The Poisoned Pediatric Patient

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Education Gap

Poisonings remain a frequent source of morbidity and mortality in the pediatric age group. All pediatricians, whether in training or in practice, encounter these patients, yet toxicologic training is lacking in most pediatric residencies.

Objectives

After completing this article, readers should be able to:

1. Understand the epidemiology of pediatric poisonings and explain how developmental milestones influence behavior that may lead to a poisoning exposure.
2. Perform a focused toxicologic physical examination and describe the various toxidromes.
3. Explain the primary acid-base disturbance in salicylate toxicity.
4. Determine which patient requires treatment after acute acetaminophen ingestion.
5. Provide the differential diagnosis of an anion gap metabolic acidosis.
6. Identify which drugs can lead to QRS and QTc prolongation and the treatment for each abnormality.
7. Describe the toxicologic differential diagnosis for hypoglycemia and explain the physiologic reasons why pediatric patients are at increased risk for complications.

INTRODUCTION

This review focuses on the epidemiology and initial evaluation and treatment of the poisoned pediatric patient. We emphasize the diagnosis and treatment of acetaminophen and aspirin toxicity, identifying and treating prolonged QRS/QTc, and developing a differential diagnosis for an anion gap metabolic acidosis (AGMA) and hypoglycemia (Table 1).

EPIDEMIOLOGY OF PEDIATRIC POISONING

Pediatric exposures and poisonings continue to be a significant cause of morbidity and mortality. According to the 2014 Annual Report of the American Association of Poison Control Centers’ National Poison Data System (NPDS), 1,326,789 toxic exposures occurred in children younger than age 20 years in 2014, representing
1,595 exposures per 100,000 population compared to 344 exposures per 100,000 population in adults. (1) In addition, 88 poisoning fatalities in children younger than age 20 years were reported, representing 7.5% of all fatalities reported to the NPDS in 2014. Pediatric poisonings occur across all ages, with children younger than age 3 years representing more than 33% of all exposures, and children age 5 years and younger representing slightly less than 50% of all exposures. Pediatric poisonings in children age 5 years and younger peaked in 2008 and are now decreasing (Fig 1). The reason for this decline is unclear, but some authors postulate that newer safety packaging and passive safety features (eg, single-dose packaging) are providing an added protective barrier.

Children are exposed to a variety of foreign substances, also known as xenobiotics. In children younger than age 6 years, exposures to household cleaning products and cosmetics represent the majority of calls to poison centers. Over-the-counter liquid acetaminophen and cold and cough medication are responsible for the most emergency department visits. Buprenorphine and clonidine account for the most hospitalizations. (2)

Developmental status plays an important role in pediatric poisonings. Because newborns do not have the mobility or the manual dexterity to manipulate child-resistant packaging, a poisoned neonate should raise suspicion for medical child abuse and/or neglect. As children become more mobile and are able to explore their surroundings, the risk for unintentional ingestion increases substantially. The increase in mobility coincides with the development of a pincer grasp and oral exploratory behavior, all of which lead to an increased risk for unintentional exposures. Primary care clinicians should use the 4- and 6-month health supervision visits as opportunities to discuss safe medication and household product storage as well as to review the process for calling the local poison control center, which can be reached toll-free in the United States at 1-800-222-1222.

**TABLE 1. Introduction to the Poisoned Patient**

- Epidemiology of pediatric poisoning
- Toxicologic history, physical examination, and toxidromes
- Acetaminophen
- Aspirin
- Anion gap metabolic acidosis
- Electrocardiographic changes in the poisoned patient
- Toxic differential diagnosis of hypoglycemia

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**Figure 1.** Exposures involving children age 5 years and younger reported to the National Poison Data System (NPDS) by year. Such encounters peaked in 2008, a trend that mirrored total encounters reported to the NPDS. Data abstracted from the 2014 Annual Report of the American Association of Poison Control Centers’ National Poison Data System. 32nd Annual Report (Clin Toxicol. 2015;53(10):962–1146).
As children become preteenagers and teenagers, experimentation with illicit drugs and intentional overdoses are more common. Parents need to balance adolescent autonomy, including the self-administration of medications, with the need for safety. The primary care clinician should use the yearly physical examination to obtain a full substance abuse history. Parents should be asked to leave the examination room and patients should be asked about illicit drug use, including the use of synthetic cannabinoids (eg, “K2,” “Spice”) and synthetic cathinones (eg, “bath salts”). These drugs are often sold legally in gas stations and head shops, and adolescents may mistakenly equate their availability with safety. Patients should also be asked about prescription drug abuse, both at home and within their peer group, and be screened for depression.

**THE TOXICOLOGIC HISTORY, PHYSICAL EXAMINATION, AND TOXIDROMES**

Several key pieces of information should be collected for every patient who has had a possible xenobiotic exposure. The specific xenobiotic, including dose, quantity, preparation (eg, liquid, pill, patch), and route (eg, ingestion, inhalation, dermal, ocular, intravenous [IV], rectal) of exposure should be assessed. Additional information regarding ingestion of an immediate- versus extended-release preparation is also important. Time of ingestion can guide the need for antidotal therapy. For example, the need for antidotal therapy for acetaminophen ingestion is based on a 4-hour serum acetaminophen concentration (see the Acetaminophen section in this article). Similarly, activated charcoal may be recommended if ingestion occurred within the previous 1 to 2 hours and the patient is able to swallow safely. If the exposure was unwitnessed or the patient is unresponsive, a comprehensive home medication list should be obtained.

A focused toxicologic physical examination should be performed on every poisoned patient. The toxicologic physical examination seeks to identify a group of signs and symptoms that are reliably caused by a specific xenobiotic. These groups of particular signs and symptoms are referred to as toxic syndromes or toxidromes. Identifying toxidromes allows a clinician to narrow the differential diagnosis to a subset of xenobiotics that correspond to the given toxidrome.

As with most patients, a careful review of the vital signs is paramount. The autonomic nervous system is frequently affected by xenobiotics, which can result in frequent vital sign abnormalities. The use of age-appropriate vital sign norms is imperative; a respiratory rate of 18 breaths/min may be normal in a teenager, but it is well below the 1st percentile in a 1-year-old child. Recognition of abnormal vital signs is particularly important in settings where ancillary staff is not accustomed to pediatric patients and treating clinicians might not be immediately cognizant of vital sign derangements. Fever in a poisoned patient could suggest excessive neuromuscular agitation from sympathomimetic or anticholinergic agents or may be the result of uncoupling of oxidative phosphorylation due to salicylate or dinitrophenol ingestion. On the other hand, hyperthermia could indicate a sedative-hypnotic exposure, such as baclofen or a barbiturate. Tachycardia often signals excess sympathetic tone or anticholinergic activity, while the combination of bradycardia and hypotension has its own toxicologic differential diagnosis (Table 2). Tachypnea and hyperpnea could suggest respiratory compensation for a metabolic acidosis or may be due to direct medullary stimulation from a salicylate. Conversely, bradypnea points to an opioid overdose.

A thorough neurologic examination should be performed, including assessment of mental status, presence of miosis or mydriasis, accommodation, and nystagmus. Clonus and/or hyperreflexia should be tested for because these are signs of serotonergic excess and are often seen in selective serotonin reuptake inhibitor overdose. Examination of the oropharynx should focus on the presence or absence of moist mucous membranes and include investigation for any ulceration that

### TABLE 2. Toxicologic Differential Diagnosis for Bradycardia and Hypotension

<table>
<thead>
<tr>
<th>DRUG CLASS</th>
<th>EXAMPLES</th>
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<tbody>
<tr>
<td>Central α2-adrenergic receptor agonists</td>
<td>Clonidine, guanfacine, dexmedetomidine, oxymetazoline, tetrahydrozoline</td>
</tr>
<tr>
<td><strong>β</strong>-adrenergic receptor antagonists</td>
<td>Propranolol, metoprolol, esmolol</td>
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<tr>
<td>Calcium channel blockers</td>
<td>Diltiazem, verapamil, amlodipine</td>
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<tr>
<td>Cardiac glycosides</td>
<td>Digoxin, oleander (Nerium oleander), yellow oleander (Thevetia peruviana), foxglove (Digitalis species), lily of the valley (Convallaria majalis), red squill (Urginea maritima)</td>
</tr>
<tr>
<td>Acetylcholinesterase inhibitors</td>
<td>Organophosphates, carbamates, neostigmine, sarin, VX nerve gas</td>
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could suggest caustic ingestion. The respiratory evaluation should make note of excess secretions and/or wheeze, findings that may be present in organophosphate poisoning. Auscultation of the abdomen should be performed to assess for hypo- or hyperactive bowel sounds. Skin assessment should note the presence or absence of diaphoresis, flushing, or impaired peripheral perfusion.

Once vital signs have been assessed and a focused toxicologic examination has been performed, the treating physician should be able to ascertain if a patient fits into a defined toxidrome (Table 3). These characterizations help narrow the differential diagnosis and guide subsequent treatment. Unintentional ingestions by toddlers frequently involve a single substance, which can increase the likelihood of identifying a toxidrome. As expected, polysubstance exposures can cloud the picture, and treating physicians must integrate multiple pieces of information to arrive at the correct diagnosis. Consultation with a medical toxicologist is advised for critically ill patients.

**ACETAMINOPHEN**

**Epidemiology**

Acetaminophen, or N-acetyl-para-aminophenol (APAP), remains one of the most commonly ingested xenobiotics, both intentionally and unintentionally. APAP is responsible for one-third of all pediatric emergency department visits for unsupervised over-the-counter liquid medication exposures in children younger than age 6 years. In addition, APAP is the cause of almost one-fifth of medication exposures involving oral over-the-counter solid medications, the highest single agent in each category. (3)

The reasons for such high exposure rates are varied. First, APAP is extremely prevalent in the community, with most homes having APAP in their medicine cabinets. Second, APAP is perceived as a safe medication by the lay public. (4) Third, multiple APAP-containing products are used to treat a variety of common maladies and families are often unaware that they are administering APAP. (5) Finally, dosing errors are common in APAP administration; parents frequently unknowingly administer supratherapeutic doses. (6)

**Sources**

As mentioned previously, a multitude of APAP-containing products are commonly prescribed. Oxycodone-APAP and hydrocodone-APAP combination products are frequently prescribed for the treatment of moderate-to-severe pain; over-the-counter cold and cough remedies commonly contain APAP in addition to dextromethorphan and chlorpheniramine or doxylamine; and APAP is used in combination with butalbital and caffeine to treat migraines. Families may be unaware that a medication contains APAP and administer concomitant doses, producing an unintentional toxic

<table>
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<th>TABLE 3. Toxic Syndromes</th>
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<td><strong>GROUP</strong></td>
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<td>---------------------</td>
</tr>
<tr>
<td>Anticholinergics</td>
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<tr>
<td>Cholinergics</td>
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<tr>
<td>Ethanol or sedative-hypnotics</td>
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<tr>
<td>Opioids</td>
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<tr>
<td>Sympathomimetics</td>
</tr>
<tr>
<td>Withdrawal from ethanol or sedative-hypnotics</td>
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<tr>
<td>Withdrawal from opioids</td>
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</tbody>
</table>

concentration. It is useful to remember that medication names ending in “-cet” always contain APAP (eg, Percocet, Roxicet, Fioricet).

**Metabolism/Pharmacokinetics/Toxicokinetics/Pathophysiology**

Orally administered APAP is rapidly absorbed from the gastrointestinal (GI) tract, with complete absorption occurring within 4 hours, although coingestion with anticholinergic drugs such as diphenhydramine or opioids can delay absorption. The metabolism of APAP is depicted in Fig 2. Of greatest concern to the treating clinician is generation of the toxic metabolite N-acetyl-p-benzoquinoneimine (NAPQI). In therapeutic dosing, the body has sufficient stores of glutathione (GSH) to reduce and detoxify NAPQI. In overdose, alternative metabolic pathways become saturated, and there is increased formation of NAPQI, leading to depletion of GSH and accumulation of NAPQI.

As NAPQI accumulates, it binds to various cellular proteins, inducing hepatocellular death and liver inflammation. Toxicity manifests as rising aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values. In addition, depletion of GSH leaves the body susceptible to endogenous reactive oxygen species, leading to further damage. Histologically, damage is most profound in hepatic zone III due to the high concentration of the enzyme CYP2E1.

**Clinical Effects**

The stages of APAP toxicity are listed in Table 4. Clinicians must have a high index of suspicion due to the absence of specific signs and symptoms early in intoxication. Often patients present without symptoms or with vague abdominal pain, nausea, and emesis. As the toxic metabolite NAPQI accumulates, evidence of liver injury, namely, elevation of AST and ALT serum concentrations and prolongation of prothrombin time/International Normalized Ratio, develop. Of note, the accumulation of NAPQI takes time; APAP must be metabolized first, followed by depletion of the patient’s supply of GSH. If a patient presents within 4 hours of ingestion and is already exhibiting signs of hepatocellular injury, the time of ingestion must be re-examined. Finally, every patient may not necessarily progress to the next stage of toxicity.

**Diagnosis and Management**

As previously mentioned, APAP ingestions are common in the pediatric population. As such, we recommend routine assessment of serum APAP concentration in all unknown ingestions and instances of self-harm. When the time of ingestion is known, we recommend obtaining a serum APAP concentration at 4 hours after ingestion or later; by this time, absorption from the GI tract is complete and the need for antidotal therapy can be determined. Treatment with N-acetylcysteine (NAC) should be initiated if the patient’s APAP concentration is above the treatment line on the Rumack-Matthew nomogram (Fig 3). Interestingly, the original treatment line, depicted by the dotted line in Fig 3, began at 200 µg/mL, but the Food and Drug Administration (FDA) required a 25% reduction for safety reasons. Thus, the current treatment line begins at 150 µg/mL. We recommend against empirical treatment with NAC within the first 8 hours of ingestion because research has shown no...
change in morbidity when treatment is initiated within 8 hours. \(^7\) Therefore, it is reasonable to delay NAC therapy if the ingestion occurred within the last 8 hours, the patient is a reliable historian, and a serum APAP concentration can be obtained to determine the need for antidotal therapy. It is important to note that use of the Rumack-Matthew nomogram requires a single, one-time ingestion with a known ingestion time. Coingestion with drugs that alter GI absorption (eg, anticholinergics, opioids) can alter the pharmacokinetics of APAP absorption, necessitating additional assessments of serum APAP concentrations.

NAC is used to protect the liver and body from the oxidative stress of NAPQI and functions by detoxifying NAPQI, regenerating GSH, and scavenging for reactive oxygen species. It is available in IV and oral (PO) formulations. The decision to treat enterally versus parenterally is complex. Both formulations have been shown to be effective in treating APAP toxicity. The IV formulation is associated with a non-immunoglobulin E-mediated anaphylactoid reaction. Patients are at greatest risk early in treatment, typically during the loading dose, when the dose and concentration of NAC is the greatest. Nausea and vomiting are common with the PO formulation, raising the possibility of delayed treatment. The clinician must consider these issues with each patient.

Treatment of patients who do not “rule-in” for use of the Rumack-Matthew nomogram is difficult. There is general consensus that a patient who presents with a detectable APAP concentration and elevated transaminases in the setting of an unknown time of ingestion warrants treatment with NAC, and a patient with an undetectable APAP concentration and normal transaminase values does not. Management of the patient with detectable APAP and normal transaminases or undetectable APAP and elevated transaminases is less clear. Consultation with a medical toxicologist is recommended;

**TABLE 4. Clinical Stages of Acetaminophen Toxicity***

<table>
<thead>
<tr>
<th>STAGE</th>
<th>SIGNS/SYMPTOMS</th>
<th>LABS</th>
<th>TIME FRAME</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Nausea</td>
<td>Normal AST/ALT, INR</td>
<td>0-24 hours</td>
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<tr>
<td></td>
<td>Vomiting</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Malaise</td>
<td></td>
<td></td>
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<td></td>
<td>Pallor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Hepatotoxicity</td>
<td>Rising AST/ALT</td>
<td>12-72 hours</td>
</tr>
<tr>
<td></td>
<td>Right upper quadrant tenderness</td>
<td>INR normal/elevated</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Fulminant hepatic failure</td>
<td>AST/ALT &gt;10,000 U/L (167 (\mu)kat/L)</td>
<td>72-96 hours</td>
</tr>
<tr>
<td></td>
<td>Encephalopathy</td>
<td>INR elevated</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Coma</td>
<td>Elevated Cr</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acidosis</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Lactemia</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Recovery</td>
<td>Normalization of AST/ALT, INR</td>
<td>&gt; 96 hours</td>
</tr>
</tbody>
</table>

*As acetaminophen is metabolized to the hepatotoxic metabolite N-acetyl-p-hydroquinoneimine, transaminases rise and focal tenderness develops. As hepatic injury worsens and the synthetic capability of the liver is impaired, prothrombin time/INR increase. Eventually, multisystem organ failure develops, after which patients recover, receive liver transplant, or die.

ALT = alanine aminotransferase, AST = aspartate aminotransferase, Cr = creatinine, INR = International Normalized Ratio.

**Figure 3.** Rumack-Matthew nomogram (reconstructed) for determining the risk of acetaminophen-induced hepatotoxicity after a single acute ingestion. Serum concentrations above the treatment line on the nomogram indicate the need for N-acetylcysteine therapy. Reproduced with permission from *Goldfrank's Toxicologic Emergencies*, 10th Edition, Copyright © 2015 by McGraw-Hill Education. Full text may be available from the McGraw-Hill Education website: www.mhprofessional.com.
following trends in serum APAP concentrations is key to appropriate management.

The most widely used treatment protocols involve a 21-hour course of IV NAC or a 72-hour course of PO NAC. Before discontinuing NAC, laboratory studies should be obtained, and treatment should continue until APAP is undetectable, hepatic transaminases are improving, serum prognostic markers (creatinine, prothrombin time/International Normalized Ratio, lactate, pH) are improving, and the patient is asymptomatic with no abdominal pain. (8)

ASPIRIN

Epidemiology
Aspirin, or acetylsalicylic acid (ASA), is a commonly used medication for both its analgesic and anti-inflammatory effects. It is used frequently today in the pediatric population to treat Kawasaki disease and in adult patients to mitigate the risks of myocardial infarction, colon cancer, and transient ischemic attacks. The most recent NPDS annual report states that exposures to aspirin as the sole agent in children age 19 years and younger occurred in 5,917 reported patients in 2014, with 3,459 of them occurring in children younger than age 6 years. Although aspirin was a significant cause of childhood poisonings several decades ago, the known association with Reye syndrome, coupled with the increased use of acetaminophen and nonsteroidal anti-inflammatory medications such as ibuprofen, have decreased the number of exposures reported annually to Poison Control Centers.

Sources
Aspirin can be found in various preparations, including chewable tablets and enteric-coated pills; its derivative 5-aminosalicylic acid is included in the medications sulfasalazine and mesalamine to reduce the inflammation in Crohn disease. Besides these single-ingredient medications, it can be found in combination with bismuth subsalicylate as an antidiarrheal treatment, magnesium subsalicylate in combination with caffeine as a weight loss agent, and as methyl salicylate (oil of wintergreen) as a flavoring agent or topical therapy for musculoskeletal pain. Of note, one teaspoon (5 mL) of oil of wintergreen contains approximately 7 g of salicylates, and pediatric fatalities with this amount have been reported. (9)

Metabolism/Pharmacokinetics/Toxicokinetics/
Pathophysiology
Salicylates are well absorbed from the GI tract, particularly in the acidic milieu of the stomach. Absorption continues in the small intestine, with large overdoses of enteric products having the propensity to form bezoars. Acute ingestions of 150 to 200 mg/kg produce mild symptoms; amounts in the range of 300 to 500 mg/kg are considered serious. Salicylates cause toxicity by stimulating the respiratory center in the medulla that prompts an increase in respiratory rate and subsequent respiratory alkalosis; increased insensible fluid losses are also seen. Uncoupling of oxidative phosphorylation interrupts both glucose and fatty acid metabolism, with subsequent metabolic acidosis, hyperthermia, and hypoglycemia. Salicylates are metabolized in the liver and eliminated by the kidneys.

Clinical Effects
Pediatric aspirin ingestions are typically acute as compared to ingestions in adults, who may have drug accumulation following chronic use. Vomiting is the initial symptom and is due not only to irritation of the GI mucosa but also to stimulation of the chemoreceptor trigger zone in the medulla. Tinnitus (subjective sensation of ringing in the ears), tachypnea, and hyperpnea are also seen. Tachycardia can result from insensible fluid losses. With more severe intoxications, mental status changes become prominent, including delirium, agitation, and seizures due to cerebral edema. Hypoxia and chest radiograph changes consistent with pulmonary edema are another sign of critical poisoning.

Diagnosis and Management
Salicylate poisoning is typically diagnosed by history and/or laboratory evaluation. Even in the setting of an unknown overdose, physical examination findings suggestive of salicylism include vomiting, tachypnea, hyperpnea, tinnitus, and mental status changes; laboratory abnormalities can include a mixed respiratory alkalosis and metabolic acidosis on blood gas analysis. Serum aspirin concentrations of 30 mg/dL and higher require treatment with urinary alkalinization. Levels higher than 90 to 100 mg/dL after an acute poisoning are considered life-threatening, and concentrations greater than 60 mg/dL in patients chronically taking aspirin are regarded as serious; both require treatment with hemodialysis. The mnemonic “30-60-90” may facilitate remembering these laboratory values, but clinicians must ensure that the laboratory results are expressed in units of mg/dL to use the mnemonic. Aspirin concentrations should be measured every 1 to 2 hours until a peak serum concentration is reached and then carefully followed until the values decrease to less than 30 mg/dL. Serious problems can occur when values are not obtained for several hours and a precipitous rise in the serum salicylate concentration occurs due to bezoar rupture and/or erratic drug absorption. Decontamination with activated charcoal is paramount,
especially in the setting of enteric-coated products and/or massive overdoses that may form a bezoar. Urinary alkalinization with sodium bicarbonate therapy and hemodialysis are the mainstays of salicylate overdose management in conjunction with good supportive care. By raising the urine pH to 7.3 and greater, less unionized drug is available in the renal tubule for resorption, and subsequent urinary drug elimination is enhanced. The serum pH must be monitored simultaneously to ensure that it does not exceed 7.55. Hemodialysis is recommended in the following settings: acute serum salicylate concentrations of 90 mg/dL and greater; chronic serum salicylate concentrations of 60 mg/dL and greater; and in all instances of pulmonary or cerebral edema, renal insufficiency, seizures, unremitting acidosis, or acute clinical deterioration despite aggressive supportive care regardless of serum salicylate concentration. (10)

ANION GAP METABOLIC ACIDOSIS

Assessing a patient’s acid-base status is essential when evaluating a critically ill patient or when an underlying cause of a patient’s condition is unknown. This assessment is accomplished by measuring the patient’s serum pH, bicarbonate ([HCO₃⁻]), and partial pressure of carbon dioxide. With these 3 parameters, a clinician can classify the patient as having an acidosis or alkalosis and determine whether it is metabolic or respiratory. Due to its usefulness in identifying various poisonings, this review focuses on AGMA.

The concept of the anion gap is predicated on the concept of electroneutrality, which states that the number of negatively charged ions in a solution, in this case the serum, must equal the number of positively charged ions. In a practical sense, this means that the amount of sodium and potassium (the primary cations in serum) equals the amount of bicarbonate and chloride (the primary anions in the serum). An anion gap arises in the presence of unaccounted anions in the serum. Toxic alcohol ingestion can illustrate this concept further. Ingestion of ethylene glycol leads to AGMA due to accumulation of organic acids (glycolate and oxalate) that result from metabolism of ethylene glycol via alcohol dehydrogenase and then aldehyde dehydrogenase. As the buffering capability of bicarbonate is depleted, the measured [HCO₃⁻] decreases. Replacing the [HCO₃⁻] and, thus, maintaining electroneutrality are the unmeasured glycolate and oxalate anions, with the net result of an increased anion gap. Due to the decrease in [HCO₃⁻], this becomes evident as metabolic acidosis.

The anion gap is calculated by the following formula:

$$\text{Anion gap} = ([\text{Na}^+] - ([\text{HCO}_3^-] + [\text{Cl}^-])$$

Of note, potassium ([K⁺]) is omitted from the formula because K⁺ rarely fluctuates more than 1 to 2 mEq/L above or below normal values, thus only minimally contributing to the anion gap. The definition of a “normal anion gap” varies with laboratory instrumentation; newer analyzers have the ability to detect higher chloride Cl⁻ concentrations, thus lowering the “normal anion gap.” A baseline anion gap exists and is considered normal because sodium ([Na⁺]) represents a larger proportion of the total extracellular cations compared to the contributions of [HCO₃⁻] and Cl⁻ to the total extracellular concentration of anions.

The differential diagnosis of a high AGMA is represented by the acronym “MUDPILES” (Table 5). Although the underlying principles of why an anion gap develops are the same for all of the listed xenobiotics, how each achieves an anion gap varies. Some xenobiotics induce an AGMA via the generation of exogenous acids through their normal metabolism (eg, methanol, ethylene glycol, propylene glycol). Others function to poison the mitochondria and inhibit oxidative phosphorylation (eg, carbon monoxide, cyanide, hydrogen sulfide), leading to anaerobic metabolism and acid generation. Treatment varies according to the ingestion. Patients with methanol or ethylene glycol ingestion should have the first step in alcohol metabolism, alcohol dehydrogenase, blocked with fomepizole to inhibit the formation of toxic metabolites. Patients with salicylate concentrations greater than 30 mg/dL should have urinary alkalinization with sodium bicarbonate to enhance the elimination of salicylate ions. No matter what the exposure, patients with an AGMA require close monitoring and serial laboratory monitoring. It is important to remember that such patients often develop tachypnea and hyperpnea as they attempt to “blow-off” carbon dioxide to compensate for the metabolic acidosis. If a patient decompensates and requires intubation, care must be taken to match the patient’s minute ventilation (minute ventilation = respiratory rate × tidal volume) before intubation; using a “normal” respiratory rate effectively hypoventilates the patient, leading to a harmful respiratory acidosis.

ELECTROCARDIOGRAPHIC CHANGES IN THE POISONED PATIENT

The electrocardiogram (ECG) is an integral tool in the diagnosis and management of the poisoned patient. It is a low-cost bedside diagnostic evaluation that can provide valuable, real-time information on the cardiac conduction system,
identifying dysrhythmias, heart block, conduction abnormalities, and myocardial ischemia. We recommend that an ECG be obtained on all patients who present with an unknown ingestion and in instances of self-harm. Hundreds of xenobiotics alter the normal flux of ions through various myocardial channels, which form the basis for normal cardiac function (Fig 4), with antiepileptics, antipsychotics, antidepressants, local anesthetics, and antiarrhythmics frequently causing ECG abnormalities. Two specific intervals deserve special consideration: the QRS complex and the QT interval.

The QRS Complex

In the most basic sense, the QRS complex represents ventricular depolarization. Ventricular depolarization results from the influx of sodium into the myocardial cell through voltage-sensitive sodium channels during phase 0. These channels are susceptible to blockade by a myriad of xenobiotics (Table 6), with the net effect of sodium-channel blockade being prolongation of the QRS complex. Interestingly, most xenobiotics preferentially block the right-sided conduction pathway, producing an incomplete right bundle branch block that is detected on ECG. In addition to QRS prolongation, sodium-channel blockade can manifest in an elevation in the terminal R-wave in lead aVR, with previous research suggesting that an R-wave greater than 3 mm is predictive of seizure or dysrhythmia in patients who have tricyclic antidepressant poisoning. (11)

In the poisoned patient, we consider a QRS greater than 100 msec to be abnormal, and such a prolongation warrants treatment with antidotal therapy. (12)(13) Previous research on patients poisoned with tricyclic antidepressants showed that those who had a QRS less than 100 msec had no instances of seizure or ventricular dysrhythmias, but a QRS greater than 100 msec was associated with an ~30% chance of seizure and a QRS greater than 160 msec was associated with a 50% chance of ventricular dysrhythmia. (14) In patients with known cardiac conduction delays, the treating clinician must weigh the risks and benefits of treatment. Because most pediatric patients have healthy conduction systems, a QRS greater than 100 msec warrants treatment unless the patient has a known cardiac conduction abnormality, such as a right bundle branch block.

Treatment of a widened QRS complex is aimed at reversing the inhibition of ventricular depolarization. As mentioned previously, ventricular depolarization is a sodium-dependent process, and xenobiotics (eg, tricyclic antidepressants, local anesthetics, class 1a and 1c antiarrhythmics) that affect the QRS primarily do so through blockade of fast-sodium channels. To overcome this blockade, IV sodium bicarbonate is administered to increase the extracellular concentration of sodium and disrupt the sodium-channel blockade. The effect of sodium bicarbonate therapy is twofold. First, by increasing the extracellular concentration of sodium, the number of sodium ions that may enter the myocardial cell through unblocked channels is increased, thus promoting depolarization. Second, by making the blood more alkaline, the amount

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<th>TABLE 5. Toxicologic Differential Diagnosis for Anion Gap Metabolic Acidosis</th>
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<td><strong>U</strong></td>
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Figure 4. Relationship of electrolyte movement across the cell membrane (A) to the action potential and the surface electrocardiographic (ECG) recording (B) over a single cardiac cycle. Ca = calcium, K = potassium, Na = sodium. Reproduced with permission from Goldfrank’s Toxicologic Emergencies, 10th Edition, Copyright © 2015 by McGraw-Hill Education. Full text may be available from the McGraw-Hill Education website: www.mhprofessional.com.
of uncharged xenobiotic, which has a lower affinity for sodium channels, is increased, thus decreasing channel blockade. (15)(16)

In pediatric patients, we recommend a bolus of 1 to 2 mEq/kg of sodium bicarbonate followed by a continuous infusion of 150 mEq of sodium bicarbonate in 1 L of 5% dextrose to infuse at 1.5 to 2 times the maintenance IV fluid rate. It is important to closely monitor the patient’s QRS complex and the serum pH and potassium because bicarbonate administration causes progressive alkalemia as well as hypokalemia as potassium is shifted intracellularly and excreted by the kidneys. Bicarbonate therapy should be continued until the QRS is less than 100 msec or has returned to the patient’s baseline. Continuing to monitor the patient’s QRS after the bicarbonate infusion has been discontinued is critical because patients are at risk for rewidening the QRS after discontinuation of therapy.

**QTC interval**
The QT interval is measured from the onset of the QRS complex to the end of the T-wave and encompasses ventricular depolarization, onset, and completion of repolarization. The QT increases with bradycardia and shortens with tachycardia. As such, various formulas have been used to adjust for rate variation, with the Bazett formula being one of the most common to calculate the QT corrected for heart rate (QTC):

$$QTC (\text{msec}) = \frac{QT (\text{msec})}{\sqrt{RR \text{ interval (sec)}}}$$

Many drugs induce QTC prolongation through potassium channel blockade, specifically by blocking the HERG-encoded subunit of the delayed rectifier potassium channel (IKr) (Table 6). This leads to prolongation of the repolarization (phase 3) portion of the cardiac action potential. In addition, alterations in serum electrolytes, primarily calcium, magnesium, and potassium, can alter the QTC. Finally, xenobiotics that affect the fast-sodium channel prolong the QRS and, thus, can cause QTc prolongation.

The result of a prolonged QTC interval is an increased chance of early afterdepolarizations, which are spontaneous depolarizations of myocardial tissue before repolarization is complete. If depolarization is large enough, premature ventricular contractions can occur, with the possibility of progressing to ventricular tachycardia, ventricular fibrillation, or torsade de pointes.

Treatment of a prolonged QTC includes electrolyte supplementation, including potassium, magnesium, and calcium. A goal serum magnesium concentration of 2 mEq/L and an ionized calcium of 2 mmol/L is recommended. If a patient progresses to torsade de pointes, magnesium sulfate should be infused, and if the patient is hemodynamically unstable, electrical defibrillation is required. It is also critically important to stop all nonessential QTc-prolonging agents. Many common drugs, such as ondansetron, antipsychotics, antidepressants, and a variety of antibiotics, can prolong the QTc and place the patient at further risk for ventricular dysrhythmia. For the purposes of simplicity, we define a potentially dangerous prolonged QTC interval as a QTC greater than 500 msec, with the understanding that age-specific normal values exist.

### TOXICOLOGIC DIFFERENTIAL DIAGNOSIS OF HYPOGLYCEMIA

The definition of hypoglycemia in the pediatric patient continues to be controversial. As valuable as it would be to have a serum glucose concentration that identifies hypoglycemia in every patient, the fact remains that individuals differ in their response to glucose concentrations. One patient may be symptomatic at a serum glucose concentration of 60 mg/dL (3.33 mmol/L) and another may not. As such, the definition of hypoglycemia should be a serum

---

**TABLE 6. Xenobiotics Associated with QRS and QTc Prolongation on Electrocardiography***

<table>
<thead>
<tr>
<th>QRS WIDENING AGENTS</th>
<th>QTc PROLONGING AGENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupivacaine</td>
<td>Antipsychotics</td>
</tr>
<tr>
<td>Bupropion</td>
<td>Class Ia, Ic, and III antiarrhythmics</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Fluoroquinolones</td>
</tr>
<tr>
<td>Class Ia and Ic antiarrhythmics</td>
<td>Macrolides</td>
</tr>
<tr>
<td>Cocaine</td>
<td>Methodone</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>Ondansetron</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Selective serotonin and norepinephrine reuptake inhibitors (eg, duloxetine, venlafaxine)</td>
</tr>
<tr>
<td>Quinidine</td>
<td>Selective serotonin reuptake inhibitors (eg, fluoxetine, sertraline, citalopram)</td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td></td>
</tr>
</tbody>
</table>

*Agents that prolong the QRS block fast-acting sodium channels and delay phase 0 of the myocardial action potential and ventricular depolarization. Drugs that prolong the QTC inhibit phase 2 or 3, often through IKr blockade.
neurologic changes. Stimulation due to adrenergic blockade but should have expected hypoglycemic may not exhibit the symptoms of autonomic cerebral blood glucose, the brain changes occur in response to a decrease in the amount of available concentrations in response to hypoglycemia; central nervous system.

Most notably alanine, due to lower muscle mass reserve. In infants, hypoglycemia is often due to inborn errors of metabolism and congenital hyperinsulinism. As patients become mobile, the risk of xenobiotic-induced hypoglycemia increases.

The pediatric patient is at increased risk of hypoglycemia due to a child’s higher baseline rate of glucose utilization and relatively limited supply of gluconeogenic precursors, most notably alanine, due to lower muscle mass reserve. In infants, hypoglycemia is often due to inborn errors of metabolism and congenital hyperinsulinism. As patients become mobile, the risk of xenobiotic-induced hypoglycemia increases.

The first component of the counterregulatory response is a decrease in insulin secretion, which occurs when blood glucose concentrations fall below 80 to 85 mg/dL (4.45-4.72 mmol/L). Further decreases in blood glucose concentrations cause an increase in glucagon secretion, which commonly appears at a blood glucose concentration of less than 70 mg/dL (3.89 mmol/L). Glucagon acts on the liver to promote glycogenolysis and gluconeogenesis. Next, autonomic stimulation, manifested by rising epinephrine concentrations, occurs, which produces many of the clinical symptoms of hypoglycemia (Table 7). Of note, adrenergic receptor antagonists (eg, β-adrenergic receptor antagonists such as propranolol) can blunt this response. Finally, cortisol concentrations rise to promote hepatic gluconeogenesis.

The toxicologic differential diagnosis for hypoglycemia is displayed in Table 8 and can be remembered by the acronym “HOBBIES.” Ethanol is a common acquired cause of hypoglycemia in the pediatric patient and should be on the differential diagnosis list for any child who presents to the emergency department with ataxia, acute change in mental status, and hypoglycemia. Via ethanol’s metabolism by alcohol dehydrogenase, nicotinamide adenine dinucleotide is depleted, inhibiting the oxidation of lactate to pyruvate. Pyruvate is a key step in gluconeogenesis, and depletion can lead to fasting hypoglycemia in the pediatric patient.

Sulfonylurea exposure can be potentially life-threatening in the pediatric population due to its ability to produce profound hypoglycemia. Any patient with potential exposure to sulfonylureas, such as glyburide and glipizide, should be admitted for overnight monitoring and frequent blood glucose evaluations for several reasons. The overnight period is a physiologic period of fasting during which blood glucose hemostasis is dependent on gluconeogenesis and glycogenolysis. In addition, cortisol concentrations are at their lowest point overnight.

Sulfonylureas and meglitinides induce hypoglycemia via the release of endogenous insulin from the pancreatic β-cell. Treatment involves administration of dextrose-containing fluids to immediately correct hypoglycemia as well as octreotide to suppress further insulin secretion. Octreotide is a semisynthetic somatostatin analog that inhibits pancreatic β-cell insulin release. Research has shown that prompt administration of octreotide to hypoglycemic patients exposed to sulfonylureas leads to fewer dextrose boluses and fewer episodes of hypoglycemia. (17)

Finally, β-adrenergic receptor antagonists induce hypoglycemia through their inhibition of gluconeogenesis and glycogenolysis, both of which are adrenergic-mediated processes. As mentioned previously, many of the clinical

### TABLE 7. Clinical Manifestations of Hypoglycemia*

<table>
<thead>
<tr>
<th>Neurogenic Symptoms Due to Autonomic Nervous System Stimulation</th>
<th>Neuрогlyceropenic Symptoms Due to Low Cerebral Blood Glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tachycardia</td>
<td>Headache</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>Visual changes</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>Confusion</td>
</tr>
<tr>
<td>Pallor</td>
<td>Somnolence</td>
</tr>
<tr>
<td>Hyperthermia</td>
<td>Coma</td>
</tr>
<tr>
<td>Weakness</td>
<td>Seizure</td>
</tr>
</tbody>
</table>

*Autonomic symptoms are the result of elevated epinephrine concentrations in response to hypoglycemia; central nervous system changes occur in response to a decrease in the amount of available cerebral blood glucose, the brain’s preferred energy source. Patients who are exposed to a β-adrenergic receptor antagonist and become hypoglycemic may not exhibit the symptoms of autonomic stimulation due to adrenergic blockade but should have expected neurologic changes.

### TABLE 8. Toxicologic Differential Diagnosis for Hypoglycemia

<table>
<thead>
<tr>
<th></th>
<th>Hypoglycemics, oral (eg, sulfonylureas, meglitinides)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Other (eg, unripe fruit from the Ackee (Blighia sapida) tree, lychee fruit, intravenous quinine)</td>
</tr>
<tr>
<td>O</td>
<td>β-adrenergic receptor antagonists (“β-blockers”)</td>
</tr>
<tr>
<td>BB</td>
<td>Insulin</td>
</tr>
<tr>
<td>I</td>
<td>Ethanol</td>
</tr>
<tr>
<td>E</td>
<td>Salicylates</td>
</tr>
</tbody>
</table>
manifestations of hypoglycemia are adrenergically mediated and as such, are absent in a patient who has β-adrenergic receptor antagonist-induced hypoglycemia.

**Summary**

- Pediatric poisonings are common, representing more than 60% of all calls reported to the National Poison Data System in 2014.
- A 4-hour or later serum acetaminophen (APAP) concentration should be obtained on all patients who present after intentional ingestion. On the basis of evidence from research as well as expert consensus (level C), we recommend against empirical treatment with N-acetylcysteine if the APAP ingestion occurred within the previous 8 hours. (7)
- QRS prolongation is due to fast-sodium channel blockade and results in delayed ventricular depolarization. On the basis of some research evidence as well as consensus (level C), if the QRS is greater than 100 msec, a trial of sodium bicarbonate is warranted. (12)(13)(14)
- Sulfonylureas can cause life-threatening hypoglycemia. Pediatric patients are at increased risk for hypoglycemia, especially overnight. Treatment is with dextrose-containing fluids and octreotide (level C).
- The local poison center can be reached toll-free in the United States at 1-800-222-1222.

References and Suggested Readings for this article are at http://pedsinreview.aappublications.org/content/38/5/207.
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1. You are preparing for a number of well-child visits for the day in your outpatient clinic. The first patient that you see is a 2-week-old male coming for nursery follow-up evaluation. This is the firstborn child of a young mother who is concerned about him getting into household products. In thinking about the necessary anticipatory guidance messages regarding poisoning prevention, which well-child visits are ideal opportunities to discuss safe medication, household product storage, and how to reach the poison control center?
   A. First and second newborn visits.
   B. Four- and 6-month well-child visits.
   C. One- and 2-year well-child visits.
   D. Preteen and teenage well-child visits.
   E. Six- and 7-year well-child visits.

2. You are in the emergency department caring for a teenage girl with acetaminophen (APAP) ingestion. The patient went to her room last night upset because she broke up with her boyfriend. This morning, her mother came to her room to wake her up for school and found her asleep with an opened bottle of acetaminophen on the floor. There were multiple pills on the floor and on the bed and the bottle was empty. The parents do not recall how many pills were in the bottle before last night. They brought her to the emergency department. She is acting and feeling normal. You obtain serum studies. Which of the following findings and contexts would warrant initiation of treatment for APAP ingestion?
   A. APAP concentration of 30 μg/mL, elevated transaminases, and ingestion 9 hours ago.
   B. APAP concentration of 30 μg/mL, elevated transaminases, and ingestion time unknown.
   C. APAP concentration of 30 μg/mL, normal transaminases, and ingestion time 9 hours ago.
   D. APAP concentration undetectable, elevated transaminases, and ingestion 9 hours ago.
   E. APAP concentration undetectable, normal transaminases, and ingestion time unknown.

3. You are admitting a 2-year-old child who ingested an unknown quantity of homeopathic oil while at her aunt’s house. Initial blood gas analysis shows a mixed respiratory alkalosis and metabolic acidosis. This suggests ingestion of which of the following xenobiotics?
   A. Acetylsalicylic acid.
   B. Clonidine.
   C. N-acetyl-para-aminophenol.
   D. Synthetic cannabinoids.
   E. Synthetic cathinones.

4. A 14-year-old boy is brought to the emergency department after being found unresponsive at home. An empty pill container was found next to him, with a label for a tricyclic antidepressant. Electrocardiography reveals a QRS of greater than 100 msec. Which of the following intravenous treatments is indicated?
   A. Fomepizole.
   B. Magnesium sulfate.
   C. N-acetylcysteine.
   D. Ondansetron.
   E. Sodium bicarbonate.
5. You are caring for a 20-month-old child brought to the emergency department after he was found lethargic next to a viscous pool of an unknown substance. Initial laboratory findings show a blood glucose of 60 mg/dL (3.33 mmol/L). You discuss with the medical student working with you the causes of hypoglycemia in a child of this age. Which of the following factors places children of this age, who are mobile, at increased risk of hypoglycemia?

A. Decreased risk of xenobiotic ingestion.
B. Greater muscle mass reserve.
C. Increased supply of gluconeogenic precursors.
D. Limited alanine supplies.
E. Lower baseline rate of glucose utilization.

Additional Resources for Pediatricians

AAP Textbook of Pediatric Care, 2nd Edition

Point-of-Care Quick Reference

Parent Resources from the AAP at HealthyChildren.org

For a comprehensive library of AAP parent handouts, please go to the Pediatric Patient Education site at http://patiented.aap.org.
The Poisoned Pediatric Patient
Michael S. Toce and Michele M. Burns
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