapy in DKA and other acidotic states is discussed in the section on metabolic acidosis. Generally, bicarbonate is not recommended, because the acidosis should self-correct during fluid resuscitation and insulin therapy. Some advocate its use in DKA with a pH less than 6.9 or significant hyperkalemia or arrhythmias. The American Diabetic Association recommends consideration of bicarbonate in the pediatric patient if the pH remains less than 7.0 after the first hour of hydration [16]. If given for DKA, bicarbonate can be mixed as an isotonic solution (2 ampules of sodium bicarbonate in 0.45% normal saline) and given over 1 hour.

These treatment guidelines have been based on concerns of how to best avoid the development or worsening of cerebral edema. The pathophysiology of cerebral edema is not well described, but DKA and its treatment

have both been implicated. Perhaps the most common theory involves fluid entry into the brain due to a rapid drop in serum osmolality concomitant with vigorous fluid resuscitation. One should not infuse more than 50 mL/kg over the first 4 hours of treatment because higher volumes have been associated with an increased risk of cerebral edema [13]. Recent studies also suggest a vasogenic, rather than cytotoxic, mechanism of cerebral edema [9,12,13]. Patients who are at greatest risk for cerebral edema tend to be those who present with extreme acidosis, have high levels of blood urea nitrogen, and hypocapnia. Cerebral edema can be present before the initiation of therapy or within 4 to 24 hours after treatment [9,11–13]. Radiographic imaging can be normal early on with later signs of focal or diffuse edema, hemorrhage, or infarction. Cerebral edema should be suspected in infants with persistent vomiting, bradycardia, hypertension, labile oxygen saturation, irritability, lethargy, or in the presence of neurologic findings. Treating cerebral edema has been attempted with mannitol (0.25–1.0 g/kg) or hypertonic saline (3%) given 5 to 10 mL/kg over a period of 30 minutes. Hyperventilation in intubated patients should not be beyond the patient's physiologic tendency.

Hyponatremia

Although not as common as hypoglycemia in the emergency department, hyponatremia is one of the most common electrolyte abnormalities in hospitalized children [17]. Hyponatremia can be caused by salt-losing states, such as vomiting or diarrhea, diuretic excess, and adrenal insufficiency, or by excess total body water states such as the infection-induced syndrome of inappropriate secretion of antidiuretic hormone (SIADH), nephrotic syndrome, and cirrhosis. Factitious, or pseudohyponatremia, can occur with hyperglycemia, hyperlipidemia, or hyperproteinemia. In infants, hyponatremia is commonly due to excess gastrointestinal loss from prolonged vomiting or diarrhea, or from inappropriately diluted formulas. Pyridoxine-dependent seizures are a rare cause of intractable seizures in neonates.

Hyponatremia is typically defined as a serum sodium level less than 125 to130 mEq/L, although clinical symptoms are not usually seen until serum sodium falls below 120 mEq/L. Manifestations include altered mental status, lethargy, vomiting, diarrhea, seizures, and circulatory collapse. Vomiting can be a cause and manifestation of hyponatremia. The presence of symptoms is dependent in part on the rate of change in serum sodium. A gradual or chronic progression of hyponatremia may not become clinically evident even at levels below 110 mEq/L. Conversely, less severe hyponatremia may be symptomatic if the decline in serum sodium is rapid.

Treatment should be geared toward the underlying cause. Aggressive treatment with 3% hypertonic saline (514 mL/kg) should only be initiated if significant symptoms are present, such as seizures or coma. A dose of

5 mL/kg over 10 to 15 minutes should raise the sodium level by approximately 5 mEq/L; smaller additional doses of 2 to 3 mL/kg can be considered if there is no clinical improvement. The exact sodium deficit can be calculated as follows: mEq Na^+ needed = 0.6 × weight (kg) × (Na^+ desired − Na^+ measured). Acute correction to a level of 125 mEq/L should alleviate symptoms in most cases. After acute correction for symptoms, the goal is to raise the sodium level slowly at a rate of 0.5 mEq/L per hour (maximum, 12 mEq/L per day) by using 0.9% normal saline infusion. If SIADH is suspected, one should consider fluid restriction to two-thirds maintenance and administration of furosemide, 1 to 2 mg/kg. Pyridoxine, 100 mg intravenously, should be considered for neonates with intractable seizures of unclear etiology [18].

Central pontine myelinolysis is a potential complication of hypertonic saline use, although it has been less well described in children than adults [17]. This observation may reflect the fact that hyponatremia in the pediatric population tends to occur acutely rather than chronically, and most cases of central pontine myelinolysis after a rapid rise of sodium are described in a setting of chronic hyponatremia. Infants can apparently tolerate rapid and large increases in sodium levels without sequelae.

Metabolic acidosis

Metabolic acidosis occurs via three major mechanisms: (1) loss of bicarbonate from the kidney or gastrointestinal tract, (2) excess acid from endogenous production or an exogenous source, or (3) underexcretion of acid by the kidneys. Neonates and infants are more susceptible than are older children to acidosis owing to their lower renal threshold for bicarbonate reabsorption and limited maximum net acid excretion. Young infants have a relatively limited compensatory mechanism for an excess acid load.

The presence of metabolic acidosis has important diagnostic considerations depending on the classification of acidosis as a normal anion gap or increased anion gap. The anion gap is calculated as the difference between serum sodium and the sum of serum chloride and bicarbonate [$Na^+ - (Cl^- + HCO_3^-)$]. A normal anion gap range is somewhat age dependent but in children is 12 ± 4, and an anion gap of greater than 16 is considered elevated. Causes of metabolic acidosis based on the anion gap are listed in Box 2. Lactic acidosis is the most common cause of an increased anion gap acidosis in critically ill neonates [19].

Clinical manifestations of metabolic acidosis are nonspecific and include altered mental status, vomiting, respiratory distress, and poor perfusion. An important sign, particularly in infants, that can alert the emergency department physician of metabolic acidosis is tachypnea, a compensatory mechanism creating a respiratory alkalotic response. This breathing can range from mild shallow tachypnea to deep Kussmaul respirations of severely acidotic patients.

Box 2. Causes of metabolic acidosis

Normal anion gap
Gastroenteritis/diarrhea
Renal tubular acidosis
Adrenal (mineralocorticoid) insufficiency

Increased anion gap
MUDPILES
  Methanol, uremia, DKA, paraldehyde, iron or isoniazid, lactic acidosis, ethylene glycol, salicylates
Inborn errors
  Carbohydrate, amino acid, or fatty acid metabolism
Starvation
Chronic renal insufficiency

Treatment is focused toward appropriate fluid resuscitation and specific therapy for the underlying cause of the acid-base disturbance. The use of sodium bicarbonate is controversial. Most clinicians would only recommend it if an inborn error is suspected or if the metabolic acidosis is causing significant arrhythmias or hemodynamic instability. Some advocate its use in DKA with a pH less than 6.9 or significant hyperkalemia or arrhythmias, or in non-DKA metabolic acidosis with a pH less than 7.1 refractory to other treatments. The dose of sodium bicarbonate is 1 to 2 mEq/kg given intravenously. Bicarbonate potentially improves cardiac output and blood pressure, but these benefits are thought to be only transient in neonates [20]. Bicarbonate therapy is potentially harmful because it shifts the oxygen-hemoglobin dissociation curve to the left and can worsen tissue hypoxia, particularly in hypovolemic patients. It can also cause hypernatremia, hypokalemia, and a paradoxical drop in central nervous system pH leading to decreased consciousness. A 5% albumin infusion in neonates has been shown to be less effective than bicarbonate in correcting metabolic acidosis [21].

Adrenal insufficiency

Adrenal insufficiency is due to primary adrenal disease or secondary to pituitary suppression and can be inherited or acquired. Congenital adrenal hyperplasia (CAH) is an important cause of primary adrenal insufficiency in the newborn period, whereas Addison's disease is a more common etiology in children and adolescents. Secondary adrenal insufficiency is more common in older children and almost always involves exogenous steroid use for a chronic disease with subsequent discontinuation. Acute adrenal

insufficiency or crisis occurs when the adrenal glands fail to produce adequate glucocorticoid and mineralocorticoid in response to stress. The common emergency department presentation involves a newborn male with an uneventful birth history who presents within the first 2 weeks of life with apparent dehydration or sepsis and circulatory collapse unresponsive to fluid resuscitation.

The term *congenital adrenal hyperplasia* refers to a group of inherited autosomal recessive disorders with defects in adrenal biosynthesis of the glucocorticoid cortisol. The low cortisol production stimulates pituitary production of ACTH which causes the characteristic hyperplasia of the adrenal cortex. Depending on the affected enzyme, the synthesis of other steroids such as mineralocorticoids (aldosterone) and androgens may also be affected, and the clinical expression will vary depending on the accumulated biosynthetic precursors. Deficiency of 21-hydroxylase accounts for up to 95% of CAH cases, and the discussion herein is limited to this particular form of CAH. This disorder occurs in 1 in 10,000 to 15,000 live births worldwide [22]. Up to 75% of affected newborns have the classic salt-losing virilizing variant, which is associated with aldosterone deficiency and androgen overproduction (17-hydroxyprogesterone); up to 25% have the non–salt-losing simple virilizing type. The degree of virilization and other clinical signs are usually more pronounced and seen earlier in life in the salt-losing variant.

Many states now screen newborns for CAH; however, these results may not be available for several weeks, allowing for an acute adrenal crisis to occur during this time. Males are particularly prone to missed diagnosis because their genitalia may appear normal at birth. Females usually exhibit some degree of ambiguous genitalia, such as clitoral enlargement or fusion of the labial folds. Another physical examination sign is hyperpigmentation, which may be present in the axilla and scrotal/labial areas and is due to the accumulation of a corticotropin precursor that stimulates melanocytes. With the classic salt-losing type, symptoms may begin 1 to 2 weeks after birth and include weight loss, poor feeding, vomiting, polyuria, and dehydration. Progression can occur rapidly, particularly in the setting of infection or trauma, to altered mental status, hypotension, or death.

Acute adrenal insufficiency, whether acquired or from CAH, is associated with hyponatremia, hyperkalemia, and hypoglycemia. A normal anion gap metabolic acidosis is often seen due to aldosterone deficiency. Unexplained hypotension unresponsive to intravenous fluids is another sign of steroid deficiency. Treatment should be geared toward aggressive fluid resuscitation and rapid stress doses of corticosteroids. Before treatment, if possible, blood should be collected for non-emergent testing of specific endocrine hormones and metabolites.

Acute adrenal insufficiency is treated with stress doses of corticosteroids. Table 1 lists various options. Hydrocortisone is the steroid of choice because it has equal glucocorticoid and mineralocorticoid effects; cortisone is an

Table 1
Corticosteroids for adrenal insufficiency

Drug	Dose	Potency effect (per mg)	
		Glucocorticoid	Mineralocorticoid
Glucocorticoid			
Hydrocortisone	25–50 mg/m^2 IV/IM Infant: 25 mg Child: 50 mg Teen: 75 mg	1	1
Cortisone	1 mg/kg IM	0.8	1
Dexamethasone	0.1–0.2 mg/kg IV/IM	40	None
Mineralocorticoid			
Fludrocortisone	0.1 mg PO daily	15	400

Abbreviations: IV/IM, intravenous/intramuscular; PO, by mouth.

alternative but cannot be given intravenously. The stress parenteral dose of hydrocortisone is 25 to 50 mg/m^2 (approximately 2–3 mg/kg), followed by 100 mg/m^2/d in divided doses. The typical dose in a neonate or young infant is 25 mg. Dexamethasone has no mineralocorticoid effect but is advocated by some over hydrocortisone in normotensive patients with an unconfirmed diagnosis owing to its noninterference with diagnostic ACTH stimulation testing. An oral mineralocorticoid such as fludrocortisone can be started after initial stabilization with intravenous fluids and glucocorticoids. Hyperkalemia should correct with fluids and steroid therapy and rarely needs individual correction, because neonates can tolerate elevated potassium levels better than children and adults.

Inborn errors of metabolism

This diverse group of hereditary disorders involves gene mutations, usually of a single enzyme or transport system, causing significant blocks in metabolic pathways and accumulation or deficiency of a particular metabolite. Due to the large number and complexity of inborn errors of metabolism (IEMs), the reported incidence of these disorders varies greatly, ranging from 1 in 1400 to 200,000 live births [23,24]. It is now possible to screen for many of these defects in the newborn as well as prenatal periods. Some IEMs manifest clinically in the newborn period or shortly thereafter, and failure of early diagnosis may lead to permanent neurologic sequelae and death if specific treatment is not initiated. Although collectively numerous, IEMs that are amenable to specific emergency medications are limited; however, the majority of them should respond to removal of the offending metabolite from the diet. The most common emergent clinical manifestations in the neonatal period include vomiting, neurologic abnormalities, metabolic acidosis, and hypoglycemia [25,26]. These nonspecific findings

can mimic other disorders, such as sepsis or adrenal crisis, but an IEM should be considered in a previously normal neonate with acute clinical deterioration. Conversely, the presence of infection does not exclude the possibility of IEMs, because these patients frequently deteriorate and become septic quickly. Standard laboratory values, particularly blood ammonia, electrolytes, and urinalysis can be helpful in further classifying the IEM and tailoring treatment in the emergency department (Fig. 1).

IEMs can be divided into disorders of amino acid metabolism (phenylketonuria, nonketotic hyperglycinemia), fatty acid oxidation/metabolism (medium-chain acyl-CoA dehydrogenase deficiency, primary carnitine deficiency), energy metabolism (primary lactic acidemias), and carbohydrate metabolism (glycogen storage diseases, galactosemia). Organic acidemias and acidurias (methylmalonic, propionic, and isovaleric acidemias, maple syrup urine disease) refer to a specific group of disorders of amino and fatty acid metabolism in which high levels of non-amino organic acids accumulate in serum and urine.

Many patients with IEMs exhibit symptoms as newborns after feedings have been initiated, but a minority may go undetected into childhood with only psychomotor delay until a stressor causes acute deterioration. Recurrent vomiting, dehydration, and acute metabolic encephalopathy are common clinical manifestations. Neurologic symptoms can range from hypotonia to seizures to frank coma. Intractable seizures are characteristic of nonketotic hyperglycinemia and pyridoxine-dependent seizures. Hepatomegaly is a common finding on physical examination and can be

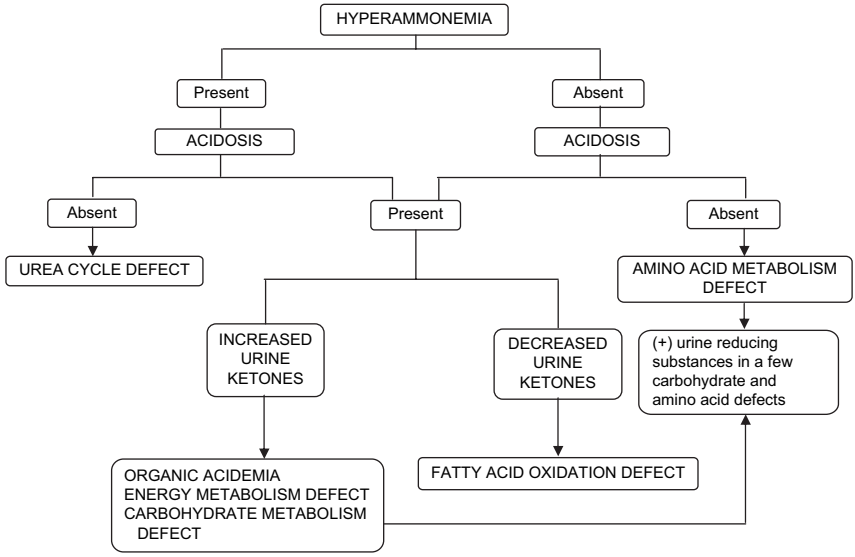

Fig. 1. Diagnostic pathway for inborn errors. (*Modified from* Brousseau T, Sharieff G. The critically ill newborn. Critical Decisions in Emergency Medicine 2003;18:5; with permission.)

pronounced in glycogen storage diseases and galactosemia, although it tends to be less evident in infancy. The risk of infection, particularly *Escherichia coli* sepsis, and liver failure are also increased in patients with galactosemia. A peculiar odor in body fluids can be associated with specific disorders and may offer an invaluable aid to diagnosis when present. Maple syrup urine disease is named for its characteristic sweet sugar odor, isovaleric acidemia is associated with a "sweaty feet" scent, and methylmalonic and propionic acidemias can exude a fruity ketotic odor similar to that of diabetic ketoacidosis. Metabolic acidosis with an increased anion gap is common in many IEMs and can aid in further classification. Hypoglycemia is also common and can be pronounced, particularly in glycogen storage diseases and defects of fatty acid oxidation [27]. Hyperammonemia is most commonly seen in organic acidemias and urea cycle defects.

Urea cycle defects are a specific classification of IEMs which lead to hyperammonemia due to the inability to detoxify ammonia to urea. Common disorders include ornithine transcarbamylase deficiency, arginase deficiency (argininemia), and argininosuccinic acid synthetase deficiency (citrullinemia). Clinical manifestations parallel those seen in other IEMs. Neonates frequently present after a few days of protein feeding of either breast milk or formula. Symptoms include vomiting, poor feeding, and post-prandial neurologic alterations. Older infants and children may present with recurrent vomiting, ataxia, or developmental delay. Tachypnea is common due to stimulation of the respiratory center by ammonia. The level of hyperammonemia tends to be higher than that seen in organic acidemias. Blood ammonia is usually above 200 μmol/L (normal, $<$35–50 μmol/L), with some complete enzyme defects reaching levels greater than 500 to 1000 μmol/L [28,29]. Although sicker infants tend to have higher ammonia levels, no strict correlation exists between ammonia levels and clinical findings. The degree of neurologic impairment is thought to be related more to the duration of hyperammonemia rather than the level itself. Blood urea nitrogen is usually low, but a normal level does not exclude a urea cycle defect. Metabolic acidosis does not occur with these disorders unless they are associated with a concurrent dehydrating illness. The lack of acidosis is helpful in differentiating urea cycle defects from many of the other IEMs.

Treatment for IEMs consists of general measures as well as specific medications if a probable type of IEM is suspected. Unless the infant has a known IEM and is already on a special formula, all dietary intake should be withheld and feedings reintroduced after consultation with a specialist. Intravenous fluid containing dextrose may be indicated, particularly if a urea cycle defect is suspected, because stimulating endogenous insulin will minimize protein catabolism and ammonia production. After appropriate fluid boluses of normal saline to correct shock, most IEMs can be managed with a standard intravenous fluid consisting of 10% dextrose in one-fourth normal saline at 1.5 times maintenance. Metabolic acidosis unresponsive to intravenous fluids should be treated with sodium bicarbonate boluses of

1 to 2 mEq/kg. Although controversial for other diseases, bicarbonate use for IEMs is indicated, but standard calculations of bicarbonate requirements will underestimate actual needs owing to ongoing production of acidic metabolites [28,30]. Correction of severe acidosis will often require large doses of bicarbonate, up to 20 mEq/kg in some organic acidemias [31]. Liberal use of bicarbonate should be performed in consultation with a metabolic specialist. The rapid removal of toxins may be life-saving in some cases, particularly with severe hyperammonemia. An ammonia level greater than 120 μmol/mL in a newborn is considered neurotoxic. Hemodialysis to remove excessive ammonia is more effective than peritoneal or other extracorporeal routes [28,32]. Temporizing empiric therapy with arginine with or without sodium benzoate/phenylacetate can reduce ammonia levels acutely in most urea cycle defects. Table 2 lists specific therapies to consider when suspecting particular IEMs.

Thyroid disorders

Neonatal thyrotoxicosis, also called congenital hyperthyroidism, is usually due to in utero passage of thyroid-stimulating immunoglobulins from the mother to fetus. The incidence is 1 case per 4000 to 50,000 live births [33]. By far, most cases are due to maternal Graves' disease, an autoimmune disorder that produces thyroid-stimulating hormone (TSH) receptor antibodies causing increased thyroid hormone release. The prevalence of Graves' disease in pregnant women is 0.1% to 0.4%, with hyperthyroidism seen in 0.6% to 10% of infants born to these mothers [34]. Euthyroid mothers treated for hyperthyroidism are still at risk for having a newborn with thyrotoxicosis. Diagnosis is made by measuring neonatal levels of serum-free thyroxine (T_4) and TSH shortly after birth. Normal ranges of T_4 and TSH concentrations are higher in neonates than older infants and

Table 2
Specific therapies for inborn errors of metabolism

Drug	Dose	Indication
Arginine HCl 10%[a]	210–600 mg/kg IV	Urea cycle defects
Biotin	10 mg IV or PO	Organic acidemias
Carnitine	50–400 mg/kg IV or PO	Fatty acid defects, organic acidemias
Pyridoxine	100 mg IV	Pyridoxine-dependent seizures
Sodium benzoate[a] and/or phenylacetate[a]	250 mg/kg IV	Urea cycle defects
Thiamine	25–100 mg IV	MSUD, primary lactic acidosis

Abbreviations: IV, intravenous; PO, by mouth; MSUD, maple syrup urine disease.
[a] Can infuse over 1 to 2 hours in dextrose-containing solution.
Data from Refs. [24,27,28,32].

children. Also, thyroid function tests may be unreliable in the first few days of life if the mother was taking antithyroid medications.

Infants with neonatal hyperthyroidism are commonly born preterm with low birth weight, microcephaly, and craniosynostosis. They usually present within a few days of life but can sometimes be delayed 10 days or more. Symptoms are transient and usually last less than 12 weeks, the duration of which is dependent on the persistence of maternally transmitted immunoglobulins. Symptoms include vomiting, diarrhea, poor feeding and weight loss, sweating, and irritability. Most infants will have a goiter, and many will also have exophthalmos, hyperthermia, tachycardia, hepatomegaly, and jaundice. Although transient, neonatal thyrotoxicosis can be life-threatening, with a reported mortality rate of up to 20%, usually from heart failure [33].

Hyperthyroidism in older infants and children is almost always due to Graves' disease. Nearly 5% of all patients with hyperthyroidism are less than 15 years old, with the majority being adolescents. Unlike adults, children with hyperthyroidism usually have an indolent progression of symptoms over months, although it may occur more abruptly. Personality disturbances or motor hyperactivity may be the earliest symptoms, followed by the classic symptoms of weight loss, heat intolerance, diaphoresis, palpitations, diarrhea, and amenorrhea. A goiter is present in nearly 100% of cases, and exophthalmos, tachycardia, and hypertension are common [35]. Thyroid storm can occur in the pediatric population and consists of extreme signs and symptoms of hyperthyroidism combined with a high fever and altered mental status. It is usually precipitated by infection, trauma, or dehydration. Thyroid storm is life-threatening and treatment should be aggressive and similar to adult management.

Neonatal hyperthyroidism and thyroid storm have many therapeutic options. Beta-adrenergic blockade can be achieved with propanolol in a 0.01 mg/kg/dose intravenously and titrated to clinical effect; alternative oral dosing is 2 mg/kg/d in three to four divided doses. Thyroid hormone synthesis can be blocked using propylthiouracil, 5 to 10 mg/kg/d, or methimazole, 0.5 to 1 mg/kg/d, both in three divided oral doses. Iodine can be given in the form of Lugol's solution (8 mg iodine/drop), 1 to 3 drops daily. Iodine should be started at least 1 hour after administering an anti-thyroid drug like propylthiouracil to avoid increasing thyroid gland stores before the anti-thyroid effect occurs. Glucocorticoid treatment with hydrocortisone or prednisone may also be helpful in severe cases, because it inhibits thyroid hormone release and decreases peripheral conversion of T_4 to T_3.

Hypothyroidism does not occur with acute signs or symptoms and is rarely classified as an emergent condition. Congenital hypothyroidism may occasionally be missed due to laboratory errors in newborn screening, and early emergency department detection and treatment within the first few weeks of life are important to prevent irreversible brain damage. The incidence is 1 case per 4000 live births, and it is the most common treatable

cause of mental retardation. Classic symptoms include prolonged jaundice, poor feeding, hoarse cry, constipation, somnolence, and hypothermia. Classic signs include coarse puffy facies, large fontanelles, macroglossia, hypotonia, dry skin, jaundice, and a distended abdomen with umbilical hernia.

Emergency department evaluation

Initial emergency department management for a suspected metabolic disorder should begin with the standard ABCs approach. Poorly perfusing or hypotensive infants require standard intravenous fluid replacement, and antibiotics should be administered promptly when sepsis is suspected. If DKA is suspected or confirmed, aggressive fluid resuscitation should be avoided in normotensive infants due to its association with cerebral edema.

A careful history may reveal important clues suggestive of metabolic disease. Questions about prenatal care and maternal medications may elucidate an endocrine disorder. Newborn screening test results are important inquiries when considering an IEM, as is a history of consanguinity or sudden infant death in the immediate family. Feeding difficulties, weight loss, or an association of symptoms with dietary intake or particular types of food are important inquiries, especially in newborns. Vomiting is a prominent feature in most metabolic disorders, both as a primary symptom and a compensatory mechanism by which excess body acid is eliminated via the gastrointestinal tract.

Physical examination should focus on the patient's neurologic and circulatory status. Alterations in consciousness can range from mild lethargy to seizures and coma. Hypotonia with poor suck and Moro reflexes are frequently seen. Dehydration with tachycardia, poor perfusion, or hypotension should be recognized early and treated aggressively. Tachypnea is a characteristic sign in acidotic infants, and the degree of tachypnea frequently correlates with the severity of acidosis. A fruity breath can be seen in DKA or other ketotic diseases, whereas other unusual or peculiar body fluid odors suggest IEMs. Hepatomegaly and jaundice may be prominent, especially in glycogen storage diseases and galactosemia.

Emergent diagnostic testing should begin with bedside glucose testing, which should be verified by standard laboratory testing. Electrolytes with calculation of the anion gap are important for diagnostic classification (see Box 2). Acid-base status can be more precisely measured with an arterial blood gas, although in the absence of hypoxia or poor perfusion, a venous or capillary measurement may be adequate and less invasive in infants. Serum calcium, magnesium, and liver function tests should also be obtained. Urinalysis will reveal the presence or absence of ketones, which can help to differentiate particular metabolic disorders; the lack of an appropriate ketonuric response to metabolic acidosis is indicative of a fatty acid oxidation defect. The pH of urine is normally less than 5 in organic

acidemias, whereas the most common urea cycle defect, ornithine transcarbamylase deficiency, may contain urinary orotic acid crystals. The finding of urine reducing substances in the absence of glucosuria is indicative of galactosuria and presumptive galactosemia. Urine reducing substances can also be seen in a few select disorders of amino acid metabolism, such as tyrosinemia. Urine electrolytes and osmolality can better classify a hyponatremic disorder. Serum osmolality, both measured and calculated, is important in managing DKA. Along with drug screens and levels, osmolality can help to exclude a toxicologic cause. Concurrent with these studies should be standard investigations for infection, including a complete blood count, cerebrospinal fluid studies, and body fluid cultures.

The blood ammonia level should be obtained in any altered infant in whom metabolic disease is suspected. Testing for ammonia levels need to be completed within 30 minutes of the blood draw to avoid falsely elevated levels. Ammonia is significantly elevated in urea cycle defects and many of the organic acidemias. Mild transient elevation of ammonia is common in asymptomatic neonates, especially premature infants. Lactate and pyruvate levels can be of use. Although both acids can be elevated in sepsis and IEMs, the lactate-to-pyruvate ratio tends to be increased in sepsis (greater than 10:1), whereas in some IEMs such as primary lactic acidosis the ratio is usually normal. Because stat thyroid function testing is now available in many laboratories, these tests should be initiated in the emergency department when indicated. Although variable studies exist, essential testing should include levels for TSH and free thyroxine (T_4).

Additional archival body fluid samples should be appropriately collected and stored if an undiagnosed metabolic disease is considered in the emergency department and preferably before initiation of any therapy. For adrenal insufficiency and CAH, additional blood studies to consider include cortisol, ACTH, 17-hydroxyprogesterone, aldosterone, renin, insulin, and growth hormone. For organic acidemias and other defects in amino acid and fatty acid metabolism, quantitative blood amino acids and urinary amino and organic acids will aid in definitive diagnosis. Although these tests are nonemergent, the emergency department physician may on occasion be requested to order these studies by a consultant.

Most symptomatic patients with a known or suspected metabolic disorder will require hospitalization, usually in an intensive care setting for frequent monitoring of metabolic parameters and neurologic status. Prompt consultation should be initiated with a pediatric endocrinologist or metabolic specialist. If appropriate resources are unavailable, transfer should be arranged with a pediatric center skilled in managing metabolic disorders. This transfer should be done expeditiously after resuscitation and empiric treatment for likely causes have been started.

In the event of a failed resuscitation or imminent death in a patient with a suspected IEM, permission for autopsy and specimen testing should be thoughtfully discussed with the parents. Perimortem samples to consider

obtaining include frozen blood, plasma, and urine specimens, a skin biopsy, and a needle liver biopsy [28,31]. These studies will allow for appropriate genetic counseling for current family members and future siblings.

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