The Emergency Department Approach to Newborn and Childhood Metabolic Crisis

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For most emergency medicine physicians, the phrases “newborn workup” and “metabolic disease” are, at best, uncomfortable. This article, however, provides a simple approach to the recognition, evaluation, and treatment of infants with all manners of metabolic issues, including hypoglycemia, inborn errors of metabolism, jaundice, and electrolyte abnormalities. The disorders are grouped based on symptomatology, and have simple guidelines for work-up and management, with an emergency department practitioner perspective in mind.

The workup of a newborn with metabolic disease in the emergency department (ED) is a daunting endeavor for any physician. This article provides a simple approach to the recognition, evaluation, and treatment of infants with all manner of metabolic issues, including hypoglycemia, inborn errors of metabolism, jaundice, and electrolyte abnormalities.

Hypoglycemia

Definition

For years, the definition of hypoglycemia in neonates has varied widely, with some authors accepting a blood glucose of 30 mg/dL, while other sources change thresholds as an infant progresses through the first few days of life. More recently, neonatologists have accepted plasma glucose levels <45 mg/dL as a clear indication of hypoglycemia in any symptomatic

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neonate. In asymptomatic neonates, serum glucose \( \leq 35 \) is considered an indication for treatment and close monitoring [1]. This change in thinking is predicated on several recent studies looking at neurologic outcomes of neonates with low glucose. Lucas [2] retrospectively showed poor intellectual performance in 18-month-old ex-premature babies who had been persistently below a serum glucose of 47 mg/dL as neonates. In 1999, Kinnala [3] observed abnormal cerebral magnetic resonance images and cranial ultrasounds at 2 months of age in 39% of otherwise well full-term neonates with blood glucose below 45 mg/dL versus 10% of euglycemic infants. Abnormal evoked potentials have also been measured in this population [4]. Because presentation to an ED selects for ill neonates, some of whom will have poor neurologic outcomes despite the most expeditious treatment, setting 45 mg/dL (2.5 mmol/L) as the threshold for hypoglycemia in all neonates is probably safest [5]. As reagent strips designed for rapid bedside glucose testing are widely variable in performance for this indication [6], the definition of hypoglycemia relies on confirmation by laboratory measurement of the serum glucose.

**Physiology**

Neonates are generally born with a serum glucose of 60% to 80% of maternal glucose. Within 2 to 4 hours, they stabilize and begin to regulate themselves. Maintenance of serum glucose requires the interplay of several systems. As the primary regulator, insulin stimulates the uptake of glucose by cells. Its counterregulatory hormones, specifically cortisol, glucagon, epinephrine, and growth hormone, are prevalent in times of starvation to encourage glycogenolysis and lipolysis. The liver both synthesizes glucose from amino acids, glycerol, and lactate, and converts glycogen to glucose during fasting. When compared with adults, infants have decreased glycogen stores and poorly matured glycogenolysis [7]. In the normal well-nourished neonate, by 2 to 3 hours following a meal, insulin is suppressed and counterregulatory hormones are high. By 12 to 16 hours of fasting, the hepatic stores are depleted, and muscle and adipose begin to break down. Muscle can use its own glycogen stores during fasting, and although the glucose created is not released systemically, amino acids are released to the liver [8].

**Emergency department presentation**

Symptoms of hypoglycemia fall into two major categories: adrenergic and neuroglycopenic. Adults manifest high adrenergic tone as palpitations, anxiety, tremulousness, and diaphoresis, and neuroglycopenic symptoms as headache, fatigue, confusion, seizure, and unconsciousness. Neonates present similarly, but often translate the symptoms reported by adults into more subtle clues, such as jitteriness, tachycardia, apnea, cyanosis, tachypnea, hypotonia, temperature instability, lethargy, irritability, or an abnormal cry. Also, secondary hypoglycemia may be a concern for
children presenting in extremis, regardless of etiology. In these children, signs of respiratory or cardiac failure may be attributed to the primary illness, leaving the hypoglycemia unrecognized. In one study, 9 of 49 children requiring resuscitative care for a medical condition exhibited hypoglycemia, suggesting glucose should be checked promptly on every patient requiring emergent resuscitation. The mortality in children with secondary hypoglycemia is higher than in nonhypoglycemia children with matched diagnoses [9].

*Differential diagnosis*

Primary hypoglycemia has an extensive differential, and the definitive underlying diagnosis is not the role of the emergency physician. However, low glucose may indicate another condition, like sepsis, requiring emergent diagnosis and attention. More commonly, the emergentologist has a unique opportunity to facilitate the workup of a hypoglycemic child. Insulin, cortisol, and growth hormone levels must be obtained while a child is hypoglycemic. If they are not drawn before treatment in the ED, a child will be subjected to the risks and discomfort of prolonged fasting in the hospital to replicate the hypoglycemia. Obviously, no reasonable physician would leave a seizing child untreated while an extensive workup is completed, but setting aside an additional red top tube before the administration of glucose may greatly assist the pediatrician or endocrinologist who assumes care.

Once the child is stabilized, a differential can be formed based on the presence of urinary ketones and the child’s response to treatment. Ketones require lipolysis, which is suppressed by insulin and stimulated by the counterregulatory hormones. Therefore, diseases involving high levels of insulin production generally do not allow the formation of ketones. The quintessential disease in this category is hyperinsulinism from islet cell adenomas or overproduction, which can present either in the neonatal period or later in life. Although uncommon to see in a child returning to the ED after a hospital birth, infants of diabetic mothers have similar overproduction of insulin during the first 24 hours. Due to the lack of counterregulatory hormones, congenital panhypopituitarism may cause hypoglycemia, and is generally nonketotic (although individual hormone deficiencies may cause ketosis). Adrenal insufficiency, most commonly in the form of congenital adrenal hyperplasia (CAH), can cause a hyperinsulinism as well. Fatty acid oxidation deficiencies rarely present in the first month of life, but may cause a nonketotic hypoglycemia [10]. Finally, a rare condition known as Beckwith-Wiedemann can cause hyperinsulinism, and is usually recognized by hemihypertrophy of the patient’s body and internal organs. Most of the nonketotic forms of hypoglycemia involve an inability of the body to produce glucose and other forms of energy despite appropriate glycogen storage. Therefore, glucagon has an important diagnostic and therapeutic role. If it is effective in
normalizing serum glucose, this confirms that hepatic energy stores are present, suggesting one of these diagnoses.

On the other hand, children with ketotic hypoglycemia often lack the glycogen stores to respond to glucagon [11]. Children who are thin, when subjected to prolonged fasting or gastroenteritis, can easily become hypoglycemic. In fact, simple ketotic hypoglycemia from fasting is the most common etiology in a nondiabetic child. One study showed this to account for 24.4% of episodes of hypoglycemia presenting to the ED in nondiabetic children over 6 months [12]. Of course, there are more serious etiologies for a ketotic hypoglycemia, and metabolic diseases such as galactosemia, hereditary fructose intolerance, and glycogen storage disease type 1 should be considered in a neonate who appears ill or has abnormal physical findings like hepatomegaly [13].

Common secondary reasons for hypoglycemia include ingestions (ethanol, insulin, oral hypoglycemia, salicylates, and propranolol), liver failure [14], and sepsis. One study of septic neonates demonstrated hypoglycemia in 20 of 56 babies, suggesting prompt diagnosis and treatment of hypoglycemia is warranted in this population [15].

Infants born in the department

Early discharge of neonates has been a convenient and cost-effective measure, but increases the likelihood of a 1- to 2-day-old hypoglycemia infant presenting, undiagnosed, to the ED. Even without this consideration, many of us have witnessed the “virginal” teen with abdominal pain give birth in the department, and the risk factors for hypoglycemia in these children must be discussed. Of paramount importance is to recognize the symptoms of hypoglycemia. The unexpected birth of a child in the department can cause significant stress, particularly if the baby is not doing well. Any concern of respiratory difficulty, vital sign instability, or neurologic findings should prompt performance of a bedside glucose.

Infants of diabetic mothers have a significant risk of early hypoglycemia—most sources quote 25% [17], but in one study 47% of infants of diabetic mothers developed hypoglycemia in the first 2 hours of life [18]. The glucose crossing the placental barrier causes hypertrophy of the islet cells, which continues for 24 hours following birth [17]. Large-for-gestational-age babies, even without maternal diabetes, may have sufficient hyperinsulinism to become hypoglycemic [7]. On the opposite end of the spectrum, premature or small-for-gestational-age babies can lack the stores to maintain their glucose. Transient hyperinsulinism without predisposing factors is rare, but has been reported [19]. Maternal factors, such as use of sympathomimetic medications, may also cause low blood sugar in the neonate [16]. If proper incubators and warming lights are not used, the cold stress alone can cause the glucose to plummet. Many of these children will not become hypoglycemic until 2 to 4 hours after birth. Therefore, if awaiting a bed or a transfer requires a high-risk
neonate to remain in the ED for several hours, a repeat assessment and bedside glucose is warranted, even in the absence of symptoms, and certainly immediately if symptoms develop.

Emergency department evaluation

As previously stated, hypoglycemia is a symptom, rather than a diagnosis. The hypoglycemia may be suggested on a bedside glucose, and confirmed by a laboratory run serum glucose, but additional labs can confirm the etiology. A minimum workup includes serum glucose, growth hormone, insulin level, cortisol, and ketones obtained while the patient is hypoglycemia. A urinalysis can give an early indication regarding the presence of ketones, as the serum ketones may take hours to run. Electrolytes are indicated, although mild acidosis is often associated with hypoglycemia and will correct without intervention. A more significant acidosis may be due to ketosis or may indicate the presence of lactic acid from sepsis or metabolic diseases [11]. Second tier tests that may be ordered from the ED or later include lactate, free fatty acids, ammonia, acylcarnitine, organic acid profiles.

Emergency department management

Significant alterations in mental status may resolve slowly, even after the child has been given adequate glucose [8]. For children in whom intravenous (IV) access cannot be obtained, oral or nasogastric glucose is an option, as is intramuscular glucagon. Once IV access is obtained, a small bolus 0.25 to 0.5 g/kg of dextrose should be administered. Neonatologists would suggest administering this as 2 to 4 mL/kg of D$_{10}$, but D$_{25}$ is likely also safe if the IV is secure in a large vein at a dose of 1 to 2 mL/kg. The bolus should be followed by an infusion, and generally a D$_{10}$ with 0.2NS drip at 1.5 times maintenance [8] will provide 6 to 8 mg/kg/min, which is a physiologic glucose delivery rate. Clearly, hyperinsulinemic or ill neonates may require a higher glucose delivery rate. If a concentration above D$_{12.5}$ is required to maintain the blood glucose, central access should be obtained. If the hypoglycemia is refractory to glucose administration, glucagon, a pancreatic polypeptide hormone [20], may be administered, and may be followed 1 hour later by hydrocortisone. However, these modalities require substrate and, therefore, are unlikely to work in a patient with ketotic hypoglycemia, or in the absence of simultaneous IV glucose. If a patient responds to glucagon transiently, an IV glucagon drip has been proven effective in the glucagon-responsive neonate [21,22]. Diazoxide or an octreotide drip may also work for hyperinsulinism-induced hypoglycemia [14]. Clearly, if an underlying disease is suspected, it should be treated as well, with attention to antibiotics if sepsis is suspected, and to hormone replacement if panhypopituitarism or CAH are possible. These treatments are summarized in Table 1.
Goals of treatment are markedly different than definitions of hypoglycemia. For an otherwise well baby requiring treatment, a level of \(45 \text{ mg/dL}\) is acceptable [1]. For a child with other incurrent medical issues, prematurity, or suspected hyperinsulinism, maintenance of glucose between 72 to 90 mg/dL is prudent [6].

**Disposition**

Clearly, most patients with hypoglycemia will require admission, either to the floor, or to a more monitored setting if frequent neurologic checks or bedside glucose checks are required. In a healthy older child with ketotic hypoglycemia, disposition home is acceptable once the hypoglycemia resolves and the child is taking food well [14]. In a neonate, however, admission for further workup and observation is indicated.

**Long term**

As previously mentioned, hypoglycemia in the early neonatal period can have devastating long-term neurologic consequences, particularly when symptomatic, prolonged, or early in onset. Hyperinsulinism as a cause of hypoglycemia may also be a risk factor for poor neurologic outcome. In one study, 52% of patients requiring subtotal pancreatectomy for hyperinsulinemia suffered mental retardation [25]. Meissner also demonstrated a poorer outcome in the hyperinsulinemic children with neonatal onset of hypoglycemia than in those with an onset later in childhood [26].

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**Table 1**  
**Treatment for hypoglycemia**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Indication</th>
<th>Route</th>
<th>Dose</th>
<th>Maximum (adult) dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dextrose</td>
<td>Hypoglycemia</td>
<td>IV</td>
<td>0.25–0.5 g/kg given as 1–2 cc/kg D25 or 2–4 cc/kg D10</td>
<td>25 g (1 amp)</td>
</tr>
<tr>
<td>Glucagon</td>
<td>Nonketotic hypoglycemia</td>
<td>IV or IM</td>
<td>0.03 mg/kg</td>
<td>1 mg</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>Suspected hormone deficiency without shock</td>
<td>IV or IM</td>
<td>1–2 mg/kg (shock dose is higher)</td>
<td>100 mg</td>
</tr>
<tr>
<td>Diazoxide</td>
<td>Hyperinsulinemia</td>
<td>PO</td>
<td>5 mg/kg/dose</td>
<td>150 mg</td>
</tr>
<tr>
<td>Octreotide</td>
<td>Hyperinsulinemia</td>
<td>SC or IV</td>
<td>1 µg/kg bolus followed by 1 µg/kg/h infusion</td>
<td>100 µg</td>
</tr>
</tbody>
</table>

study of 90 patients with persistent hyperinsulinemic hypoglycemia, seven patients had severe mental retardation, 12 patients had intermediate delay, and 16 had epilepsy. Early onset of neonatal hypoglycemia was highly correlated with these outcomes [27].

**Inborn errors of metabolism**

Whether due to the large variety of diseases or the intricacy of the biochemical pathways, studying inborn errors of metabolism is daunting. Yet despite their seeming complexity, an emergency physician or pediatrician can easily care for these children by remembering several basic underlying principals. The hundreds of specific diseases involved generally cause symptoms by three major mechanisms of illness: (1) the acute accumulation of toxic small molecules, (2) energy deficiency, or (3) the chronic accumulation of large molecules. These are summarized in Table 2. With some overlapping and exceptions, these different mechanisms lead to three different categories of presenting signs, abnormalities on diagnostic testing, and treatment modalities. All these disorders have in common that each is caused by a genetic mutation that disables a protein, resulting in a blocked metabolic pathway. The defective proteins are generally enzymes, although increasingly defects in proteins involved in crossmembrane transport, assembly, and cofactor maintenance are being identified as the cause of various metabolic disorders. Inborn errors of metabolism can present in older children, but this article will address the inborn errors of metabolism that commonly present in the neonatal period.

**Emergency department presentation**

Defects in enzymes/proteins involved in small molecule catabolism generally cause disease due to a toxic intermediate that accumulates at high concentration because of the metabolic block. Pathology does not begin until after birth because the placenta easily removes these small molecules. When enzymatic function is absent or minimal, these toxic intermediates can accumulate rapidly, and reach concentrations sufficient to cause disease generally between the second and fifth postnatal days [28]. Many, but not all, of these disorders involve the catabolic pathway of one or more amino acids (“aminoacidemias/urias” or “organicacidemias/urias”), and the accumulating toxic intermediates are acids. Thus, severe metabolic acidosis is a feature common to many of these disorders. Hyperpnea/tachypnea can be secondary to metabolic acidosis or hyperammonemia, which is also commonly present. Many, but not all, of these toxic intermediates cause acute neurologic dysfunction, and thus altered mental status (irritability or lethargy) and vomiting are frequently the presenting signs of early illness. Altered mental status and vomiting interfere with feeding, leading to
<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Classes of disorder</th>
<th>Examples</th>
<th>Signs</th>
<th>Labs</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxic small molecules</td>
<td>Organic and amino acidemias</td>
<td>Methylmalonic acidemia, propionic acidemia, maple syrup urine disease</td>
<td>Altered mental status (irritability, lethargy, coma), poor feeding, vomiting, neurologic symptoms, hyperpnea/tachypnea, Frequently present at age 2–5 days</td>
<td>Anion gap acidosis, ketonuria, increased ammonia, uric acid, and lactate, low glucose (rare)</td>
<td>NPO IV glucose, L-carnitine, Insulin HD Liver transplantation</td>
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<tr>
<td>Urea cycle disorders</td>
<td></td>
<td>Citrullinemia, ornithine transcarbamoylase deficiency</td>
<td>Elevated ammonia, respiratory alkalosis</td>
<td></td>
<td>NPO IV glucose, L-arginine (some disorders) Na benzoate, Na phenylacetate and/or Na phenylbutyrate^a Insulin HD</td>
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<tr>
<td>Sugar intolerances</td>
<td>Galactosemia</td>
<td>Liver failure with jaundice hemorrhage, ascites, and edema</td>
<td>Elevated transaminases and bilirubin, low glucose, coagulopathy</td>
<td></td>
<td>NPO IV glucose, Antibiotics</td>
</tr>
<tr>
<td>Exceptions (amino acidemias with distinct presentations)</td>
<td>Nonketotic hyperglycinemia</td>
<td>Lethargy, apnea, Hypoventilation, and seizures in the first week</td>
<td>Elevated CSF to peripheral glycine ratio</td>
<td>None effective</td>
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</tr>
<tr>
<td>Tyrosinemia Type 1</td>
<td>Liver failure at 2 months hepatomegaly at 3 weeks</td>
<td>Liver failure</td>
<td>NTBC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Energy deficiency</td>
<td>Mitochondrial disorders</td>
<td>Electron transport chain and related disorders</td>
<td>Neurological dysfunction, seizures, hepatomegaly cardiomyopathy, birth defects</td>
<td>Metabolic acidosis, elevated lactate, LFTs may be abnormal</td>
<td>IV glucose L-carnitine</td>
</tr>
<tr>
<td>Storage disorders</td>
<td>Lysosomal disorders</td>
<td>Gaucher disease Hurler syndrome</td>
<td>Progressive neurologic disease, hepatosplenomegaly, coarse facies, Skeletal dysplasia</td>
<td>Specific enzymatic tests for disease, biopsy, urine mucopoly and oligosacrides</td>
<td>Increasingly enzyme replacement, bone marrow transplantation</td>
</tr>
<tr>
<td>Peroxisomal disorders</td>
<td>Zellweger syndrome</td>
<td></td>
<td></td>
<td>Very long chain fatty acids</td>
<td>None effective</td>
</tr>
</tbody>
</table>

**Abbreviations:** NPO, non per os; NTBC, 2-nitro-4-trifluoromethylbenzoyl-1, 3 cyclohexanedione.

*are often used for the hyperammonemia of organic and aminoacidemias as well, but are not approved for that indication.*

*From Refs. [28,31,32,35,36].*
a fasting-induced catabolic state. The resultant release of endogenous amino acids, which also cannot be metabolized, creates a cycle of acidosis and neurologic dysfunction that rapidly leads to coma, multisystem failure, and death in the absence of appropriate treatment.

It is not uncommon for these same disorders to present later in life. Milder degrees of enzymatic dysfunction may not present until prolonged fasting results in a sufficient degree of catabolism. Although these “late-onset” disorders can present at any time from the second month through adulthood, the most common presentation is in toddlers with common viral illnesses, especially gastroenteritis. The clinical signs and laboratory features are identical to the early-onset varieties, except that the patient is older and there are generally signs and symptoms of a viral infection with associated fasting. As intravenous glucose-containing fluids are both part of routine emergency management and the mainstay of therapy for these disorders, a child may be successfully treated without the presence of the metabolic disorder being revealed. These children sometimes suffer many such episodes of acute encephalopathy associated with subsequent viral infections.

There are exceptions in which, toxic small molecules accumulate rapidly after birth, yet they cause damage only slowly over months and years. Thus, these disorders generally present at some point after the neonatal period. A classic example is phenylketonuria, in which the accumulating metabolite, phenylalanine, is neurotoxic, resulting in mental retardation. In another example caused by a block further down in the same metabolic pathway, several hepatotoxic intermediates accumulate in tyrosinemia type 1, resulting in liver failure that occurs at about age 2 months in the early-onset variety, or at any age thereafter in the later onset varieties.

High-energy phosphates such as adenosine triphosphate cannot cross membranes, and thus fetuses with disorders of energy metabolism (“mitochondrial disorders”) are not protected by the placenta and can present prenatally (eg, birth defects, dysmorphic facies, Intrauterine growth retardation) or immediately after birth without a symptom-free period. Although mitochondrial disorders are highly complex in terms of their genetics, treatment, prognosis, diagnosis, and pathophysiology, those individuals presenting as neonates generally have autosomal recessive inheritance, an ultimately fatal prognosis, and are characterized by severe lactic acidosis and multisystem failure. Seizures, cardiomyopathy, and hepatocellular disease are common hallmarks.

Finally, the chronic accumulation of large molecules (“lysosomal storage disorders”) results in a progressive disease burden related to the volume of stored material. Clinical manifestations depend on what tissues preferentially accumulate the stored material, and how quickly this material is stored. Again, as large molecules cannot cross membranes, storage begins prenatally and disease may be apparent at birth or soon thereafter [29]. Storage predominately in connective tissues results in some combination of coarse facial features, joint contractures, cardiac valvular disease, and
cataracts. Storage predominately in the brain often results in the failure to achieve or a loss in acquired milestones, or leukodystrophy noted by magnetic resonance imaging. The lysosomal storage disorders rarely present emergently; therefore, the remaining sections concentrate on disorders in the other two previously mentioned categories.

Common to many specific diseases in all three metabolic disorder categories are neurologic signs such as seizures, apnea, hyperventilation, opisthotonus [30], stroke (often of the basal ganglia with resultant dysatonia), and abnormal tone (frequently central hypotonia possibly with peripheral spasticity). Abnormal odors, from that of maple syrup to smelly socks, have also been associated with some of the metabolic disorders of small molecule and energy metabolism [30]. Abnormal odor can be very helpful when present, but is an infrequent occurrence. Almost all of the metabolic disorders are autosomal recessive; thus, a history of consanguinity or affected siblings (including unexplained early death) certainly helps support the suspicion of a metabolic disorder. However, most children with metabolic disease have a completely noncontributory family history.

Differential diagnosis

Most metabolic disorders are initially misdiagnosed as sepsis [31], as the presentations can be difficult to distinguish. Vital sign abnormalities are similar, with metabolic patients often demonstrating a low core temperature [32,33], an elevated heart rate (due to dehydration), and a rapid respiratory rate (due to acidosis or hyperammonemia). In a metabolic disorder, however, the alteration in mental status far outweighs other signs early on, and a child is more likely to present comatose, but with a preserved blood pressure. Previous episodes of culture negative “rule-out sepsis” may provide an additional clue to an inborn error of metabolism. Certainly, the coexistence of sepsis and a metabolic disorder is not a rare phenomenon: in many metabolic disorders clinical disease is triggered by either a viral or a bacterial infection, and certain disorders, quintessentially galactosemia, are frequently associated with sepsis [8]. Therefore, ill-appearing neonates should be fully cultured and given antibiotics, even in light of a suspected metabolic disorder [30]. Many of these children present with hyperventilation or apnea; thus, pneumonia and other respiratory conditions must be considered. Additionally, hypoxia, hypoglycemia, child abuse with intracranial hemorrhage, electrolyte disturbances, CAH, seizure disorders, gastrointestinal catastrophe (eg, malrotation), and congenital cardiac disease should all be considered in the acutely ill neonate.

Emergency department evaluation

Each disorder has specific associated laboratory abnormalities, and these are listed in Table 3. In the ED, when metabolic disease is suspected, or
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Causes of decompensation</th>
<th>Signs and symptoms</th>
<th>Labs</th>
<th>Treatment following stabilization with glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 Glycogen Storage Disorder</td>
<td>Period of brief fasting</td>
<td>Growth failure, hepatomegaly</td>
<td>Lactic acidosis</td>
<td>Frequent feedings, cornstarch</td>
</tr>
<tr>
<td>Galactosemia</td>
<td>Often postprandial hypoglycemia (from galactose-containing foods)</td>
<td>Jaundice, vomiting, hepatomegaly, Gram-negative sepsis, cataracts</td>
<td>Hyperuricemia, Positive urine for reducing substances</td>
<td>Stop formula or breast feeding</td>
</tr>
<tr>
<td>Hereditary fructose intolerance</td>
<td>Often postprandial hypoglycemia (from fructose-containing foods)</td>
<td>Vomiting, poor feeding, hepatomegaly, jaundice</td>
<td>Nongap acidosis, proteinuria</td>
<td>Avoidance of fructose or sucrose in diet</td>
</tr>
<tr>
<td>Disorders of fatty chain metabolism</td>
<td>Rarely symptomatic before 6 months unless prolonged fasting or infection</td>
<td>Reye-like syndrome, Sudden death (SIDS) AMS ± Hepatomegaly, heart failure</td>
<td>Rarely ketotic Send organic acids and acylcarnitines</td>
<td>Carnitine Avoid fasting</td>
</tr>
<tr>
<td>Ketotic hypoglycemia</td>
<td>Often in thin child with recurrent illness; usually in ages 1–5 years</td>
<td>Evidence of gastroenteritis or upper respiratory infection with po intolerance (or water only)</td>
<td>Positive urine and serum ketones</td>
<td>po or IV glucose, depending on mental status and ability to take pos</td>
</tr>
<tr>
<td>Condition</td>
<td>Physiology</td>
<td>Clinical Features</td>
<td>Management</td>
<td></td>
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<tr>
<td>Hyperinsulinism</td>
<td>Postprandial</td>
<td>May be familial (AR)</td>
<td>No ketones Elevated insulin level</td>
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<tr>
<td>(B-cell regulatory defect)</td>
<td></td>
<td></td>
<td>Glucagon,</td>
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<td></td>
<td></td>
<td></td>
<td>Hydrocortisone,</td>
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<td></td>
<td></td>
<td></td>
<td>diazoxide or octreotide,</td>
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<td></td>
<td></td>
<td></td>
<td>Surgery</td>
<td></td>
</tr>
<tr>
<td>Congenital hypopituitarism</td>
<td>Lack of counterregulatory hormones following insulin release</td>
<td>Microphallus, midline facial defects, mixed hyperbilirubinemia</td>
<td>± ketones</td>
<td></td>
</tr>
<tr>
<td>(component hormone deficiency)</td>
<td></td>
<td></td>
<td>Glucagon, steroids; hormone replacement</td>
<td></td>
</tr>
<tr>
<td>CAH</td>
<td>Hypoglycemia is due to cortisol deficiency</td>
<td>Females may be virilized, vomiting</td>
<td>May be hyponatremic, hyperkalemic ± ketones</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Steroids, treat electrolyte disturbances,</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hydration</td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Unless central, should be noted on newborn screen</td>
<td>Prolonged jaundice</td>
<td>± ketones Low T4</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Levothyroxine</td>
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</tr>
</tbody>
</table>

**Abbreviations:** AR, autosomal recessive; AMS, altered mental status; CAH, congenital adrenal hyperplasia; SIDS, sudden infant death syndrome. 
*From* Refs. [10,11,16].
when it is only one of many conditions on a differential diagnosis, the following widely available and relatively inexpensive laboratory tests can serve as a reasonable screening battery: electrolytes, urea nitrogen, creatinine, glucose, blood gas (can be venous), complete blood count (CBC), ammonia and possibly lactate, and urine dip stick for ketones and specific gravity. In some cases, alanine aminotranserase (ALT), bilirubin, albumin, or prothrombin time are helpful to evaluate liver function. A creatinine kinase (CK) can confirm a clinical suspicion of myopathy. If infection is in the differential, add a routine urinalysis and blood and urine cultures. Ammonia and lactate must be collected as free flowing blood without prolonged tourniquet time, and immediately placed on ice and run within 90 minutes by the laboratory [34]. Capillary blood is not acceptable [35]. Specific disorders associated with laboratory abnormalities are listed in Table 4.

The most sensitive and specific single sign of metabolic crisis due to an organic acidemia is an increase in the serum anion gap. Although mild to moderate degrees of dehydration may result in an anion gap of 16 to 17, possibly as high as 20, an anion gap above 20 is highly abnormal, with shock, diabetic ketoacidosis, renal failure, poisoning, and metabolic disease being the principal causes. Shock can be of any variety (hypovolemic, cardiogenic, septic, and so on), and shock resulting in a highly elevated anion gap should be clinically obvious. Most of the other conditions in the differential can be generally excluded by history, and blood glucose and creatinine determination, leaving only metabolic disease and cryptic poisoning as serious contenders.

An elevated ammonia (generally at least three to five times the upper range of normal, or > 150–200 micromolar) is the hallmark of an inborn error of the urea cycle. The most common presentation is a 2- to 5-day-old male who did well for the first few days of life, then developed the poor feeding, vomiting, and neurologic signs seen with significant hyperammonemia. Males are primarily affected by the X-linked disorder ornithine transcarbamylase deficiency, but both genders are affected equally by each of the other urea cycle defects. However, as acidosis from any cause results in a nonspecific downregulation of the urea cycle, hyperammonemia is frequently present in many organic acidemias as well, and can be just as severe.

Much as been written about “inappropriate ketosis” being a sign of a metabolic disorder. Although this is complicated and there are exceptions, large ketones in the first 12 hours of fasting is not normal, and is suggestive of an organic acidemia, while the absence of ketosis with frank hypoglycemia is suggestive of a fatty acid oxidation disorder. The latter group of disorders is not covered in this article, as presentation in the neonatal period is rare. Although hypoglycemia can be seen in many metabolic disorders, particularly late in the course, normoglycemia is more common, and the absence of hypoglycemia should never be used to exclude the presence of metabolic disease.
<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Likely metabolic disorder</th>
<th>Other considerations</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anion gap acidosis</td>
<td>Organic/amino acidemia, Fatty acid oxidation disorder, mitochondrial disease</td>
<td>Shock (extreme dehydration, bleeding, cardiac failure, hypoxia, sepsis, etc.), poisoning, DKA, renal failure</td>
<td>Tissue hypoxia without metabolic disease produces acidosis without urinary ketones. However, ketones may be present simply as an effect of fasting</td>
</tr>
<tr>
<td>Urinary ketones</td>
<td>Organic/amino acidemia, mitochondrial disease</td>
<td>Starvation DKA poisoning</td>
<td>Trace ketones in neonate who has not eaten for hours can be normal. Lab dependent, but often: normal &lt;50 concerning &gt;80 Ill or asphyxiated neonate up to 180 likely metabolic disease &gt;200 (early presentations may be lower)</td>
</tr>
<tr>
<td>Elevated ammonia</td>
<td>Urea cycle disorder, organic acidemia, fatty acid oxidation deficiency</td>
<td>Primary liver disease, shock of any cause, Inappropriate collection, transient hyperammonemia of the neonate</td>
<td>Lab dependent, but often: normal &lt;50 concerning &gt;80 Ill or asphyxiated neonate up to 180 likely metabolic disease &gt;200 (early presentations may be lower)</td>
</tr>
<tr>
<td>Liver failure /dysfunction</td>
<td>Tyrosinemia type 1, galactosemia, hereditary fructose intolerance, glycogen storage disease, Hemochromatosis, Zellweger, rare mitochondrial disorders</td>
<td>Primary liver disease, sepsis</td>
<td>Nonglucose reducing substances in carbohydrate disorders</td>
</tr>
<tr>
<td>Respiratory alkalosis</td>
<td>Urea cycle defect</td>
<td>Agitated neonate Aspirin overdose</td>
<td>May become neutropenic only during times of crisis</td>
</tr>
<tr>
<td>Neutropenia and/or thrombocytopenia</td>
<td>Methylmalonic and propionic acidemia, glycogen storage disorder 1b, some mitochondrial disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated CK</td>
<td>Glycogen storage disorders, fatty acid oxidation disorders, mitochondrial disorders</td>
<td></td>
<td>Is evidence of myopathy, aldolase may also be affected</td>
</tr>
</tbody>
</table>

*Abbreviation: DKA, diabetic ketoacidosis.*
In the absence of an associated infection, the CBC is frequently normal, but certain disorders can have an associated neutropenia or thrombocytopenia [32]. Tests of liver function frequently are mildly abnormal in the acute phase of many different metabolic disorders. Hepatocellular dysfunction can also be the result of a metabolic disorder. Of course, primary liver disease of any cause can result in hyperammonemia. Elevated muscle enzymes such as CK or aldolase can confirm myopathy.

Although confirmation of the specific metabolic diagnosis is not the role of the emergency physician, there are advantages to collecting specimens in the emergency department. Not only is early diagnosis helpful [35,37], but occasionally the definitive diagnostic test (ie, urine organic acids) is only positive when the child is acutely decompensated. Therefore, at a minimum it is recommended that urine and plasma be collected in the ED and frozen for potential future testing. Whole blood should not be frozen.

Emergency department management

Early treatment involves the withdrawal of potentially toxic substances, typically meaning stopping breast milk or formula, and the administration of intravenous dextrose. As the mainstay of therapy, dextrose infusions provide energy as well as result in an endogenous insulin excretion that combats catabolism. A standard intravenous order that is applicable to most metabolic disorders and clinical conditions is 10% dextrose in 0.2 normal saline to run at 1.5 times maintenance. If the patient is clearly dehydrated or in hypovolemic shock, a normal saline bolus can be run concurrently through a “Y” connector or a second line. Do not stop the dextrose infusion to give a normal saline bolus. Another option is to give 10 cc/kg of D5NS over 30 to 60 minutes, which provides volume as well as a moderate dextrose infusion. However, unless shock is present, the bulk of rehydration should be done slowly, over 48 hours, to prevent cerebral edema. Cerebral edema is frequently present even before treatment, and care must be taken not to overwhelm the infant with fluid or sodium. Highly concentrated dextrose solutions given through central access is a strategy often successfully employed to provide large quantities or dextrose without resulting in cerebral or pulmonary edema. Because many of the adjunctive treatments involve large doses of sodium containing medicines, a lower concentration of sodium is often preferred in the rehydration fluid (0.2 normal saline). Bicarbonate, if required, should be used sparingly to prevent cerebral edema and hemorrhage [30]. Some patients may need additional stabilizing care, such as intubation for apnea, or correction of hypoglycemia (2–4 cc/kg of 10% dextrose) as well.

In critical patients, simultaneous insulin and dextrose drips may be beneficial in terminating catabolism rapidly and reversing metabolic acidosis and hyperammonemia. Clinical experience suggests starting at 0.05 units/kg/h of insulin and 10 mg/kg/min of glucose, and titrate both upwards,
frequently obtaining rapid blood glucose measurements, until the patient is on 0.1 to 0.2 units/kg/h of insulin, and about 8 to 12 mg/kg/min of glucose. In the converse of the logic employed in the treatment of diabetic ketoacidosis, in critical metabolic decompensation the glucose infusion is titrated to maintain the desired insulin dosage. The goal is to achieve a serum glucose between 120 to 170 mg/dL [33]. If protein-containing feedings have been not tolerated or withheld for greater than about 48 to 72 hours, essential amino acid deficiency can result in a catabolic state regardless of the dextrose infusion, yet will respond to about 0.5 to 0.7 g/kg/d of amino acids delivered in hyperalimentation.

Toxic metabolites, specifically ammonia, can generally be removed pharmacologically with sodium benzoate, sodium phenylacetate, or sodium phenylbutyrate. The intravenous form of these medications are only approved for urea cycle defects, but acutely should be administered in the presence of severe hyperammonemia until the etiology is determined. Symptoms of hyperammonemia generally occur at a level three to five times normal, and this is also a reasonable threshold for hospitalization and directed treatment [37]. If pharmacologic treatment fails and the patient’s ammonia remains greater than 10 times normal, hemodialysis should be considered. Peritoneal dialysis, although much easier in this age group, is less effective [32].

Administration of cofactors may be helpful, and should be done under the guidance of a consulting metabolic specialist, particularly if the specific metabolic disorder is not yet known. If a metabolic specialist is not available, L-carnitine may be beneficial [3], and is highly unlikely to cause harm. Until infection is excluded, antibiotics, generally ampicillin and either cefotaxime or gentamicin, should be administered. Indications and dosing of common medications are listed in Table 5.

Treatment of children with a known metabolic disorder

For several disorders, special synthetic formulas are used to restrict the precursors of the defective enzyme to the minimal intake needed to promote normal growth. The resultant diets are highly unpalatable, and noncompliance by ingesting either too little or too much can result in metabolic decompensation and substantial morbidity. In particular, children with inborn errors of metabolism are highly dependent on maintaining their caloric intake, and any intercurrent illness that causes the refusal or the inability to eat can precipitate a crisis [31]. During viral illnesses, patients are commonly instructed to take a sick-day regimen of protein free juices at home for 24 to 48 hours [38], and to monitor their mental status and urinary ketones by dipsticks. Altered mental status, vomiting, or other feeding intolerance, or “large” ketones (80 or greater) are indications for evaluation by a physician. If the child presents to the ED, several hours of 1.5 times maintenance with 10% dextrose in 0.2 normal saline may avert the crisis and return the patient’s anion gap and
urine ketones to normal; hyperammonemia corrects slowly over multiple hours. Antiemetics, especially phenothiazines, which may alter mental status should be used with caution, but the administration of ondansetron may allow a patient to tolerate oral intake. However, if the patient has acute neurologic signs or laboratory abnormalities that persist or worsen, or the child remains unable to take the appropriate formula, he/she will require hospitalization [39]. Patients with methylmalonic acidemia, propionic acidemia, glycogen storage disease type 1b, and certain mitochondrial disorders require a complete blood count and differential, as they are prone to neutropenia or thrombocytopenia during periods of acute illness. Certain medications, such as valproic acid, haloperidol, or steroids can precipitate hyperammonemia in some children with metabolic disorders and should be used with caution.

Death

Some of these disorders have a mortality as high as 50% with their initial presentation, so it is not uncommon to encounter a patient with a suspected metabolic disorder who dies in the ED or is dead upon arrival [40]. Generally, the cause of death is cardiovascular compromise, arrhythmia, hypoglycemia, pulmonary hemorrhage, or cerebral edema. Some sudden infant death syndrome deaths are thought to be attributable

<table>
<thead>
<tr>
<th>Condition, Medication</th>
<th>Route</th>
<th>Dose</th>
<th>Caution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most conditions, L-carnitine</td>
<td>IV/PO</td>
<td>100 mg/kg/d</td>
<td></td>
</tr>
<tr>
<td>Hyperammonemia, Sodium benzoate</td>
<td>IV</td>
<td>0.25 g/kg bolus over 2–4 h, then infusion of 0.25 g/kg over 24 h</td>
<td>Hypernatremia, hypokalemia, acidosis, transient hyperammonemia, confusion, cerebral edema, hypotension</td>
</tr>
<tr>
<td>Citrulinemia, Argininosuccinate lyase deficiency, L-arginine</td>
<td>IV</td>
<td>0.2–0.6 g/kg then infusion of 0.25 g/kg over 24 h</td>
<td>Acidosis, extravasation, can be harmful in some urea cycle disorders</td>
</tr>
<tr>
<td>Biotinidase deficiency, Biotin multiple carboxylase deficiency, Biotin</td>
<td>PO</td>
<td>10 g/d</td>
<td></td>
</tr>
</tbody>
</table>

treatments for metabolic disorders [28]. An autopsy later may be diagnostic, but often body fluids are not available or reliable by the time an autopsy is performed. It is recommended to collect blood and urine for the tests listed in the “workup” section above, plasma amino acids (2 cc, green top heparin sulfate tube), an additional tube of heparinized plasma for freezing, urine organic acids, and additional urine for freezing. In addition, facilitating that an autopsy be performed on the recently deceased infant may allow the family to obtain appropriate genetic counseling and possibly prevent a similar death in a future (or possibly a current) sibling.

**Outlook**

Prognosis varies widely in terms of morbidity, mortality, and cognitive abilities, depending on the specific metabolic defect and the care given. Infants presenting with severe hyperammonemia (generally >1000 micromolar) or prolonged coma (generally >3 days) have a poor long-term neurologic prognosis. Neonatal screening by tandem mass spectroscopy is performed in many states and foreign nations, and despite many false positives and false negatives, can identify a substantial proportion of affected infants with several different metabolic disorders, in some cases before symptom onset, improving outcomes. Liver or bone marrow transplantation has been employed to provide a long-term cure for some metabolic disorders [41]. Enzyme replacement is increasingly being made available for the treatment of lysosomal storage disorders. Gene therapy has not yet been successfully applied toward metabolic disease treatment, but is a future possibility.

**Jaundice**

Hyperbilirubinemia is a very common finding in the newborn, with 60% of newborns having some degree of jaundice [42]. Therefore, ED physicians must be very comfortable with diagnosis and management of newborn hyperbilirubinemia.

**Emergency department presentation**

Most infants will present with parental concerns regarding a change in skin color, but jaundice may be noted first by the physician in the course of treating a dehydrated or ill neonate.

**Pathophysiology**

Bilirubin is produced, via the intermediary metabolite biliverdin in the breakdown of hemoglobin. Initially, bilirubin is soluble in lipids, but not water. In the blood stream, it is albumin bound, and any substrate
competing for binding sites, such as organic acids or drugs, can increase the amount of free bilirubin available. In this unconjugated state, bilirubin is difficult to excrete, and can pass easily into the central nervous system, causing the toxicity known as kernicterus. Bilirubin is then conjugated in the liver, converting it to a water-soluble compound that can be excreted via the biliary or renal tract. Decreased enzyme activity in the liver and low amounts of binding substrate in neonates predispose them to the development of jaundice.

The first step in the evaluation of newborn jaundice is to determine whether the hyperbilirubinemia is unconjugated or conjugated by measurement of the fractionated serum bilirubin. As the further workup, differential diagnosis, and management depends completely upon whether an infant has a pure unconjugated hyperbilirubinemia, or a component of conjugated hyperbilirubinemia, these abnormalities will be discussed independently.

Unconjugated hyperbilirubinemia

Differential diagnosis

Physiologic jaundice refers to the normal bilirubin released by the breakdown of red cells and exacerbated by the immature conjugation ability of the liver. Levels generally peak at a level of 12 mg/dL when a term infant is 72 hours old, but may climb as high as 17 mg/dL in breast-fed infants [43]. This higher peak with breast feeding is likely due to mild dehydration, and should be differentiated from “breast milk jaundice,” which occurs in babies at 1 to 2 weeks of age due to a poorly understood property of breast milk that interferes with the conjugation of bilirubin. Studies show that preterm infants mount higher bilirubin levels, with nearly any degree of prematurity [44], and peak a few days later [43]. Although physiologic jaundice is quite common, it remains a diagnosis of exclusion, and pathologic causes must be excluded. Indicators for pathologic jaundice in patients with unconjugated hyperbilirubinemia include jaundice in the first 24 hours of life, a rapid rate of rise of the bilirubin level (0.5 mg/dL/h or 5 mg/dL/d), or in the presence of anemia or hepatosplenomegaly [43,45,46].

In any neonate who is significantly compromised from any illness, jaundice may be a secondary finding. It is particularly common in the infant suffering from dehydration, infection, and inborn errors of metabolism. Some of the inborn errors of metabolism, such as hereditary fructose intolerance and tyrosinemia, can cause liver failure, and jaundice may be the most notable sign of that. Significant hemolysis may be also be responsible for hyperbilirubinemia, either from a disease inherent to the infant itself, like hereditary spherocytosis, or due to an incompatibility with the maternal Rh or ABO blood type. Breakdown of extravascular blood, like cephalohematomas or swallowed maternal blood, may also increase bilirubin if the quantity is sufficient. Rarer causes include an upper gastrointestinal obstruction like pyloric stenosis, or duodenal atresia, congenital hyperathy-
roidism, Crigler-Najjar syndrome, Lucey-Driscoll syndrome, Down’s syndrome, or maternal diabetes [45].

**Emergency department evaluation**

Clearly, the workup must be guided by the appearance of the infant. However, in a well-appearing, afebrile infant, fractionated bilirubin and hemoglobin are a reasonable place to begin. If the hyperbilirubinemia is indeed unconjugated and the hemoglobin normal, no further tests are required. It has recently been shown that physiologic jaundice is associated with asymptomatic urinary tract infections, and some practitioners would also check a urinalysis and culture [47]. If, on the other hand, anemia is present, a CBC with peripheral smear, Coomb’s test, and maternal and fetal blood types should be analyzed. If there is a positive coombs test, ABO or Rh incompatibility is a likely cause for the jaundice. Most other causes of hemolysis will be Coombs negative [48]. Most recently, it is recommended that glucose-6-phosphate dehydrogenase level be checked for any infant receiving phototherapy with an appropriate genetic or geographic background or for any infant who does not respond well to phototherapy.

**Emergency department management and disposition**

Clearly, if a serious illness is identified, priority must be given to its treatment. For the majority of children with physiologic jaundice, the goal of management is prevention of kernicterus. The likelihood of kernicterus depends not only on the bilirubin level, but also on the age of the child and their comorbidities. Age-appropriate criteria for treatment of jaundice are included in Table 6. It is important to remember that certain factors increase the risk of kernicterus, and many practitioners reduce these thresholds slightly in patients with evidence of hemolysis or dehydration.

If initiated, treatment requires correction of dehydration with normal saline boluses and initiation of phototherapy. This is generally done as an inpatient, but home bili-blankets and home nursing services make outpatient treatment an option as well. After correction of dehydration, oral feeds should be reinstituted, as frequent feeds and frequent stooling help excrete bilirubin. Discontinuation of breast feeding is not recommended. Continuation of breast feeding with close monitoring, supplementation with formula, or a brief interruption of breast feeding and substitution of formula are all accepted strategies, each done with or without adjuvant phototherapy, depending on the degree of hyperbilirubinemia [45]. In the event that bilirubin levels are dangerously high, exchange transfusion in an intensive care setting should be considered.

In cases of breast milk jaundice, many practitioners would encourage temporary cessation of breast milk with reintroduction after the bilirubin has fallen to a safe level.
Conjugated hyperbilirubinemia

As mentioned above, conjugated bilirubin lacks the toxicity potential of unconjugated bilirubin, but is a marker for a serious underlying disease of either hepatocellular damage or cholestasis [43]. Other findings associated with conjugated hyperbilirubinemia are pale, acholic stools, and dark urine, although these are not always present in a newborn. Most cases will present with clinical jaundice in the first 4 weeks of life. The differential diagnosis can be seen in Table 7.

Emergency department evaluation

Appropriate evaluation of patients with conjugated hyperbilirubinemia is directed at identifying the underlying condition. Infection is not only a common cause for conjugated hyperbilirubinemia, but one that requires prompt identification and treatment. A complete septic workup, including a CBC, blood and urine cultures, as well as cerebral spinal fluid and stool studies when appropriate, should be sent on any ill-appearing infant, and jaundice itself should be included as a risk factor for neonatal sepsis. Keep in mind that the presence of sepsis, however, does not exclude an associated serious underlying disease [46]. Most of the TORCH infections are associated with jaundice and a TORCH panel as well as hepatitis B virus serology, and urine for cytomegalovirus should be sent. Inborn errors of metabolism may present with jaundice and should be worked up as outlined previously. Alpha 1-antitrypsin deficiency, cystic fibrosis, and Wilson’s

Table 6
Management of hyperbilirubinemia in the healthy term newborna

<table>
<thead>
<tr>
<th>TSB Level, mg/dL (pmol/L)</th>
<th>Exchange Transfusion if Intensive Phototherapy Failsb</th>
<th>Exchange Transfusion and Intensive Phototherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, hours</td>
<td>Consider Phototherapyb</td>
<td>Phototherapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤24d</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>25–48</td>
<td>≥12 (210)</td>
<td>≥15 (260)</td>
</tr>
<tr>
<td>49–72</td>
<td>≥15 (260)</td>
<td>≥18 (310)</td>
</tr>
<tr>
<td>&gt;72</td>
<td>≥17 (290)</td>
<td>≥20 (340)</td>
</tr>
</tbody>
</table>

a TSB indicates total serum bilirubin.
b Phototherapy at these TSB levels is a clinical option, meaning that the intervention is available and may be used on the basis of individual clinical judgment. For a more detailed description of phototherapy (see the Appendix).
c Intensive phototherapy (Appendix) should produce a decline of TSB of 1 to 2 mg/dL within 4 to 6 h and the TSB level should continue to fall and remain below the threshold level for exchange transfusion. If this does not occur, it is considered a failure of phototherapy.
d Term infants who are clinically jaundiced at ≤24 h old.

disease may also cause liver damage, resulting in a conjugated hyperbilirubinemia and, as with the inborn errors of metabolism, may have an insidious onset heralded by inconstant jaundice and failure to thrive. Complete liver function studies including aspartate aminotransferase, ALT, and gamma-glutamyltranspeptidase, ammonia, albumin, total protein, alkaline phosphatase, and coagulation studies should also be ordered. Electrolytes, blood urea nitrogen (BUN), creatinine, and blood glucose are recommended as well. Urine for reducing substances, alpha 1-antitrypsin, sweat chloride, and red blood cell galactose-1-phosphate uridyltransferase activity may be useful for the ultimate diagnosis. Finally, it is crucial to identify those cases of biliary atresia or obstruction early, as they require surgical intervention, and if missed, may have poor surgical outcomes. Due to their healthy appearance, patients with biliary atresia may be initially missed. Infants with complete obstruction should have a history of clay-colored stools, but obstruction can be intermittent and stools may remain pigmented for a few weeks. Abdominal ultrasonography and hepatobiliary scintigraphy should identify cases of biliary atresia and cholydocal cyst, mandating surgical intervention.

**Emergency department management and disposition**

The treatment of conjugated hyperbilirubinemia is aimed at treating the underlying pathology. For sepsis or infectious causes, appropriate antimicrobials are indicated. For suspected inborn errors of metabolism, withholding galactose and fructose from the diet may be prudent until definitive diagnosis is made. Other treatment, again, depends on the underlying cause: infants should be admitted to the hospital for further workup and definitive therapy [49].
**Electrolyte disturbances**

As with many of the inborn errors of metabolism, infants presenting to the ED with electrolyte disturbances may have a myriad of nonspecific symptoms. With the atypical presentations seen in this age group, and the likelihood of coexisting abnormalities, it is difficult to present electrolyte disturbances in a truly symptom-based manner. However, some of the more common disturbances tend to be associated with jitteriness and seizures, while tend to manifest as weakness and vomiting, or as cardiovascular embarrassment. Therefore, they are grouped here by characteristic presenting symptoms.

**Electrolyte abnormalities associated with seizures**

Although much attention has been given to the judicious use of electrolyte testing in pediatric and adult patients with new onset seizures [50–52], studies support metabolic screening the newborn population [53–55]. In a newborn or infant, seizure activity may be less obvious than in adult or older pediatric patients. Neonatal seizures may be subtle, and frequently are not recognized as seizure activity by caretakers or medical personnel. Subtle symptoms of neonatal seizures include sucking or chewing motions, lip smacking, bicycling of the legs, apnea, eyelid fluttering, eye deviation, laughter, or tonic posturing. This group of neonatal seizures, in particular, is often not associated with EEG findings. Tonic, clonic, and myoclonic neonatal seizures may be either focal or generalized and are more commonly associated with EEG abnormalities [56].

Overall, there are relatively few medical conditions that account for the majority of neonatal seizures [57], and metabolic causes are common, in particular sodium abnormalities and hypocalcemia. The complete differential diagnosis must include hypoxic–ischemic encephalopathy, metabolic abnormalities (including electrolyte disorders, hypoglycemia, pyridoxine deficiency, and inborn errors of metabolism), intracranial hemorrhage, infections, cerebral dysgenesis, drug withdrawal, toxins (ie, lidocaine), and familial epilepsy [57]. Some maternal and birth conditions will predispose an infant to electrolyte abnormalities and subsequently seizure activity. Therefore, it is imperative that the ED physician, as with any infant patient, obtain a thorough history of the pregnancy, delivery, and resuscitation, as well as a detailed description of the presenting complaint.

**Hyponatremia**

In a well infant with seizures and without fever, hyponatremia, defined as serum sodium levels less than 130 mEq/L [58], should be foremost on the differential [59,60]. Hyponatremia is second only to febrile seizure as a cause
for first-time seizure in an infant [61]. For those patients presenting to the ED, water intoxication and gastrointestinal losses are the most frequent causes, with water intoxication more likely in infancy [58]. Neonates lack the ability to appropriately concentrate their urine to accommodate for serum sodium shifts. Therefore, a parent who gives their young infant free water, or inappropriately dilutes the formula to make it last longer, may induce hyponatremia in their child. This phenomenon is often associated with poverty, and may be increasing in the United States [62–64].

Emergency department presentation

Symptomatology in hyponatremia is more reflective of the rate of fall of the serum sodium than on the absolute value. Significant symptoms generally begin to appear with serum sodium values less than 120 mEq/L, but may be observed with a rapid fall of the sodium levels into the normal range [43,58]. Symptoms such as anorexia, agitation, disorientation, and apathy may be difficult to appreciate in an infant. More pronounced symptoms include lethargy, muscle cramping or decreased deep tendon reflexes (DTRs), vomiting, acute respiratory failure, and seizures [57]. When seizures occur in these patients, they tend to be refractory to standard anticonvulsant therapy and often require high enough doses of medication to necessitate ventilatory support, unless the hyponatremia is recognized and corrected promptly [59,65,66]. Hyponatremic children frequently have a concomitant hypothermia and hyperglycemia [59,60,62,63,66].

As with adults, pediatric hyponatremia is classified based on total body water content into hypervolemic, hypovolemic, and euvoilemic hyponatremia.

Differential diagnosis

Most cases of hyponatremia in infants are associated with either dietary causes or gastrointestinal illness. Euvolemic hyponatremia is most likely due to water intoxication in healthy infants. This can occur as a result of inappropriate dilution of formula or with the addition of solute-poor fluids to the diet [60,62–64]. A change in diet is often due to recent gastrointestinal illness or summer weather dehydration, and so careful interviewing may reveal this history. Most hyponatremic infants studies were formula fed, so this may be another risk factor [62–64,66]. Moreover, patients with a history of vomiting, diarrhea, and dehydration are likely to have hypovolemic hyponatremia due to gastrointestinal losses, another common cause for pediatric hyponatremia. This is more likely when replacement fluid is solute poor. Other causes to consider include syndrome of inappropriate secretion of antidiuretic hormone (SIADH), in light of a history of underlying neurologic or pulmonary disease, CAH if the hyponatremia is associated with hyperkalemia and hypoglycemia, or in edema-forming states such as
congestive heart failure, cirrhosis, and nephrosis. Other renal disorders may result in excessive renal excretion. Finally, hyperglycemia or hyperlipidemia may be the cause for pseudo or factitious hyponatremia, respectively [67].

Emergency department evaluation

The immediate workup of hyponatremia should include complete serum electrolytes, BUN, creatinine, and glucose and urinanalysis with specific gravity. As most cases are due to dietary or gastrointestinal causes, this will likely suffice for the ED evaluation. If the history, physical examination, and initial laboratory studies do readily suggest a cause, there is probably a more serious underlying condition, and the infant should be admitted for additional workup. The constellation of hyponatremia, hypoglycemia, hyperkalemia, and acidosis may indicate CAH. Serum and urine osmolality should be tested, as urine osmolality greater than serum osmolality suggests SIADH. Liver function testing may be necessary if there is evidence of cirrhosis, nephrosis, or hypoalbuminemia in association with edema. Additionally, urine sodium, and creatinine should be tested [58].

Emergency department management and disposition

Any infant with severe symptoms of hyponatremia should be treated immediately with IV administration of 3% NaCl at a dose of 10 to 12 mL/kg over 1 hour. Another method is to calculate the volume required to raise serum sodium by 10 mEq/L using the following formula: volume of 3% NaCl to give = 10 mEq/L × body weight (kg) × 0.6 (extracellular fluid space). For less symptomatic patients, treatment is based on the cause. For water intoxication, restriction of daily free water by 25% to 50% is the treatment of choice. For hyponatremia associated with dehydration and gastrointestinal losses, serum sodium should correct with rehydration with isotonic saline over approximately 24 hours. SIADH will require fluid restriction as well, and in edema-forming states diuretics may be appropriate. Most hyponatremic patients will require admission, and certainly symptomatic hyponatremia without obvious cause mandates hospital admission [58].

Hypernatremia

Emergency department presentation

Hypernatremia may also be a cause for seizures and altered mental status in the newborn period [58,67]. Other signs and symptoms may include increased DTRs, tetany and tonic spasm, and tremulousness, rigidity, fever, and high-pitched cry [67].
Differential diagnosis

Hypernatremia is defined as serum sodium greater than 145 mEq/L, and is also divided based on total body sodium and water content [58]. Insensible free water losses leading to hypovolemic hypernatremia account for most cases of hypernatremia likely to be seen in the ED, with diarrhea (especially if fluid replacement has a high sodium relative to water content) the most common cause overall in pediatric ED patients [58]. As with hyponatremia, improper diet (boiled milk) or formula preparation can be a cause of hypernatremia. Furthermore, hypernatremia has been found in breast fed infants, due to poor oral intake [68–70]. Other causes include vomiting, insensible skin or respiratory losses, diuretic use, hypertonic sodium-containing enemas, or diabetes insipidus (more likely with a history of central nervous system pathology). Euvolemic hypernatremia may be essential, iatrogenic, or due to formula errors. Hypervolemic hypernatremia is very rare, and can result from hyperaldosteronism, although it is usually iatrogenic in origin [67].

Emergency department evaluation

Evaluation of hypernatremia is much the same as hyponatremia: initial laboratory studies should include complete chemistries, BUN, creatinine, and glucose, and a urinalysis in the ED. Additional workup will likely be done on an in-patient basis and will include liver enzyme analysis, serum, and urine osmolality and serum electrolyte testing.

Emergency department management and disposition

The treatment of hypernatremia depends on the underlying cause and the relative total body water content. In patients with underlying disease, such as a premature neonatal intensive care unit (NICU) graduate or a history of anoxic ischemic event, diabetes insipidus is much more likely, and treatment for this is slow correction with free water replacement, along with initiation of ddAVP. Without a history of underlying medical disease, a history of improper formula preparation should be sought. In this case, the rate of correction of sodium should reflect the rate of sodium rise. Without a history of salt poisoning, one should search for any signs or symptoms or history consistent with dehydration. Treatment for hypertonic dehydration depends on degree of dehydration. Emergently, severely dehydrated infants with signs of shock require volume expansion with isotonic saline. Water and sodium losses may be replaced with hypotonic electrolyte solutions over 48 hours. It is recommended that for every 1 mEq/L of serum Na greater than 145 mEq/L, a free-water deficit of 4 mL/kg should be replaced over 48 to 72 hours [57]. As free water should not be given IV, it may either be given by mouth, or calculated out so that a child gets an appropriate volume of 0.45 or 0.2 normal saline. For mildly dehydrated infants, 10 to 20 cc/kg normal saline bolus is appropriate, and may be repeated as needed. Finally,
without stigmata or findings of dehydration, hyperaldosteronism, obstructive uropathy, osmotic diuretic use, and essential hypernatremia remain in the differential. These are rare in infants and will mandate further workup with treatment reflective of the underlying condition.

**Hypocalcemia**

*Emergency department presentation*

Hypocalcemia is one of the most common electrolyte abnormalities encountered in the newborn period, and often presents with jitteriness or seizures. It is important for the ED physician to recognize hypocalcemia as a cause of newborn seizures, as patients are frequently treated without assessment of serum calcium [71]. Other symptoms of hypocalcemia may include lethargy, poor feeding, irritability, and vomiting. As with adult patients, the QT interval on ECG may be increased and infants are at risk for myocardial depression and sudden cardiac death. Unlike older patients Chvostek and Trousseau signs will likely not be present in this age group [72].

Hypocalcemia is defined as a level <6 mg/dL in preterm newborn, <7 mg/dL in a term newborn, and <8 mg/dL in a term infant over 1 week of age [73], and is divided into early-onset hypocalcemia, delayed hypocalcemia, and childhood hypocalcemia thereafter [73].

*Differential diagnosis*

All infants have a slight decline in serum calcium levels just after birth with the nadir at approximately 24 to 48 hours of age. Generally, this is asymptomatic and resolves without therapy by the fifth day of life. Symptomatic hypocalcemia is much more common in infants of diabetic mothers, preterm infants, and infants with a history of anoxic encephalopathy, and may be an exaggeration of the normal fall in serum calcium after birth [72,74]. With the trend toward 24- and 48-hour newborn discharge, ED physicians may see more of this early neonatal population. Up to 80% of infants with symptomatic early neonatal hypocalcemia have concomitant hypomagnesemia and will not respond to calcium therapy without correction of the hypomagnesemia [72].

Delayed neonatal hypocalcemia is a disease of term-healthy infants, presenting at 5 to 10 days of age, and is associated with hyperphosphatemia [72]. Classically, this was the result of a diet of unmodified cow’s milk formula, which has a very high phosphate-to-calcium ratio. Similar cases have been described with phosphorus overload, such as with administration of a phosphate containing enema [75].

Any form of vitamin D deficiency or resistance may lead to hypocalcemia associated with rickets. Congenital rickets, although now a rare condition
[74], is the result of severe maternal vitamin D deficiency. It should be noted that rickets can occur secondary to hypophosphatemia due to renal wasting or dietary insufficiency as well [71]. Rickets of prematurity is secondary to birth before sufficient in utero skeletal calcification and subsequent dietary phosphorous deficiency.

Findings of arrhythmia, congenital heart disease, or heart murmur on examination, dysmorphology, and a history or seizures or jitteriness should prompt a workup for hypocalcemia secondary to DiGeorge syndrome. Familial hypocalcemia with hypercalciuria is a dominantly inherited condition associated with hypocalcemia, severe hypercalciuria, and nephrolithiasis.

Other less common causes of late hypocalcemia include pseudohypoparathyroidism (insensitivity at the parathyroid hormone receptor), maternal hypocalcemia with downregulation of parathyroid production, and secondary to citrate chelation associated with blood transfusions.

Emergency department evaluation

In an infant presenting with hypocalcemic seizures or tetany, obtaining a serum calcium level is critical, preferably ionized serum calcium [71], as treatment needs to be initiated immediately. Magnesium and phosphorus abnormalities should also be identified and treated in the ED. Ideally, before treatment is started, intact PTH and vitamin D metabolites should be drawn (an extra red top placed on ice or frozen), as these will help the consultant to identify the specific cause for the hypocalcemia [73]. Spot urine for calcium, phosphate, and creatinine should be collected within a few hours of the hypocalcemic event if possible, to assist the primary physician in a specific diagnosis. Additional workup will include renal and liver function testing may also aid in definitive diagnosis [73]. If indicated, radiographs of the skull and long bones may be useful in rickets [71].

Emergency department management and disposition

Treatment for hypocalcemia is much as with adult patients. Severely symptomatic patients, such as patients with seizures or myocardial dysfunction, need immediate IV calcium replacement. Ten percent calcium gluconate should be given, starting with 0.5 to 1.0 cc/kg up to 2 cc/kg, given over slow continuous infusion. As with adults, calcium infusions must be given very carefully, with close monitoring for cardiac arrhythmias, IV infiltration, and levels should be followed closely [58,74]. The infusion should be stopped for any signs of bradycardia and once symptoms have resolved [58]. Continuous replacement can then be started with 20 to 100 mg/kg of elemental calcium added to IV fluids [58,74], or by oral supplementation. Again, hypomagnesemia frequently accompanies hypocalcemia and must also be corrected. Generally, mild asymptomatic
hypocalcemia does not need therapy, but levels less than 7.0 to 7.5 mg/dL in neonates warrant treatment to prevent tetany [74].

**Hypomagnesemia**

*Emergency department presentation*

As mentioned above, hypomagnesemia should be suspected in any infant with evidence of hypocalcemia, and can be associated with tetany and seizures. In fact, most of the symptoms of hypomagnesemia parallel those of hypocalcemia: lethargy, nausea, muscle cramping, paraesthesias, fasciculations, and irritability [76]. There may be similar ECG changes as well.

*Differential diagnosis*

Causes for hypomagnesemia in children include gastrointestinal losses or malabsorption, renal losses due to renal insufficiency, or medications, as with the pseudo-Bartters syndrome (described later), or due to underlying metabolic conditions, such as primary hypomagnesemia. For the newborn, it is imperative to keep in mind that infants of diabetic mothers and infants with a history of anoxia are at increased risk of hypomagnesemia [77].

*Emergency department evaluation*

The evaluation of hypomagnesemia should, thus, be much the same as that of hypocalcemia with complete electrolyte testing, assessment of renal and liver function, urine electrolytes, and ECG testing. Recent studies have recommended ionized magnesium as a more accurate measurement [78], but this may be impractical in the ED.

*Emergency department management and disposition*

Any symptomatic patient with hypomagnesemia needs treatment. IV replacement is recommended, although it can be given intramuscularly. An IV dose of 25 to 50 mg/kg can be given as a 10% solution (100 mg/mL) or as a 50% solution (500 mg/mL) every 4 to 6 hours as needed [58].

*Electrolyte abnormalities associated with weakness and vomiting*

Infants who present with poor tone, vomiting, lethargy, or alterations in consciousness need prompt evaluation for common causes, such as sepsis or dehydration, but also should be evaluated for electrolyte abnormalities. In particular, hypercalcemia and hypokalemia can cause this clinical picture.
Hypercalcemia

Emergency department presentation

Hypercalcemia is very rare in infancy [79], but can have serious sequelae. Patients may present with poor feeding, vomiting, and constipation with associated failure to thrive and dehydration. They may have poor tone, weakness, and irritability as well [72]. Hypercalciuria will lead to polyuria and dehydration, exacerbating the potential for nephrocalcinosis and renal insufficiency. Patients are often hypertensive, and may even present with seizures [79].

Hypercalcemia is defined by ionized serum calcium levels greater than 5.4 mg/dL with or without the total serum calcium greater than 10.8 mg/dL [79]. Other diagnostic findings include bradycardia, a narrow QT interval, and, as mentioned above, hypertension. On renal function analysis, patients frequently have elevated creatinine with evidence of hematuria and pyuria due to urine calcium excretion [79].

Differential diagnosis

Although individually rare, the causes of infantile hypercalcemia are many. Overall, iatrogenic exposure is the most common etiology, but in ED patients the most common cause is idiopathic infantile hypercalcemia (IIH) [79]. IIH is divided into mild and severe forms. Mild IIH, otherwise know as Lightwood variant IIH, has been associated with elevated vitamin D metabolites or increased sensitivity to vitamin D with increased gut absorption of calcium. It is generally self-limited, resolving by 12 months of age, and treated with diet. Severe IIH is now recognized as Williams syndrome. A history of small-for-gestational age, hypotonia, feeding difficulties, and cardiac murmur on exam should tip the ED physician to screen for hypercalcemia associated with Williams syndrome. The hallmark “elfin facies,” loquaciousness, and mental retardation may not become evident until later in life. As with mild IIH, the hypercalcemia of William’s syndrome patients may have increased sensitivity to vitamin D metabolites, and the hypercalcemia generally resolves spontaneously by 1 year of age. It should be recognized that although an astute ED physician could make this diagnosis with a careful history and physical and a high index of suspicion, the marked hypercalcemia is often not recognized until many weeks of age, and is not a cause for the mental retardation [74].

Hypercalcemia due to severe neonatal hyperparathyroidism, while very rare, is an absolute medical emergency. This is the result of homozygous mutations in a calcium-sensing receptor. These patients will have critically high calcium levels and require immediate correction. It is imperative to recognize these patients, as they will require surgical treatment with parathyroidectomy. Heterozygosity for this leads to only modest
asymptomatic hypercalcemia, so parents do not need medical intervention, but should have genetic counseling [79].

Infants may also have secondary neonatal hyperparathyroidism due to exposure to maternal calcium hypocalcemia. This is a self-limited, transient disorder requiring only symptomatic treatment of the hypercalcemia [79].

One other cause for infantile hypercalcemia is vitamin D intoxication. This can be exogenous, due to inappropriate choice of formulas, or due to over production. Extensive neonatal fat necrosis can cause excess vitamin D synthesis. In any infant with symptoms of hypercalcemia and a history of large-for-gestational age or traumatic delivery, the examination should focus on signs of fat necrosis, and this diagnosis should be entertained [72,79].

Emergency department evaluation

ED workup of hypercalcemia should include a complete set of electrolytes, BUN, and creatinine to assess degree of dehydration and to look for renal insufficiency and other associated electrolyte abnormalities. If at all possible, measurement of an intact serum PTH level at the time of hypercalcemia is crucial. High levels of PTH in the face of markedly elevated calcium suggest neonatal hyperparathyroidism requiring surgical management, and thus will affect management, consultation, and disposition. Low levels of PTH will mandate further calcitrophic hormone testing [79].

Emergency department management and disposition

Asymptomatic hypercalcemia does not need treatment emergently. Mild hypercalcemia can be managed with a low calcium diet and close follow-up [79]. This is best done by the primary care provider given the risk of calcium and phosphate depletion in a growing child [74]. For more significant hypercalcemia, intervention is warranted. The goals of treatment for hypercalcemia are: rehydration, increasing calcium excretion, decreasing gut absorption, and treatment of the underlying disorder. Intravenous normal saline should be used to expand the extracellular fluid compartment at approximately 1.5 to 2.5 times maintenance therapy [79]. This will also enhance calcium excretion by inducing a calciuresis [72]. Furthermore, furosemide at 0.5 to 1.0 mg/kg IV every 6 hours will enhance this calciuresis [79]. These steps are simple and familiar to the ED physician, and are effective for all causes of hypercalcemia [79].

In severe cases, additional therapy can include calcitonin subcutaneously at 4 IU/kg every 6 hours. Glucocorticoids, while ineffective in hyperparathyroidism, may be helpful in cases of hypervitaminosis D as a short-term measure [74,80]. Bisphosphonates have not been tested well in infants, but may have a future role for PTH-mediated hypercalcemia and vitamin D toxicity [81]. Ultimately, dialysis may be required if these methods are unsuccessful.
Hypokalemia

Emergency department presentation

Hypokalemia is an uncommonly described electrolyte disturbance in infants, and is defined as a serum potassium level below 3.5 mEq/L [58]. Symptoms range from muscle weakness, polyuria, ileus, tetany, areflexia, and paralysis [58]. Disturbances in cardiac conduction can be seen as well including ST depression, T-wave reduction, and the hallmark finding of U waves on ECG. Patients with severe hypokalemia can progress to acute respiratory failure, and can develop myoglobinuria from muscle paralysis leading to acute renal failure [58].

Differential diagnosis

In previously healthy patients gastrointestinal losses can cause hypokalemia. Gastric potassium loss from vomiting can cause hypokalemia. Metabolic alkalosis from vomiting can exacerbate this by inducing renal potassium wasting and shifting potassium intracellularly. This, coupled with diarrhea, can frequently be the cause for hypokalemia in an otherwise well child [58]. Hypokalemia may be an associated finding in an infant with pyloric stenosis as well [58].

Bartter syndrome, although rare, may present in infancy with polyuria, salt craving, muscle weakness, constipation, tetany, and failure to thrive [82]. It is characterized by hypokalemia and hypochloremia associated with metabolic alkalosis without hypertension. Patients may also have hypotremia, hypercalcemia, hypomagnesemia, and hyperuricemia [82]. Although Bartter syndrome is a very rare disease, it should be noted that there have been reported cases of transient Bartter syndrome associated with gentamycin therapy continuing weeks to months after discontinuation of the drug [83,84]. Hence, the index of suspicion for hypokalemia should be heightened in infants with a history of gentamycin therapy in the NICU.

Many underlying disease are associated with hypokalemia. Renal tubular acidosis is another cause of hypokalemia. In contrast to Bartter syndrome, this causes a nonanion gap metabolic acidosis with hyperchloremia and an alkaline urine pH [58]. Another underlying condition that leads to hypokalemia is cystic fibrosis. Diabetic ketoacidosis is well recognized as a cause of hypokalemia in older pediatric patients, but is extremely uncommon in the newborn period. Pediatric hypokalemia, in association with normal acid-base status, is generally reflective of unusual diets, Cushing’s syndrome, or hyperaldosteronism [58].

Emergency department evaluation

The immediate workup of hypokalemia should start with the serum electrolytes, BUN, creatinine, glucose, and urinalysis. In addition, an arterial
blood gas should be obtained to ascertain acid-base balance. Additionally, an ECG should be done for any suspicion of conduction abnormalities and an ultrasound or upper gastrointestinal series to rule out pyloric stenosis when appropriate [58]. If a cause is not identified, additional evaluation with urine Na, K, Cl, pH, and osmolality may be helpful, but may be done in conjunction with hospital admission or consultation.

Emergency department management and disposition

The treatment of hypokalemia in infants does not differ from that in adult patients. Treatment can generally be slow oral or intravenous potassium supplementation, and will be dependent somewhat on the cause of the hypokalemia. In alkalosis with associated intracellular potassium shifts, treatment of the underlying alkalosis is appropriate. For familial periodic hypokalemic paralysis judicious oral potassium supplementation is recommended with close monitoring. Any patient with life-threatening symptoms from hypokalemia requires immediate IV potassium replacement. Intravenous potassium should be given at 0.5 to 1 mEq/kg per hour with continuous cardiac monitoring. For patients with associated alkalosis, potassium chloride should be used, and for patients with acidosis, potassium bicarbonate can be used. In addition, infants with evidence of dehydration will also need volume replacement to prevent further renal losses. Most infants with a serum potassium less than 3.0 mEq/L require admission, and certainly those who are symptomatic and requiring correction [58].

Cardiovascular or respiratory compromise

A subset of electrolyte disorders may present with signs of cardiac or respiratory failure. Hyperkalemia can cause conduction abnormalities in addition to skeletal muscle weakness. Hypermagnesemia is associated with respiratory depression and can progress to apnea. Finally, CAH, causing a constellation of electrolyte abnormalities, can present with profound hypotension and shock.

Hyperkalemia

Emergency department presentation

Symptomatic hyperkalemia, as with adult patients, is a true medical emergency. The clinical findings of hyperkalemia can range from weakness and paralysis to significant cardiac conduction abnormalities, arrhythmia, and cardiac arrest. ECG changes tend to parallel the degrees of hyperkalemia if it has occurred acutely. As in adults, the earliest finding is peaking of the T-wave, then widening of the PR interval, followed by first degree heart block, loss of the P wave, ventricular arrhythmia, and ultimately, asystole.
Hyperkalemia is defined as serum potassium levels greater than 5/5 mEq/L. It is relatively common to find elevated potassium levels on laboratory serum analysis due to hemolysis and this should be considered in the face of significantly potassium elevation without peaking of the T-wave on ECG.

**Differential diagnosis**

Extracellular shift of potassium due to acidosis may also result in an elevated serum potassium value, although the true total body potassium may be normal or decreased. Significant burn or crush injury can release extracellular potassium from damaged cells, and these patients should be screened for hyperkalemia, even in the absence of symptoms. Finally, potassium levels can rise with decreased renal excretion, and this is nearly always the case with life-threatening hyperkalemia [58]. As with older patients, acute renal failure, especially with oliguria, can result in hyperkalemia. In the infant age group, acute adrenal insufficiency due to CAH must be ruled out.

**Emergency department evaluation**

In the ED, it is imperative to assess renal function: measurement of the BUN and creatinine is mandate. Neonates have such little muscle mass that a creatinine level that is acceptable in adults may be abnormal in neonates, and values should be compared with age-appropriate normals. Complete electrolytes and glucose should also be obtained to screen for other electrolyte abnormalities and evidence of CAH. An ABG is recommended to establish if acidosis is present and serum creatinine phosphokinase should be included to exclude rhabdomyolysis as a cause for hyperkalemia. ECG testing should be done in any patient with abnormalities in serum potassium, especially in the face of hyperkalemia [58]. As with other electrolyte abnormalities, urinalysis, urine electrolytes (Na, K, Cl), urine pH, and osmolality will help the pediatrician evaluate more esoteric causes such as renal tubular acidosis, but need not be done emergently. Finally, for patients with elevated laboratory values and normal ECG or no history compatible with hyperkalemia, repeating the test is prudent.

**Emergency department management and disposition**

The treatment of hyperkalemia in newborns and infants is exactly the same as with adult patients. Any patient with evidence of arrhythmia or serum potassium level above 8.0 mEq/L needs immediate treatment. Calcium is given to restore the membrane potential at a dose of 0.5 mL/kg of 10% calcium gluconate over 2 to 5 minutes. This must be followed
with a reduction in serum potassium. The most expeditious way to achieve this is to force potassium out of the extracellular component and into the intracellular space. This is can be achieved by the use of IV bicarbonate therapy (Na bicarbonate 7.5% 2–3 mL/kg over 30–60 minutes), and a combination of IV glucose and insulin (1 unit of insulin for every 5–6 g of glucose given) [57]. Patients with only minimal elevation of serum potassium can be treated with Kayexalate (sodium polystyrene sulfate) at a dose of 1 g/kg. This is appropriate for longerterm treatment, but should be considered in more acute patients in addition to symptomatic treatment, as the above measures are only temporizing. Diuresis with furosemide will also enhance renal potassium excretion. For asymptomatic patients with mildly elevated K+ levels (<6.5 mEq/L) and a normal or near normal (peaked T-waves only) ECG, no specific treatment is needed other than correction of acidosis if present and withdrawal of supplemental potassium. However, if the hyperkalemia is the result of acute renal failure or rhabdomyolysis, more active treatment is indicated, as levels may climb rapidly. In these patients, dialysis should be considered if the underlying condition cannot be quickly reversed. Admission to the hospital is warranted for patients with potassium levels greater than 6.5 mEq/L or if symptomatic [58].

**Hypermagnesemia**

*Emergency department presentation*

Hypermagnesemia, although rare, can be seen in the newborn period. Symptoms associated with hypermagnesemia correlate well with serum levels. Decreased DTRs are noted first, with magnesium levels of 4 to 5 mEq/L. ECG changes (increased P-R, QRS, and QT intervals) and a drop in blood pressure can be seen with levels above 5 mEq/L. At levels of 8 to 10 mEq/L, decreased respirations and apnea ensue, and at levels greater than 15 mEq/L, heart block can occur [58].

*Differential diagnosis*

Hypermagnesemia is seen in the NICU in infants of mothers who received magnesium therapy for hypertension and seizure prophylaxis. Hypoxic ischemic encephalopathy has been described in association with hypermagnesemia [77], as well as hypomagnesemia. Infants have also presented with hypermagnesemia when inappropriately given such medications as magnesium hydroxide [85].

*Emergency department evaluation*

Serum magnesium levels should be ordered, in addition to complete serum electrolytes for any suspicion of hypermagnesemia. BUN, creatinine, and urinalysis should also be checked.
Emergency department management and disposition

Treatment for mild hypermagnesemia includes hydration and diuresis. For any severe signs or symptoms, IV calcium gluconate can be given at a dose of 0.5 mL/kg of 10% Ca gluconate, with careful monitoring as described earlier. For any patient with evidence of renal failure, dialysis is indicated.

Congenital adrenal hyperplasia

Finally, CAH should be mentioned, as it is associated with many of the described electrolyte abnormalities and can cause severe symptoms related to corticosteroid insufficiency and salt wasting.

Emergency department presentation

The symptomatology of CAH is twofold. There can be virilization or ambiguous genitalia present at birth. Other affected infants who have symptoms of acute salt-wasting crisis generally present in the second week of life and may initially have nonspecific symptoms of poor feeding or weight gain, lethargy, irritability, and vomiting. Symptoms progress to profound shock and death if not recognized and treated [86].

Differential diagnosis

CAH is often misdiagnosed with a delay in treatment [86]. Symptoms may suggest gastroenteritis, formula, or feeding intolerance, or a number of the diseases already described. Careful physical examination will alert the astute ED physician to this disorder. Appreciation of an enlarged clitoris, fusion of the labial folds, or testes palpable in the labia in females or a micropenis, hypospadias, or palpable gonads in the inguinal canal or labioscrotal folds is highly suggest of CAH and electrolyte abnormalities should be sought.

Emergency department evaluation

The first priority for workup of these infants includes serum electrolytes and glucose. Most commonly the infant will be found to have hyperkalemia and hyponatremia, often associated with hypoglycemia and acidosis. As mentioned before, an adrenal steroid profile, including 17-hydroxyprogesterone, dehydroepiandrosterone, and testosterone should be obtained before treatment with hydrocortisone [86]. That said, if the clinical suspicion is high and the patient unstable, these studies should not delay treatment.

Emergency department management and disposition

For these patients, as with any infant with shock, fluid rehydration will be the first step in resuscitation. An IV bolus of 20 mL/kg on normal saline should
be initiated immediately and repeated as needed to correct the volume deficit. IV hydrocortisone should be given in the ED at a dose of 25 mg, followed by hydrocortisone 50 mg/m² over 24 hours continuous infusion. If IV access cannot be established, intramuscular cortisone acetate at a dose of 25 mg may be life saving. The hydrocortisone should provide some mineralocorticoid activity, but some patients will require fludrocortisone for long-term management. Electrolyte correction may occur with volume and glucorticoid replacement [86]. For any significant symptoms secondary to the electrolyte abnormalities, treatment is as outlined earlier in the article. Infants diagnosed with CAH should be admitted, and consultation with an endocrinologist is recommended.

References

Approach to Newborn and Childhood Metabolic Crisis


