OVERDOSES

Overdose, General

GENERAL PRINCIPLES

- According to the American Association of Poison Control Centers (AAPCC), there were over 2 million exposures and 1,146 fatalities related to toxins in 2010 (Clin Toxicol 49(10):910). Overdoses are common in the emergency department, and although they are rarely fatal, it is important to follow some general guidelines while caring for the poisoned patient.
- Patients who present to the hospital with an overdose can be challenging for the clinician. This section will begin with a review of the general approach to the poisoned patient, followed by a discussion of specific ingestions.
- When managing the poisoned patient, as with all patients, it is vital to make sure the patient has patent airway, intact breathing, and palpable pulses. Beyond the basics of general emergency management, it is important to remember physiologic principles when approaching the poisoned patient. Quite often, patients can be categorized into one of the five toxidromes based on simple clinical examination findings.

Definition

A toxidrome, or toxic syndrome, is a constellation of clinical examination findings that assists in the diagnosis and treatment of the patient who presents with an exposure to an unknown agent. The toxicologic physical examination should include documentation of vital signs, pupillary diameter, skin findings (dry, flushed, or diaphoretic), as well as the presence or absence of bowel sounds, and urinary retention.

Classification

There are five general toxidromes that encompass a variety of xenobiotic exposures. They include the following:
- **Sympathomimetic**: This toxidrome is characterized by widespread activation of the sympathetic nervous system. The vital sign abnormalities include hypertension due to α-adrenergic stimulation and tachycardia due to increased β-adrenergic tone. Patients may also present with pyrexia. Physical examination will reveal pupillary dilatation, diaphoresis, and occasionally, altered mental status. Drugs that can cause this type of toxidrome include cocaine and amphetamines. Likewise, vasopressors and β-adrenergic agonists can cause a partial syndrome depending on which agent is being used.
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• **Cholinergic**: This toxidrome is characterized by the widespread activation of the parasympathetic nervous system. Classically, the vital signs associated with a cholinergic toxidrome include **bradycardia** due to increased vagal tone, **respiratory depression** due to paralysis, and **decreased oxygen saturations** on pulse oximetry, due to **bronchoconstriction** and **bronchorrhea**. Excess acetylcholine (ACh) affects muscarinic receptors leading to the development of pinpoint pupils and the SLUDGE syndrome of **salivation**, **lacrimation**, **urination**, **defecation**, gastrointestinal (GI) **distress**, and **emesis**. Excess ACh at the neuromuscular junction (NMJ) results in a depolarizing blockade of the muscles, leading to **fasciculations** and **paralysis**. In the central nervous system (CNS), cholinergic overload is associated with the development of **seizures** and **coma**. Agents linked with the development of this toxidrome all block the function of acetylcholinesterase (AChE), resulting in the accumulation of ACh in the synapse. These agents include organophosphate insecticides and nerve gases, as well as carbamate pesticides. Carbamates are also used therapeutically in anesthesia, myasthenia gravis, and the treatment of anticholinergic toxidromes.

• **Anticholinergic**: This toxidrome should perhaps be more appropriately described as an antimuscarinic syndrome. Its features include **tachycardia** due to vagal blockade and **hyperthermia** (which may be mild to severe). CNS effects include **agitation**, **delirium**, and in severe cases, seizures. Other peripheral effects include **mydriasis**; **dry**, **flushed skin**; **urinary retention**; and **decreased intestinal motility**. Therapeutic agents that cause this toxidrome include atropine, scopolamine, and antihistamines.

• **Opiate**: The opioids produce a classic vital sign combination of **respiratory depression** and oxygen desaturations in conjunction with **miosis**, **decreased GI motility**, and **coma**. Opioids produce this toxidrome by binding to one of the four G protein receptors on the cell membrane, leading to analgesia. However, respiratory depression, miosis, and physical dependence are secondary, undesirable effects. Other agents that produce a similar toxidrome include the imidazolines, including clonidine, tetrahydrozoline, and oxymetazoline.

• **Sedative hypnotic**: The benzodiazepines bind to γ-Aminobutyric acid (GABA) receptors in the brain and cause a clinical picture of **sedation or coma** in the setting of **normal** vital signs. A common misconception is that ingested benzodiazepines cause respiratory depression. While this may be true in the setting of intravenously administered benzodiazepines, patients with a benzodiazepine ingestion generally do not develop respiratory compromise.

**DIAGNOSIS**

**Diagnostic Testing**

If patients do not fall into any of the aforementioned categories, suspect a mixed or undifferentiated exposure, and several diagnostic tests should be ordered.

**Laboratories**

• **Finger stick blood glucose (FSBG)**: This test should be considered one of the vital signs in the patient with altered mental status.

• **Chemistry**: A basic metabolic profile should be ordered on any patient with a toxic exposure. The two important pieces of information gleaned from the basic metabolic panel (BMP) include the presence or absence of a low bicarbonate and the creatinine. If the patient has a low bicarbonate, a metabolic acidosis is present.
and the clinician should calculate the **anion gap**. Patients who present with an elevated anion gap acidosis are often subjected to a battery of unnecessary studies because the differential diagnosis is enormous. In order to tailor the diagnosis, the clinician should focus on a mechanistic approach and check serum **ketones** and **lactate**. If these are negative and the **creatinine** is normal, then one should suspect the presence of a toxic alcohol and send the appropriate studies.

- **Blood gas:** In most cases of intoxication, pH rather than oxygenation is of great relevance. Therefore, it is reasonable to send **venous blood gases (VBGs)** rather than arterial blood gases (ABGs) in routine cases of poisoning. However, if adequate oxygenation is a concern (e.g., cyanide, CO poisoning, methemoglobinemia) then an ABG should be sent.

- **Serum drug screen:** In general, the studies included on this panel include acetaminophen, salicylate, and ethanol concentrations. Some laboratories include a tricyclic antidepressant (TCA) screen as well.
  - In practice, the piece of information that is critical on this panel is the serum **acetaminophen** (N-acetyl-para-aminophenol [APAP]) since patients with this ingestion are often asymptomatic upon presentation and approximately 1/500 overdoses have been found to have an unsuspected and treatable APAP concentration (*Ann Emerg Med* 1985;14:562).
  - Acute **salicylate** ingestions, while very serious, produce a clinical syndrome that is readily identifiable at the bedside. Chronic salicylate toxicity should be suspected in elderly patients taking aspirin who present with altered mental status and tachypnea.
  - **Ethanol** concentrations are NOT predictive of intoxication, despite the forensic definition of 80 mg/dL as the legal limit for driving. Intoxication is a clinical diagnosis. One of the pitfalls of routinely obtaining ethanol levels is that serious medical conditions may coexist in these often fragile patients. These conditions are frequently missed when the patient is thought to be drunk.
  - **TCA** screens are notoriously unreliable and cross-react with many therapeutic agents. In the absence of the characteristic electrocardiogram (ECG) findings and vital sign abnormalities, a positive result is meaningless and is the source of confusion, leading to unnecessary treatment.

- **Urine drug screen:** Rarely contributes to the management of the patient. Many of the assays produce false-positive or false-negative results and may, in fact, cause harm by leading the clinician to attribute a patient’s condition to intoxication rather than a medical emergency. Additionally, these tests are expensive to conduct and therefore are of limited value in the management of the poisoned patient. The urine drug screen tends to vary between hospitals but often tests for the following substances:
  - **Amphetamines:** The assay for amphetamines commonly cross-reacts with over-the-counter cold medications.
  - **Opioids:** This assay frequently misses the presence of the synthetic opioids such as fentanyl, methadone, and meperidine; therefore, it is important to rely on the toxidrome for the diagnosis.
  - **Cocaine:** This assay is not directed at the parent compound; rather, it detects the metabolite benzoylecgonine. Since the parent compound is very short lived, this test is very reliable for the identification of recent use, but in no way confirms intoxication.
  - **Cannabinoids:** Like cocaine, detection of the tetrahydrocannabinolic acid (THCA) metabolite is a reliable indicator of use; however, its presence does not have any bearing upon the diagnosis of intoxication.
Benzodiazepines: The detection of benzodiazepines most commonly relies upon the detection of oxazepam; however, some commonly used benzodiazepines (such as lorazepam) are therefore often missed by this screening (Clin Chem 2003; 49:357). Given that benzodiazepine overdoses tend to be benign, the utility of this component is questionable at best.

Phencyclidine (PCP): Screening assays may cross-react with dextromethorphan, ketamine, and diphenhydramine to produce a false-positive result. Once again, the clinical picture is more important in the diagnosis of PCP intoxication and the presence of PCP on a drug screen does not alter the management of a patient.

Specific laboratory testing will be further addressed in the following text.

Electrocardiography
- The ECG is a critical part of the toxicologic evaluation, and certain overdoses produce characteristic ECG changes that guide diagnosis and treatment plans.
- In general, the important cardiac toxins tend to prolong the PR interval (reflecting nodal blockade), the QRS (reflecting sodium channel blockade), or the QT interval (potassium channel blockade).
- Electrocardiographic changes specific to certain toxins will be further discussed in the following text.

Imaging
- In general, there is a limited role of diagnostic imaging in toxicology. However, there are a few cases when imaging may be helpful in the diagnosis and management of the poisoned patient. The most useful imaging study in overdose is the abdominal radiograph, which may reveal radiodense material in the stomach or gut in the following ingestions (Goldfrank’s Toxicologic Emergencies. 8th ed. New York: McGraw-Hill, 2006:62):
  - Chloral hydrate
  - Heavy metals
  - Iron
  - Phenothiazines
  - Enteric-coated preparations
  - Sustained-release preparations
- Occasionally, subtle abnormalities on the abdominal film will detect the presence of "rosettes" or elongated packets in the GI tract of body packers. The abdominal film is of limited utility in body stuffers (Ann Emerg Med 1997;29:596).

TREATMENT
As with any patient, it is crucial to maintain the airway, check for adequacy of breathing and circulation, and check an FSBG in the patient with altered mental status or coma.

Prevention of absorption: Traditionally, gastric emptying by either inducing emesis or lavage has been a mainstay in the treatment of the acutely overdosed patient. However, the literature regarding these methods of decontamination suggests that they are of little benefit (Med J Aust 1995;163:345). Furthermore, numerous studies have suggested that patients present approximately 3 to 4 hours after ingestion on average, which tends to make it less likely that there will be a large recovery of pills (Ann Emerg Med 1985;14:562). Therefore, the routine administration of ipecac to children and "stomach pumping" has fallen by the wayside except in very specific circumstances.
Activated charcoal (AC) has largely replaced both of these methods of gastric emptying and has been shown to be effective in the management of acute overdoses (Ann Emerg Med 2002;39:273). However, the clinical utility of this method of decontamination is limited if the ingestion occurred more than 1 hour prior to presentation (J Toxicol Clin Toxicol 1997;35:721). Certain ingestions benefit from multidose AC as they either bind to concretions in the stomach (aspirin), or they decrease enterohepatic or enteroenteric reabsorption (phenobarbital, phenytoin, theophylline). AC should be dosed at 1 g/kg body weight.

Whole-bowel irrigation is appropriate in patients who have ingested sustained-release medications, body packing, or metals that do not bind to AC. The optimal dose of polyethylene glycol is 1 to 2 L/hr until the rectal effluent is clear. This dose is a large amount of fluid to ingest, so it is often necessary to place a nasogastric tube to achieve this rate of emptying.

In cases of life-threatening ingestions such as colchicine or nondihydropyridine calcium channel blockers (CCBs), it is appropriate to consider lavage as well as AC. Cathartics have no role in the management of overdose. They are often present in the premixed AC solutions. If this is the case, only one dose should be administered.

All of these interventions are contraindicated in the presence of airway compromise, persistent vomiting, and the presence of an ileus, bowel obstruction, or GI perforation.

Enhanced elimination

Forced diuresis with normal saline and Ringer’s lactate enhances the elimination of low–molecular-weight agents such as lithium in dehydrated individuals. This should be carefully monitored and diuretics should be avoided in these patients.

Urinary alkalinization with intravenous sodium bicarbonate enhances the elimination of weak acids and is useful in the setting of salicylate overdose. Typical doses are 1 to 2 mEq/kg, with a goal of maintaining the urinary pH at approximately 7 to 8. Specific recommendations will be further discussed in the following text.

There is no role for urinary acidification in the management of overdoses.

Hemodialysis and hemoperfusion are reserved for life-threatening ingestions of substances that have a low volume of distribution, a molecular weight of less than 500 Da, a low endogenous clearance, are water soluble, and have little protein binding. This treatment modality will be further discussed under specific substances.

Antidotes will be discussed under specific toxicities. The regional poison center should be contacted for specific guidelines for treatment.

Disposition

Patients who have taken an overdose as a suicidal gesture should all receive a psychiatric evaluation prior to discharge.

Most cases of unintentional overdose do not result in significant morbidity, and in cases where the patient is stable and asymptomatic, a brief period of observation may be all that is necessary.

In cases where potentially toxic agents have been ingested, patients should be monitored for 4 to 6 hours before discharge.

Acetaminophen

GENERAL PRINCIPLES

APAP is available worldwide as an over-the-counter analgesic and antipyretic and has become the most common pharmacologic agent involved in toxicologic fatalities.
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(Am J Emerg Med 2005;23(5):589). The recommended maximum dose for adults is 4 g/d.

Classification
• An analgesic. Within the United States, APAP is sold under the trade name Tylenol. The most common trade name for APAP outside the United States is Paracetamol.
• Because of its use as an analgesic and antipyretic, APAP has become a common ingredient in various cold and flu remedies. It is also used in the treatment of fevers, headaches, and acute and chronic pain.
• APAP is often sold in combination preparations together with nonsteroidal anti-inflammatory drugs (NSAIDs), opiate analgesics, or sedatives (e.g., Tylenol #3, Percocet, Darvocet, Vicodin, NyQuil, Tylenol PM).

Epidemiology
APAP is the leading cause of toxicologic fatalities per year in the United States, and APAP-induced hepatotoxicity is the most frequent cause of acute liver failure (Hepatology 2005;42(6):1364).

Etiology
• APAP is available as tablets, capsules, liquids, and suppositories. In addition to the more common immediate-release form, there is also an extended-release preparation (e.g., Tylenol Arthritis Pain).
• Unintentional overdosing is much more common than intentional ingestion in suicide attempts, especially in elderly patients on chronic pain regimen with several APAP-containing painkillers (Hepatol Res 2008;38:3).
• All patients with presumed APAP overdose should be adequately assessed, evaluated, and treated. However, only the minority of poisoned patients require inpatient care (Acad Emerg Med 1999;6(11):1115).

Pathophysiology
• Absorption: APAP serum levels peak 30 to 60 minutes after oral ingestion; the extended-release preparations peak after 1 to 2 hours. Absorption is often delayed in overdose, and peak levels are usually reached after 2 to 8 hours. The overdose kinetics of extended-release APAP are not yet well established.
• Overdose: The hepatic conjugation pathways become saturated in overdose. A cascade of biochemical changes occurs in the liver and centrilobular cell necrosis results (Clin Pharmacol Ther 1974;16(4):676).
  ◦ Acetaminophen is metabolized predominantly via glucuronidation (47% to 62%) and sulfation (25% to 36%) by Phase II metabolism in liver as nontoxic conjugate products. However, a small percentage is metabolized via oxidation (5% to 8%) by the cytochrome P450 (2E1) pathway to a toxic metabolite, N-acetyl-p-benzoquinone imine (NAPQI). NAPQI is conjugated by glutathione to nontoxic cysteine and mercapturic acid conjugates.
  ◦ In cases of acetaminophen toxicity, the Phase II conjugation enzymes are saturated, and a higher fraction of acetaminophen is conjugated via oxidation to NAPQI. The conjugation of NAPQI to glutathione occurs until glutathione is depleted from hepatic reserves, after which the toxic NAPQI accumulates and causes damage to the hepatocytes.

Risk Factors
• Decreased glutathione stores (fasting, malnutrition, anorexia nervosa, chronic alcoholism, febrile illness, chronic disease).
P450 enzyme inducers (ethanol, Isoniazid [INH], phenytoin and other anticonvulsants, barbiturates, smoking).

**DIAGNOSIS**

**Clinical Presentation**

- **First 24 hours**—Asymptomatic stage (stage 1):
  - Early symptoms are very nonspecific and primarily related to the GI tract (nausea, vomiting, anorexia).
  - High-dose APAP can cause pallor or lethargy in some patients.
  - This initial phase is rare in symptoms and patients appear pretty unremarkable. Therefore, always think of other coingestants if a patient exhibits extreme vital sign abnormalities or other significant symptoms during the first 24 hours.
- **24 to 48 hours**—Hepatotoxic stage (stage 2):
  - Right upper quadrant (RUQ) tenderness is the most common symptom.
  - Transaminitis, bilirubinemia, and elevated prothrombin time (PT)/International normalized ratio (INR) are also common findings during the second phase.
- **2 to 4 days**—Fulminant hepatic failure stage (stage 3): Significant hepatic dysfunction develops (i.e., a peak in hepatic enzyme elevation along with jaundice, coagulopathy with high risk of spontaneous bleeding, hypoglycemia, anuria, and cerebral edema with coma or even death).
- **4 to 14 days**—Recovery stage (stage 4): If stage 3 is survived, the hepatic dysfunction usually resolves over the following days/weeks.

**History**

- In order to predict the risk of hepatotoxicity after acute overdose, a reliable time of ingestion must be obtained from the patient or family/friends.
- Also obtain information about the amount of APAP that has been ingested, in what form (e.g., combination preparations, extended-release form), and over what period of time.
- Inquire about other coingestants (alcohol, other medications, other drugs).

**Physical Examination**

Assess airway, breathing, and circulation (ABCs) and mental status. The assessment of mental status is crucial, especially in patients who are nauseated or vomiting, to intervene with airway protection in time.

**Diagnostic Criteria**

- In general, a dose of 150 mg APAP per kilogram is the potentially toxic limit that requires therapeutic intervention. This limit includes an added 25% safety margin that was added by the U.S. Food and Drug Administration (FDA) to adjust for patients with multiple risk factors for increased liver toxicity (*BMJ* 1998; 316(7146):1724).
- If the total amount of ingested APAP is above 150 mg/kg or cannot be obtained from the patient history, it is crucial to predict the risk of toxicity.
- Obtain an APAP serum level at 4 hours or later after ingestion.
- Plot the APAP concentration on the Rumack–Matthew nomogram (APAP serum concentration vs. time after ingestion) to assess the possibility of hepatic toxicity. NOTE: The nomogram should only be used for acute ingestions.
During treatment of APAP overdose, it is important to assess the risk of progressive liver failure. The King’s College Hospital (KCH) Criteria provide prognostic markers that help to predict the probability of developing severe liver damage (Gastroenterology 1989;97(2):439):

- pH <7.3, 2 days post-ingestion.
- All of the following: PT >100, serum creatinine >3.3 mmol/L, severe hepatic encephalopathy (grade III or IV).

- Elevated serum phosphate levels >1.2 mmol/L (>3.72 mg/dL) on days 2 to 4 (additional criterion, not originally part of KCH criteria) (Hepatology 2002; 36(3):659).
- Arterial serum lactate >3.0 mmol/L (>27 mg/dL) after fluid resuscitation (additional criterion, not originally part of KCH criteria) (Lancet 2002;359(9306):538).

**Diagnostic Testing**

- **APAP serum level at 4 hours** after ingestion or later (see earlier discussion).
- **Liver function tests (LFTs)**—Aspartate aminotransferase (AST) is a relatively sensitive nonprognostic marker for hepatic injury.

- **PT/INR, serum bicarbonate, blood pH, serum lactate, renal function panel, and serum phosphate level** are the prognostic markers for hepatic injury.
- APAP may interfere with some blood sugar test kits causing measurements higher or lower than actual; always recheck FSBG over the course of hospitalization (Am J Clin Pathol 2000;113(1):75).

**TREATMENT**

Gastric lavage is not useful in APAP overdose; however, it may be indicated in presence of certain other coingestants.

**Medications**

- **Activated charcoal**: Only indicated in patients with isolated APAP exposure (with no other evidence of mentally altering substances) who present less than 4 hours after ingestion. Give 1 g/kg by mouth (PO).

- **N-acetylcysteine (NAC)**: NAC is the specific antidote to prevent APAP-related hepatotoxicity (Toxicol Sci 2004;80(2):343). NAC replenishes depleted glutathione (GSH) stores. It should be administered early (i.e., within 8 hours after ingestion) to prevent any liver damage. NAC is a nonspecific antioxidant and will still provide some liver protection if given beyond this time window (J Clin Invest 1983;71(4):980).

  - **Oral dosing**: Loading dose of 140 mg/kg PO, then 70 mg/kg PO every 4 hours for a total of 17 doses (i.e., 1,330 mg/kg over 72 hours) (N Engl J Med 1988;319(24):1557).

  - **Intravenous (IV) dosing**: Prepare the infusion by adding 30 g of a 20% NAC solution (150 mL) to 1 L D$_2$W. This will result in a final concentration of 30 mg/mL. Load with a dose of 150 mg/kg NAC IV over 1 hour. Thereafter, continue to give 14 mg/kg/hr IV for 20 hours (i.e., 430 mg/kg over 21 hours) (According to IV NAC treatment protocol used by Toxicology Service at Barnes-Jewish Hospital). (See also Ann Pharmacother 2011;45(6):713.)

  - **NAC administration** can be safely stopped prior to the completion of the total regimen as soon as the APAP level returns to 0, INR <2.0, and AST normalizes (or reaches less than half of the peak level during acute intoxication).
NAC indications: NAC treatment should be started in the following:
- Any patient after acute poisoning with a toxic APAP level according to the nomogram.
- Patients who present beyond 8 hours after acute ingestion. Start NAC therapy while awaiting the initial APAP serum level. Continue treatment if the serum concentration is in the toxic range per nomogram.
- Patients who present more than 24 hours after acute ingestion and still have a detectable serum APAP level or elevated AST.
- Patients with chronic APAP exposure (i.e., >4 g/d in adults, >120 mg/kg/d in children) who present with elevated transaminases.
- Patients with signs of fulminant hepatic failure. NAC treatment should be started immediately and transfer to a transplant center arranged without fail. NAC has been shown to improve survival of patients in fulminant failure (Lancet 1990;335(8705):1572; N Engl J Med 1991;324(26):1852; BMJ 1991;303(6809):1026).

Oral Versus IV NAC:
- IV administration of NAC is the preferred route as it is used in all of the studies of patients with fulminant hepatic failure.
- Oral administration may be slightly safer compared to the IV form; however, NAC has a rather bad odor and taste. Rash, flushing, urticaria, nausea/vomiting, angioedema, bronchospasm, tachycardia, and hypotension have been reported as adverse reactions to IV administration (BMJ 1984;289(6439):217).
- If oral NAC is given, dilute the NAC with juice, provide a drinking straw, give IV antiemetics (e.g., Reglan, Zofran).
- Consider oral over IV NAC in patients who are prone to anaphylactoid reactions (e.g., severe asthmatics).
- NAC is effective either way when given within 8 hours after ingestion (N Engl J Med 1988;319(24):1557).
- AC adsorbs oral NAC. Both, PO and IV NAC regimens provide enough excess of the drug to ensure adequate therapeutic effects. Nevertheless, it is advised to administer AC 2 hours apart from NAC when given PO.

COMPLICATIONS
  - Get APAP serum level 4 hours postingestion.
  - If toxic per nomogram, treat with full NAC course.
  - If below toxic level per nomogram, get repeat APAP at 8 hours postingestion.
  - If now toxic, treat with full course. If remains below toxic level, no therapy necessary.
- Patients with progressing liver failure need to be admitted to an intensive care unit (ICU) bed with close monitoring for hyperglycemia, electrolyte imbalances, GI bleeding, acid–base disturbances, cerebral edema, infections, and renal failure.

REFERRAL
- Involve a clinical toxicologist in all cases where toxic APAP levels are documented. Discuss the initiation of NAC treatment with the toxicology service where possible.
- Inform your regional Poison Control Center (1-800-222-1222).
• Involve the liver or transplant service early in patients presenting with poor prognostic factors for hepatic failure.
• Patients with toxic liver failure should be transferred to a transplant center as early as possible (BMJ 1991;303(6796):221; J R Soc Med 1997;90(7):368).

Colchicine

GENERAL PRINCIPLES

Definition
Colchicine is the active alkaloid extracted from two plants of the Liliaceae family: Colchicum autumnale (autumn crocus) and Gloriosa superba or glory lily. It has been used in the therapy of gout for centuries.

Etiology
Colchicine has a very narrow therapeutic index. Severe poisoning and death can result from the ingestion of as little as 0.8 mg/kg of body weight (Nouv Presse Med 1977;6:1625).

Pathophysiology
Colchicine is an effective inhibitor of intracellular microtubule formation, leading to impaired leukocyte chemotaxis, and phagocytosis resulting in a decrease in the inflammatory cascade (JAMA 2003;289:2857). In overdose, colchicine causes mitotic arrest, leading to cellular dysfunction and death (J Emerg Med 1994;12:171).

Prevention
Patients who are started on colchicine for gout symptoms should be explicitly directed to stop taking the medication as soon as symptoms of diarrhea occur. They should also be told that increasing the dose in an acute flare can result in significant toxicity; therefore, if they are unable to control the symptoms at home, they should seek expert care early.

DIAGNOSIS

Clinical Presentation
Patients who present with a colchicine overdose tend to develop a syndrome that progresses through three phases. The initial phase usually begins several hours after the overdose and is characterized by nausea, vomiting, and diarrhea. Over the next 1 to 7 days, patients may develop multiorgan failure requiring intensive support; death is common at this stage. In the final phase, patients develop alopecia and myoneuropathies.

History
Patients with inadvertent overdoses will present with a recent history of an acute gouty flare, followed by the development of nausea, vomiting, and diarrhea within a few hours after the overdose. Intentional overdoses may present late and should be suspected in patients with a GI syndrome followed by multiorgan failure.
Physical Examination
The exam tends to be somewhat unremarkable in these patients. They may exhibit signs of dehydration with tachycardia and dry mucous membranes. They may also have decreased urine output. As the toxicity progresses, patients may develop signs of worsening distress and confusion requiring aggressive resuscitation measures. As the disease evolves, fatal cardiac arrhythmias and refractory cardiovascular collapse may occur, usually within a week of overdose (J Forensic Sci 1994;39:280). Reversible alopecia has been reported in survivors (J Emerg Med 1994;12:171).

Differential Diagnosis
As with any ingestion, the differential diagnosis is large. However, GI symptoms are common in patients with overdoses of methylxanthines, podophyllin, digoxin and other cardioactive steroids, chemotherapeutic agents, heavy metals, and salicylates.

Diagnostic Testing
There is a very interesting sequence of laboratory findings that should lead one to consider colchicine poisoning in patients.

Laboratories
• **Complete blood cell count (CBC):** In the initial phase of poisoning that lasts for approximately 12 to 24 hours, patients develop a leukocytosis. In the next 48 to 72 hours, signs of bone marrow suppression evolve starting with a profound decline in the leukocyte count and subsequent pancytopenia.
• **BMP:** Colchicine poisoning has also been associated with renal failure and adrenal hemorrhage (J Anal Toxicol 1991;15:151); therefore, electrolytes should be monitored.
• **LFTs:** Colchicine overdoses have been reported to cause hepatotoxicity; therefore, LFTs should be monitored.
• **Coagulation studies:** Disseminated intravascular coagulation (DIC) occasionally occurs; therefore, a full panel, including fibrinogen and fibrin split products should be obtained.
• **Colchicine concentrations:** Colchicine has a narrow therapeutic index, and plasma concentrations >3 ng/mL may produce significant toxicity. However, this laboratory test is not readily available and toxicity should be suspected if clinical symptoms and laboratory studies are supportive. This test should be thought of as a confirmatory study.
• **Other studies:** Creatine kinase (CK or creatine phosphokinase [CPK]), troponin, lipase, and other electrolytes should be obtained depending on the clinical scenario.

Electrocardiography
An ECG should be obtained at presentation, given the patient’s predilection for developing cardiac arrhythmias, and the patient should be admitted with continuous cardiac monitoring.

Imaging
Colchicine toxicity has been associated with the development of acute respiratory distress syndrome (ARDS). Therefore, a chest X-ray (CXR) should be obtained.

**TREATMENT**
Colchicine overdoses are often fatal and require aggressive supportive measures. As always, airway protection is of paramount importance followed by adequacy of breathing and support of circulation.
Medications
In cases of severe neutropenia, consider Granulocyte colony-stimulating factor (G-CSF) administration.

Other Nonpharmacologic Therapies
- If the patient is not vomiting, consider gastric lavage and AC. If the patient is altered and vomiting, consider early endotracheal intubation. Fluids and direct acting vasopressors should be used in cases of hypotension. Hemodialysis is not useful for clearing colchicine, given its large volume of distribution; however, it should be used in the setting of colchicine-induced renal failure.
- All symptomatic patients should be admitted to the ICU. Patients without symptoms should be monitored for 8 to 12 hours prior to discharge.

SPECIAL CONSIDERATIONS
Given its narrow therapeutic window and pharmacokinetics, colchicine should be used cautiously in patients with underlying renal or liver dysfunction. Likewise, colchicine is a P450 drug and is subject to many drug–drug interactions (Biochem Pharmacol 1997;10:111). A thorough review of the patient’s medication list should be conducted before starting the patient on this agent as toxic concentrations can accumulate rapidly. In this setting, consider using alternative therapies for the management of acute gouty flares.

Nonsteroidal Anti-Inflammatory Drugs
GENERAL PRINCIPLES
- NSAIDs are widely prescribed as analgesics for the management of inflammatory diseases. There are many different classes available; however, the discussion in the following text relates to over-the-counter preparations available in the United States and includes ibuprofen, ketoprofen, and naproxen as well as the selective cyclooxygenase (COX)-2 inhibitors.
- NSAIDs exert their therapeutic effects by inhibiting cyclooxygenase and thereby preventing the formation of prostaglandins. This mechanism accounts for both their therapeutic and toxic side effects, which include ulceration of the GI mucosa and renal dysfunction. In the vast majority of cases, overdose is benign.

DIAGNOSIS
Clinical Presentation
Overdose histories are often unreliable. Consider NSAID overdose in patients who present with GI distress. Massive overdose with ibuprofen occasionally presents with coma and seizures.

Diagnostic Testing
Obtain a BMP to evaluate renal function and hydration status. An APAP concentration should be obtained as many patients confuse over-the-counter analgesics.
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TREATMENT

Usually supportive care is all that is necessary for the management of this overdose. IV fluids (IVF) are beneficial for maintaining hydration in vomiting patients.

Medications
• Consider AC 1 g/kg for GI decontamination.
• Antiemetics and antacids are beneficial in patients with significant distress.
• Benzodiazepines should be used for the management of seizures associated with massive ibuprofen overdose.

Opioids

DIAGNOSIS

Clinical Presentation
Symptoms of opioid overdose are respiratory depression, a depressed level of consciousness, and miosis. However, the pupils may be dilated with acidosis or hypoxia or after overdoses with meperidine or diphenoxylate plus atropine. Overdose with fentanyl or derivatives such as α-methyl fentanyl (“China white”) may result in negative urine toxicology screens.

Diagnostic Testing
Laboratories
Drug concentrations and other standard laboratory tests are of little use. Pulse oximetry and ABGs are useful for monitoring respiratory status. Although less widely available, capnography measuring end-tidal CO₂ is more sensitive in detecting impending respiratory arrest as hypercapnia precedes hypoxemia.

Electrocardiography
• Methadone has been reported to cause a prolonged QTc. Obtain an ECG in suspected overdose.
• Propoxyphene exhibits type IA antidysrhythmic effects due to sodium channel blockade and may present with a wide complex QRS on ECG (Acta Pharmacol Toxicol 1978;42:171).

Imaging
A chest radiograph should be obtained if pulmonary symptoms are present.

TREATMENT

• Treatment includes airway maintenance, ventilatory support, and judicious use of opioid antagonist.
• Avoid gastric lavage.
• Limit use of whole-bowel irrigation to body packers. Body packers rarely require surgery, except in cases of intestinal obstruction.
• Endoscopic removal should not be attempted due to the danger of rupture.

Medications
• Naloxone hydrochloride specifically reverses opioid-induced respiratory and CNS depression and hypotension.
The lowest effective dose should be used. The goal of treatment is adequate spontaneous respiration and not necessarily alertness. The initial dose is 0.04 to 2 mg IV, although the lowest effective dose should be used.

Larger doses (up to 10 mg IV) may be required to reverse the effects of propoxyphene, diphenoxylate, buprenorphine, or pentazocine.

In the absence of an IV line, naloxone can be administered sublingually (Ann Emerg Med 1987;16:572), via endotracheal tube, or intranasally (Emerg Med J 2006;23:221). Isolated opioid overdose is unlikely if there is no response to a total of 10 mg naloxone. Repetitive doses may be required (duration of action is 45 minutes), and this should prompt hospitalization despite the patient’s return to an alert status.

Methadone overdose may require therapy for 24 to 48 hours, whereas levo-α-acetylmethadol may require therapy for 72 hours. A continuous IV drip that provides two-thirds of the initial dose of naloxone hourly, diluted in D₅W, may be necessary to maintain an alert state (Ann Emerg Med 1986;15:566).

Ventilatory support should be provided for the patient who is unresponsive to naloxone and for pulmonary edema.

**Disposition**

If the patient is alert and asymptomatic for 4 to 6 hours after a single dose of naloxone, or for 4 hours after a single treatment for an IV overdose, he or she can be discharged safely.

Body packers should be admitted to an ICU for close monitoring of the respiratory rate and level of consciousness and remain so until all packets have passed, as documented by computed tomography (CT).

### SPECIAL CONSIDERATIONS

- Heroin may be adulterated with scopolamine, cocaine, clenbuterol, or caffeine, complicating the clinical picture. Less common complications include hypotension, bradycardia, and pulmonary edema.
- Be aware of body packers who smuggle heroin in their intestinal tracts. Deterioration of latex or plastic containers may result in drug release and death (Am J Forensic Med Pathol 1997;18:312).

### Salicylates

#### GENERAL PRINCIPLES

- Salicylate toxicity may result from **acute or chronic** ingestion of acetylsalicylic acid (aspirin is a generic name in the United States, but a brand name in the rest of the world). Toxicity is usually mild after acute ingestions of <150 mg/kg, moderate after ingestions of 150 to 300 mg/kg, and generally severe with overdoses of 300 to 500 mg/kg.
- Toxicity from chronic ingestion is typically due to intake of >100 mg/kg/d over a period of several days and usually occurs in elderly patients with chronic underlying illness. Diagnosis is often delayed in this group of patients, and mortality is approximately 25%. Significant toxicity due to chronic ingestion may occur with blood concentrations lower than those associated with acute ingestions.
- Topical preparations containing methyl salicylate or oil of wintergreen can cause toxicity with excessive topical use or if ingested.
Clinical Presentation
• Nausea, vomiting, tinnitus, tachypnea, hyperapnea, and malaise are common. Hyperthermia results in uncoupled mitochondrial oxidative phosphorylation and suggests a poor prognosis.
• Severe intoxications may include lethargy, convulsions, and coma, which may result from cerebral edema and energy depletion in the CNS.
• Noncardiogenic pulmonary edema may occur and is more common with chronic ingestion, cigarette smoking, neurologic symptoms, and older age.
• Severe overdoses of >300 mg/kg may present with tachypnea, dehydration, pulmonary edema, altered mental status, seizures, or coma.

Diagnostic Testing
Laboratories
• Obtain electrolytes, blood urea nitrogen (BUN), creatinine, glucose, and salicylate concentration.
• Obtain either ABGs or VBGs.
• ABGs may reveal an early respiratory alkalosis, followed by metabolic acidosis.
  ◦ Approximately 20% of patients exhibit either respiratory alkalosis or metabolic acidosis alone (Crit Illness 1986;1:77).
  ◦ Most adults with pure salicylate overdose have a primary metabolic acidosis and a primary respiratory alkalosis.
  ◦ After mixed overdoses, respiratory acidosis may become prominent (Arch Intern Med 1978;138:1481).
• Serum salicylate concentrations drawn after acute ingestion of salicylates assist in prediction of severity of intoxication and patient disposition. However, do not rely upon the Done nomogram.
  ◦ Salicylate concentrations >70 mg/dL at any time represent moderate-to-severe intoxication.
  ◦ Salicylate concentrations >100 mg/dL are very serious and often fatal. This information is useful only for acute overdoses of nonenteric-coated aspirin.
  ◦ Enteric-coated aspirin may have delayed absorption and delayed peak concentration.
  ◦ Chronic ingestion can cause toxicity with lower salicylate concentrations.
  ◦ Bicarbonate concentrations and pH are more useful than salicylate concentrations as prognostic indicators in chronic intoxication.

Imaging
• Repeated blood salicylate concentrations that fail to decline should prompt contrast radiography of the stomach. Salicylate concretions may require endoscopy, multidose AC, or bicarbonate lavage.
• Consider whole-bowel irrigation with polyethylene glycol.

TREATMENT
Medications
• Administer 50 to 100 g AC if presentation is within 1 hour of ingestion.
• Multidose charcoal may be useful in severe overdose (Pediatrics 1990;85:594), or in cases in which salicylate concentrations fail to decline (due to possible gastric bezoar formation).
• **Alkaline diuresis** is indicated for symptomatic patients with salicylate blood concentrations >40 mg/dL.
  - Administer 150 mEq (three ampules) sodium bicarbonate in 1,000 mL D$_5$W at a rate of 10 to 15 mL/kg/hr if the patient is clinically volume depleted until urine flow is achieved.
  - Maintain alkalinization using the same solution at 2 to 3 mL/kg/hr, and monitor urine output, urine pH (target pH, 7 to 8), and serum potassium. Successful alkaline diuresis requires the simultaneous administration of potassium chloride.
  - Give 40 mEq potassium chloride intravenous piggyback (IVPB) over 4 to 5 hours. Give additional potassium chloride either orally or intravenously as needed to maintain serum potassium concentration above 4 mEq/L.
  - Use caution with alkaline diuresis in older patients, who may have cardiac, renal, or pulmonary comorbidity, as pulmonary edema is more likely to occur in this population.

• Do not use acetazolamide (carbonic anhydrase inhibitor). Although acetazolamide alkalinizes the urine, it increases salicylate toxicity because it also alkalinizes the CNS (trapping more salicylate in the brain) and worsens acidemia.

• **Hyperventilate any patient requiring endotracheal intubation.** In salicylate-poisoned patients with tachypnea and hyperapnea, the respiratory alkalosis partially compensates for the metabolic acidosis. Mechanical ventilation with neuromuscular paralysis, sedation, and “normal” ventilator rates will remove the respiratory alkalosis, worsen acidosis, and cause rapid deterioration or death.

• **Treat altered mental status with IV dextrose,** despite normal blood glucose.

• Treat cerebral edema with hyperventilation and osmotic diuresis.

• Treat seizures with a benzodiazepine (diazepam, 5 to 10 mg IV q15min up to 50 mg) followed by phenobarbital, 15 mg/kg IV. Give dextrose 25 g IV immediately following seizure control.

**Other Nonpharmacologic Therapies**

• **Hemodialysis** is indicated for blood concentrations >100 mg/dL after acute intoxication. Hemodialysis rapidly removes salicylate and corrects acidosis. Hemodialysis may be useful with chronic toxicity when salicylate concentrations are as low as 40 mg/dL in patients with any of the following: persistent acidosis, severe CNS symptoms, progressive clinical deterioration, pulmonary edema, or renal failure.

• Treatment of pulmonary edema may also require mechanical ventilation with a high fraction of inspired oxygen concentration and positive end-expiratory pressure (PEEP) (in addition to high respiratory rate).

**SPECIAL CONSIDERATIONS**

• Patients with minor symptoms (nausea, vomiting, tinnitus), an acute ingestion of <100 mg/kg, and a first blood concentration of <50 mg/dL may be treated in the emergency department. Blood concentrations should be repeated every 2 hours until they show a decline. These patients often are medically stable for discharge, and their disposition can be determined based on psychiatric evaluation.

• Admit moderately symptomatic patients for at least 24 hours. Repeat serum salicylate concentration, electrolytes, BUN, creatinine, and glucose at least every 6 hours to confirm declining salicylate concentration, improving bicarbonate concentration,
and stable potassium concentration. Measure urine pH at least every 6 hours (if patient has urinary bladder catheter) or with each spontaneous void to confirm urinary alkalinization.

- Admit patients with severe overdoses to an ICU. Monitor laboratory studies as with moderately ill patients. Closely monitor ABGs. Arrange for immediate hemodialysis. Use great caution with mechanical ventilation, and hyperventilate any patient who requires mechanical ventilation.

### Phenytoin and Fosphenytoin

#### General Principles

**Classification**
There are four major mechanisms by which anticonvulsants exert therapeutic activity—sodium channel blockade, GABA agonism, calcium channel antagonism, and inhibition of excitatory amino acids. In overdose, these features are enhanced.

**Pathophysiology**
- Phenytoin has been a first-line treatment for seizures since its introduction. Fosphenytoin was developed as a response to some of the toxicity associated with intravenous phenytoin administration. Fosphenytoin is a prodrug that is converted to phenytoin after IV or intramuscular (IM) injection and therefore will be referred to as phenytoin in the following text.
- Phenytoin exerts therapeutic activity by binding to sodium channels and inhibiting reactivation (*J Neural Transm* 1988;72:173). Phenytoin exhibits saturable kinetics, and at plasma levels above 20 μg/mL, toxic effects become rapidly apparent.
- Acute toxicity is associated with the development of a **neurologic syndrome** that appears to be cerebellar in origin. **Cardiotoxicity is not** associated with phenytoin ingestion (*Heart Lung* 1997;26:325); however, it has been **reported with IV administration** of phenytoin. Rapid IV administration slows cardiac conduction and decreases systemic vascular resistance and myocardial contractility. The cardiac toxicity associated with intravenous phenytoin administration is due in part to the presence of propylene glycol and ethanol in the diluent, which are known myocardial depressants and vasodilators (*Am J Cardiol* 1966;17:332). The introduction of fosphenytoin has decreased the incidence of cardiac complications.

**Risk Factors**
Other than overdose, risk factors for developing phenytoin toxicity are associated with the coadministration of drugs that affect the **cytochrome P450** system.

#### Diagnosis
There are several classic clinical findings that point to the diagnosis of phenytoin toxicity.
Clinical Presentation

History
Patients exhibiting toxicity from phenytoin will often be brought in by family members who will describe the patient as ataxic and increasingly confused. There is usually a history of seizure disorder and the medication list will include phenytoin. In intentional overdoses, the patient may be lethargic with slurred speech and an extrapyramidal movement disorder (Ann Emerg Med 1989;7:61).

Physical Examination
• At plasma concentrations of $>15$ $\mu$g/mL, patients will exhibit nystagmus. Ataxia develops at levels of $30$ $\mu$g/mL. Confusion and frank movement disorders occur at levels of $50$ $\mu$g/mL or greater. Chronic phenytoin ingestion is also associated with gingival hyperplasia, which is a very useful clinical finding when uncertain of the diagnosis. Ingestions are not associated with cardiototoxicity or vital sign abnormalities (Ann Emerg Med 1991;20:508). Rapid intravenous administration of phenytoin results in hypotension and bradycardia. Death has been reported (JAMA 1968;20:2118).
• Extravasation injury is a serious complication of intravenous phenytoin administration and can result in severe tissue injury described as the purple glove syndrome. This injury will occasionally require surgical debridement (Neurology 1998;51(4):1034).

Differential Diagnosis
Phenytoin toxicity is similar in presentation to carbamazepine poisoning; however, carbamazepine tends to exhibit cardiototoxicity. Other considerations include a convulsive status epilepticus, meningitis, encephalitis, or other intracerebral lesion.

Diagnostic Testing
Laboratories
• Serial phenytoin concentrations (corrected for albumin, as phenytoin is highly protein bound) should be obtained on any patient with a potential history of exposure.
• CBC: Phenytoin has been reported to occasionally cause agranulocytosis.
• LFTs: Phenytoin is associated with the occasional development of hepatotoxicity.

Electrocardiography
ECGs and telemetry are generally not needed in oral overdoses (Ann Emerg Med 1991;20:508). However, in IV infusions, it is necessary to have the patient in a monitored setting.

TREATMENT
• Admission is warranted for patients with ataxia, and serial levels should be obtained while in the hospital.
• Supportive care is the mainstay of treatment for acute or chronic phenytoin toxicity. Multidose activated charcoal (MDAC) is useful in decreasing the serum half-life; however, given the pharmacokinetic profile of this drug, it is possible to rapidly lower the serum concentration below therapeutic levels and precipitate a seizure.
• Benzodiazepines are the mainstay of treatment for seizures.
Hypotension and bradycardia in the setting of IV administration is usually self-limiting and will resolve with supportive care. In refractory bradycardia or hypotension, advanced cardiac life support (ACLS) principles apply.

Cases of agranulocytosis are responsive to G-CSF administration.

Hepatotoxicity usually resolves with the discontinuation of the drug.

Surgical Management
In cases of extravasation, it is important to have a surgical evaluation in order to determine the need for operative debridement.

SPECIAL CONSIDERATIONS
Phenytoin is generally of limited use in the treatment of active seizures. Since the mainstay of treatment is benzodiazepine administration and IV phenytoin is associated with significant toxicity, it is better to orally load patients whenever possible.

OUTCOME/PROGNOSIS
Phenytoin overdoses tend to be benign and self-limiting with supportive care. Deaths are exceedingly unusual even in the setting of massive overdose.

Carbamazepine/Oxcarbazepine

GENERAL PRINCIPLES
Definition
Carbamazepine and oxcarbazepine are structurally related to TCAs. Like fosphenytoin, oxcarbazepine is a prodrug that is metabolized to an active metabolite. An anticonvulsant.

Pathophysiology
• The therapeutic efficacy of carbamazepine and oxcarbazepine are due to sodium channel blockade, which prevents the propagation of an abnormal focus. The therapeutic serum concentration of carbamazepine is 4 to 12 mg/L. There is no routine laboratory testing for oxcarbazepine; however, the carbamazepine assay will detect the presence of oxcarbazepine.
• The toxicity associated with carbamazepine is likely due to its chemical structure. TCA-like effects include sodium channel blockade, QT prolongation, and anticholinergic features.
• In overdose, carbamazepine is erratically absorbed and may form concretions in the GI tract causing prolonged toxicity.
• Persistently high levels of carbamazepine have been reported to increase antidiuretic hormone secretion leading to syndrome of inappropriate antidiuretic hormone release (SIADH) (Prog Neuropsychopharmacol Biol Psychiatry 1994;18:211).

Risk Factors
Carbamazepine toxicity may be enhanced by concomitant use of drugs that are metabolized by the CYP450 system.
DIAGNOSIS

There are several key features of carbamazepine toxicity.

Clinical Presentation

History
Toxicity should be suspected in individuals who present with a history of a seizure disorder and altered mental status. **Delayed toxicity** has been reported after an acute overdose given the variability in GI absorption (J Toxicol Clin Toxicol 1979;14:263). Patients may exhibit a relapsing syndrome of coma and altered consciousness due to bezoar formation and enterohepatic recirculation.

Physical Examination

- The predominant clinical findings in carbamazepine toxicity are neurologic and cardiovascular effects. In mild-to-moderate toxicity, patients may present with ataxia, nystagmus, and mydriasis. In serious overdose, patients may develop **coma** and **seizures**, including status epilepticus. Vital sign abnormalities include **tachycardia** due to the anticholinergic effects of the drug as well as **hypotension** and **bradycardia** due to direct myocardial depressant effects.
- The combination of cerebellar findings on exam, in conjunction with an anticholinergic toxidrome, should prompt the clinician to consider carbamazepine as a potential toxicant.

Differential Diagnosis

Mild-to-moderate carbamazepine toxicity resembles phenytoin toxicity. Other considerations include a convulsive status epilepticus, meningitis, encephalitis, or other intracerebral lesion.

Diagnostic Testing

- Serum carbamazepine concentrations should be obtained on any patient who presents with a history of ingestion. The therapeutic range is from 4 to 12 mg/L. Serial levels should be obtained every 4 to 6 hours to evaluate for delayed toxicity or prolonged absorption. Concentrations of >40 mg/L are associated with the development of cardiotoxicity (J Toxicol Clin Toxicol 1993;31:449).
- Patients with carbamazepine overdoses will often develop signs of cardiac toxicity. ECG findings include QRS and QTc prolongation and atrioventricular (AV) conduction delays. Cardiotoxicity will occasionally be delayed, so all patients should be admitted with telemetry.

TREATMENT

Medications
Maintain airway protection at all times, treat seizures with **benzodiazepines**. Although there is a paucity of data regarding the efficacy of **sodium bicarbonate** in this setting, its use should be considered if the QRS duration is >100 milliseconds, given the structural similarity to TCAs.

Other Nonpharmacologic Therapies
Like phenytoin, carbamazepine’s half-life is reduced by the administration of **MDAC** by decreasing enterohepatic recirculation of the drug (Eur J Clin Pharmacol 1980;17:51).
Lamotrigine

GENERAL PRINCIPLES

Definition
Lamotrigine, an anticonvulsant, is widely prescribed as a mood stabilizer as well as for the treatment of partial complex seizures.

Pathophysiology
Lamotrigine exerts its therapeutic effects by blocking presynaptic and postsynaptic sodium channels. In overdose, excess sodium channel blockade may result in widening of the QRS on the ECG and conduction blocks. Idiopathic cases of dermatologic pathology including Steven–Johnson syndrome and toxic epidermal necrolysis have been reported with the therapeutic administration of lamotrigine.

DIAGNOSIS

Clinical Presentation
History
Suspect lamotrigine toxicity in patients with a seizure disorder and altered mental status.

Physical Examination
Patients with lamotrigine toxicity present with lethargy, ataxia, and nystagmus. Overdose may present with seizures as well.

Differential Diagnosis
Lamotrigine toxicity is similar to other sodium channel blocking anticonvulsant agents.

Diagnostic Testing
Laboratories
Therapeutic concentrations range from 3 to 14 mg/L; concentrations greater than 15 mg/L are associated with the development of toxicity.

Electrocardiography
Lamotrigine overdose has been associated with the development of conduction delays and QRS widening. Patients should be admitted on telemetry.

TREATMENT
AC should be administered to alert patients with an intact airway. Seizures should be treated with benzodiazepines. There are theoretical benefits of administering sodium bicarbonate, 150 mEq in 1 L of 5% dextrose, in patients with a QRS >100 milliseconds; however, there is a paucity of experimental data to support this practice. In the setting of bicarbonate administration, close monitoring of serum potassium levels is required in order to avoid life-threatening hypokalemia.
Levetiracetam

**GENERAL PRINCIPLES**

- Levetiracetam, an anticonvulsant, is becoming increasingly used in the management of several of the different subtypes of epilepsy.
- The mechanism by which levetiracetam exerts its therapeutic effect is not well described; however, it does block N-type calcium channels on the presynaptic terminals of neurons.

**DIAGNOSIS**

**Clinical Presentation**
Very little data exist on levetiracetam overdoses. Lethargy and respiratory depression have been reported in the setting of overdose.

**Differential Diagnosis**
In patients with a seizure disorder and lethargy, intoxication, infectious, and metabolic disorders should be considered.

**Diagnostic Testing**
Although a test is available for measuring serum levels, this assay is not routinely available.

**TREATMENT**
Generally, **supportive care** is required. In cases where respiratory depression is evident, the patient should be intubated and ventilated. Avoid AC in patients with an altered mental status and an unprotected airway.

Valproic Acid

**GENERAL PRINCIPLES**

Valproic acid (VPA), an anticonvulsant, is widely used for the management of seizures and mood disorders and exerts its effects by inhibiting the function of voltage-gated sodium and calcium channels as well as enhancing the function of GABA.

**Pathophysiology**
VPA is metabolized by the hepatocytes through a complicated biochemical process that involves β-oxidation in the mitochondria. This drug may result in fatty infiltrates in the liver and accumulation of ammonia.

**Risk Factors**
Hepatic dysfunction can occur even at therapeutic levels and therefore should be monitored. The therapeutic range runs from 50 to 100 mg/L. In overdose, the risk of hepatic dysfunction and hyperammonemia increases.
Clinical Presentation
Patients with valproate overdoses may present with tremor, ataxia, sedation, altered sensorium, or coma. Occasionally, patients will present with abdominal pain.

Diagnostic Testing
- Therapeutic concentrations range from 50 to 100 mg/L. Patients who present with overdoses should have a BMP drawn to evaluate for hyponatremia and metabolic acidosis.
- In cases of massive overdose, a CBC should be sent as cases of pancytopenia have been reported in the literature (Scott Med J 1987;32:85). Hematopoietic disturbances may occur up to 5 days after overdose.
- Chronic VPA therapy has been associated with the development of hepatotoxicity and may result in a fatal hepatitis. In cases of chronic toxicity, LFTs should be sent to evaluate for transaminitis. Likewise, any patient with VPA toxicity should have an ammonia level sent.
- There have been occasional reports of pancreatitis (J Toxicol Clin Toxicol 1995;33:279); therefore in massive overdose, consider sending lipase as well.

Treatment
- Most cases of toxicity resolve with supportive care. In patients who are awake with adequate airway protection, AC is warranted.
- In patients with hyperammonemia >35 mmol/L (>80 μg/dL) L-carnitine therapy should be instituted. In awake patients, oral carnitine is the preferred route at 50 to 100 mg/kg/d divided every 6 hours up to 3 g/d. In cases where patients are not able to tolerate PO, intravenous L-carnitine may be administered at 100 mg/kg IV up to 6 g as a loading dose, and then 15 mg/kg every 4 hours. Therapy may be discontinued when the patient’s ammonia level declines to <35 mmol/L.

Monoamine Oxidase Inhibitors

General Principles
Although several different classes of monoamine oxidase inhibitors (MAOIs) exist, the drugs most frequently implicated in toxicity are the first-generation antidepressant drugs: phenelzine, isocarboxazid, and tranylcypromine. Clorgiline, a later generation drug, is also associated with a similar toxic profile. The third-generation drugs, including moclobemide, have a better safety profile.

Pathophysiology
Monoamine oxidase is an enzyme responsible for the inactivation of biogenic amines such as epinephrine, norepinephrine, tyramine, dopamine, and serotonin. Inhibition of this enzyme results in an increase of synaptic concentrations of biogenic amines. An increase in norepinephrine and serotonin, in particular, is thought to be responsible for mood elevation. MAOIs are structurally similar to amphetamine. In overdose, a significant amount of neurotransmitter is released resulting in a sympathomimetic toxidrome. Phenelzine and isocarboxazid are also hydrazine
derivatives and in overdose have been associated with the development of seizure activity. As neurotransmitters become depleted, patients develop cardiovascular collapse, which is often refractory to therapy. Given the fact that MAOIs affect an enzymatic pathway, there is often a significant delay in the development of toxicity after overdose, with most cases occurring in a 24-hour period postingestion, although there are cases of toxicity occurring up to 32 hours after overdose (Ann Emerg Med 1984;13:1137). This effect may occur with seemingly small overdoses of five or six pills (J Clin Psychiatry 1983;44:280).

**Risk Factors**
The classic risk factors for developing toxicity include increasing a prescribed dose or eating foods rich in tyramine, such as aged cheddar cheese or red wine. Drug–drug interactions occur when a new antidepressant (often a selective serotonin reuptake inhibitor [SSRI]) is introduced without an adequate washout period of several weeks after discontinuing the MAOI.

**Prevention**
Patients should be well educated on the risk associated with these drugs. The duration of action in these drugs significantly outlasts their half-lives; therefore, physicians should always use a reference guide or consult a pharmacist prior to prescribing a new drug in addition to or as a replacement for the MAOI.

**Associated Conditions**
- MAOIs have been associated with severe hypertensive crises in the setting of coingestions of tyramine-containing foods such as aged cheddar and red wine. Likewise, coingestion of indirect-acting sympathomimetics, which cause presynaptic release of norepinephrine, may precipitate a hypertensive crisis. Agents included in this category are amphetamine-based drugs, dopamine, and pseudoephedrine.
- Serotonin syndrome is also associated with the coingestion of SSRIs, St. John’s wort, meperidine, and dextromethorphan.

**DIAGNOSIS**

**Clinical Presentation**
MAOI overdose is associated with a considerable risk of mortality and morbidity.

**History**
- In overdose, there may be a significant delay in the development of symptoms. Anyone who presents with normal vital signs and history of MAOI overdose must be admitted and monitored for at least 24 hours.
- Overdose should be suspected in patients who are taking MAOIs and present in extremis with a florid sympathomimetic toxidrome.

**Physical Examination**
Patients may initially present with minimal signs of toxicity. Subsequently, they will develop agitation, diaphoresis, tachycardia, severe hypertension, dilated pupils, and headache. As their illness progresses, they may develop hyperthermia, rigidity, and seizures. Ultimately, there is depletion of neurotransmitter stores and the patient develops refractory cardiovascular collapse.
Differential Diagnosis
MAOI overdose produces a clinical picture that is similar to severe serotonin syndrome and severe sympathomimetic toxicity. Serotonin syndrome has a relatively faster onset of action and occurs within minutes to hours of ingestion.

Diagnostic Testing
Laboratories
These include routine labs such as a BMP, looking for metabolic acidosis, hyperkalemia, and renal failure; CK to look for rhabdomyolysis; and troponins should be obtained to evaluate for myocardial infarction in severe cases. Coagulation studies are important as these patients may DIC.

Electrocardiography
ECG analysis may reveal a range of disorders from a simple sinus tachycardia to a wide complex dysrhythmia.

Imaging
A head CT should be obtained on altered patients and patients complaining of a headache in order to evaluate for intracranial hemorrhage.

TREATMENT
• The management of first-generation MAOI overdose can be very difficult as the patient may have dramatically variable vital signs. Patients with MAOI overdose should be aggressively managed with orogastric lavage, even if they are asymptomatic on arrival to the hospital.
• In hyperthermic patients, rapid cooling measures should be instituted.

Medications
First Line
• AC (1 g/kg) should be administered to the patient after the airway is secured. Many patients will be awake and alert and may not need immediate intubation; however, these patients should receive AC as well.
• Given the propensity for wildly fluctuating blood pressure (BP), titratable and short-acting agents are the mainstay of treatment in these patients. Hypertension should be managed with nitroglycerin, nitroprusside, or phentolamine. If the patient develops hypotension, a direct-acting α-agonist such as norepinephrine should be used. Avoid dopamine in the setting of MAOI overdose as it often fails to improve BP due to catecholamine depletion.
• Benzodiazepines should be used for seizures and agitation. Rigidity that does not respond to benzodiazepine administration may be managed with nondepolarizing paralytics. There are case reports describing the resolution of rigidity after the administration of cyproheptadine (J Clin Psychopharmacol 1993;13:312).

Second Line
In patients with refractory seizures, early administration of pyridoxine is warranted. Doses of 70 mg/kg not to exceed 5 g should be administered early as an IV infusion of 0.5 g/min.
SPECIAL CONSIDERATIONS

- Patients with MAOI overdoses require admission with monitoring for at least 24 hours, given the propensity for delayed toxicity. Aggressive decontamination measures should be taken, even if the patient seems to be asymptomatic as decompensation is rapid and frequently fatal.
- The exception to this is an overdose of moclobemide, which has a much better safety profile and tends to have a benign course because of its short duration of MAO inhibition.

PATIENT EDUCATION

- Patients who are placed on MAOIs should be educated about food and drug interactions and warned about the risk of interactions with herbal supplements, including St. John’s wort.
- A washout period of at least 2 weeks after discontinuation of an MAOI should be observed before starting another antidepressant.

Tricyclic Antidepressants

GENERAL PRINCIPLES

- Multiple TCAs are on the market, including amitriptyline, clomipramine, doxepin, imipramine, trimipramine, desipramine, nortriptyline, and amoxapine.
- TCAs interact with a wide variety of receptors with many consequent effects in the setting of an overdose. The primary antidepressant effect is due to the inhibition of serotonin and norepinephrine reuptake. Additionally, TCAs modulate the function of central sympathetic and serotonergic receptors, which is thought to contribute to their antidepressant effects.
- TCAs have antimuscarinic effects, resulting in tachycardia, dry mucous membranes and skin, urinary retention, and decreased GI motility. Patients will also have dilated pupils (Psychopharmacology 1994;114:559). Sedation is likely due to antihistamine effects. Furthermore, these agents are potent α1-antagonists leading to the development of hypotension and a reflex tachycardia. Cardiac toxicity is due to sodium channel blockade, resulting in a wide complex rhythm on the ECG (Annu Rev Med 1984;35:503). TCAs also exhibit a complex interaction with the GABA receptor, which in overdose likely contributes to seizure activity (Life Sci 1988;43:303).

DIAGNOSIS

TCA overdose exhibits its own toxidrome due to the widespread effects on various receptors as outlined earlier. Patients with an acute overdose may present to the emergency department with a normal mental status and vital signs but then rapidly decompensate.

Clinical Presentation

History
As with any overdose, a history is often unreliable. The clinical picture in serious toxicity is fairly stereotypical and a careful physical examination can help establish the diagnosis.
Physical Examination
- Often present with a rapid onset of **CNS depression**
- **Tachycardia** and **hypotension** due to vasodilatation and antimuscarinic effects
- **Dilated pupils, dry mucous membranes, and urinary retention** due to the anticholinergic effects
- May present with **seizure** activity, if significant overdose present

Diagnostic Criteria
The TCA toxidrome is a fairly consistent constellation of signs including hypotension, tachycardia, coma, and seizures.

Diagnostic Testing
Laboratories
- **Serum TCA concentrations** have a **limited role** in the management of acute TCA toxicity as they are **not predictive of severity of illness** (*N Engl J Med* 1985;313:474). Qualitative measurements of TCA concentrations in the urine are unreliable as there are many common drugs that cross-react on the assay, including diphenhydramine and cyclobenzaprine.
- Serial **VBG**s should be measured in patients undergoing alkalinization. As bicarbonate treatment can cause profound hypokalemia, serial **K**+ should be followed and repleted.
- **Dextrose** should be checked in any patient with an altered mental status.

Electrocardiography
The ECG has proved to be a valuable tool in predicting the degree of morbidity in TCA overdose. In one classic study, one-third patients with a **QRS of ≥100 milliseconds** developed **seizures**. Fifty percent of patients with a QRS of ≥160 milliseconds developed **ventricular dysrhythmias** (*N Engl J Med* 1985;313:474). A terminal 40-millisecond axis of greater than 120 degrees is found in patients who are taking TCAs and may help narrow the diagnosis in patients with an altered mental status of unknown etiology. Simply put, the ECG will show an **R’ in aVR**, and an **S** wave in leads I and aVL. An **R’ in aVR** of ≥3 mm has been demonstrated to be predictive of neurologic and cardiac complications in TCA-poisoned patients (*Ann Emerg Med* 1995;26(2):195).

**TREATMENT**
- Patients with TCA overdose require early aggressive intervention.
- In patients with altered mental status, early **intubation, resuscitation**, and **GI decontamination** are warranted.
- Orogastric lavage may be beneficial in patients who are intubated with large ingestions because of decreased GI motility. Avoid this in small children as they only typically take one to two pills.
- **Hyperventilation** to achieve rapid serum alkalinization may be used as a bridge until bicarbonate therapy is started.

**Medications**
**First Line**
- **After the patient’s airway is protected**, a dose of **AC** 1 g/kg is warranted even in delayed presentations.
• Sodium bicarbonate has been demonstrated to narrow the QRS, decrease the incidence of ventricular arrhythmias, and improve hypotension (Emerg Med 2001;13:204). A bolus of 1 to 2 mEq/kg every 3 to 5 minutes should be given with continuous ECG monitoring until the QRS narrows or the BP improves. Serial VBGs should be obtained with a goal of maintaining the blood pH at 7.50 to 7.55.
  ◦ A bicarbonate drip should be titrated to the QRS narrowing and resolution of hypotension. The patient should be monitored in an ICU with serial pH and serum potassium measurements as well as monitoring for fluid overload.
  ◦ Alkalinization should continue for 12 to 24 hours until the clinical picture and the ECG improves.
• Norepinephrine is the pressor of choice in hypotensive patients who do not respond to alkalization because of its direct effects on the vasculature.
• Lidocaine may be considered in the presence of ventricular dysrhythmias precipitated by TCA toxicity. However, class Ia and Ic antidysrhythmics are contraindicated in the management of TCA-poisoned patients.
• Benzodiazepines are the mainstay of treatment for seizures. Phenytoin should be avoided.

Second Line
Propofol and barbiturates may be beneficial in refractory seizures.

Other Nonpharmacologic Therapies

Selective Serotonin Reuptake Inhibitors

GENERAL PRINCIPLES

Classification
This class of drugs includes fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, and escitalopram. These drugs have a much better safety profile than the earlier drugs marketed for the management of depressive disorders and, as such, have largely supplanted MAOIs and TCAs in the treatment of depression.

Pathophysiology
These drugs enhance serotonergic activity by preventing its reuptake into the presynaptic terminal of the neuron, which may partially explain their antidepressant effects. Unlike other antidepressants, SSRIs have limited effects on other receptors and therefore tend to be less toxic in overdose.

DIAGNOSIS

Clinical Presentation
The vast majority of these overdoses have a benign clinical course. However, patients may present with signs of serotonin excess. Patients who have ingested citalopram or escitalopram may develop delayed toxicity.
History
Overdose histories are unreliable. Many patients who claim to have taken an overdose yet who look well actually took SSRIs.

Physical Examination
Signs of toxicity are usually absent unless the patient has taken a massive overdose. In these cases, patients may present with nausea, vomiting, and tachycardia. Patients with citalopram or escitalopram ingestions may present with seizures.

Diagnostic Testing

Laboratories
- Obtain BMP as SSRIs have been implicated in the development of SIADH.
- FSBG should be checked in patients with an altered mental status or seizures.
- Check CK, lactate, and coagulation profile in patients with serotonin syndrome.

Electrocardiography
Patients will occasionally present with a sinus tachycardia. In patients with citalopram or escitalopram, ingestions may develop QTc prolongation as late as 24 hours after an overdose (J Toxicol Clin Toxicol 1997;35:237).

TREATMENT
The vast majority of overdoses require only 6 hours of observation and supportive care. Patients with intentional citalopram and escitalopram overdoses should be admitted to the floor with 24 hours of telemetry to monitor for QTc prolongation.

Medications
- In patients who are awake and alert, 1 g/kg of AC may be administered.
- Treat seizures with benzodiazepines.
- Treat Torsades de pointes (Tdp) with magnesium, correction of electrolytes, lidocaine, and overdrive pacing.

Serotonin Syndrome

GENERAL PRINCIPLES

Definition
Serotonin syndrome is a disorder that can be precipitated by the introduction of a serotonergic agent and has been reported to occur even after ingestion of a single pill (Ann Emerg Med 1999;33:457).

Pathophysiology
Serotonin syndrome is thought to occur secondary to excess stimulation of 5HT2A receptors (J Psychopharmacol 1999;13:100). This syndrome can result from the coadministration of two or more serotonergic agents including SSRIs, MAOIs, meperidine, amphetamines, cocaine, TCAs, and various other drugs.
**DIAGNOSIS**

**Clinical Presentation**

*History*

Suspect serotonin syndrome in any patient who presents with a rapid onset of tremor and clonus after administration of a serotonergic agent. It is important to avoid the addition of other serotonergic agents in the management of these patients.

*Physical Examination*

- Patients will present with signs of excess serotonergic activity including restlessness, shivering, diaphoresis, and diarrhea.
- Patients may develop myoclonus, ocular clonus, and muscle rigidity later.
- Vital sign abnormalities include tachycardia and hyperpyrexia.

**Diagnostic Criteria**

- Serotonin syndrome is diagnosed by the presence of four of the following major criteria: alteration of consciousness, coma, or mood elevation; shivering, myoclonus, rigidity, or hyperreflexia; pyrexia; or diaphoresis.
- Additional minor criteria include restlessness or insomnia; mydriasis or akathisia; tachycardia; diarrhea; and respiratory or BP abnormalities (*Med Hypotheses* 2000;55:218).

**Differential Diagnosis**

Patients who present with altered mental status, rigidity, and hyperpyrexia may be misdiagnosed with neuroleptic malignant syndrome (NMS). NMS tends to develop over days to weeks, whereas serotonin syndrome has a faster onset, usually manifesting over a 24-hour period.

**Diagnostic Testing**

Serotonin syndrome is diagnosed by a constellation of symptoms and signs rather than any specific laboratory findings; however, as the disease evolves, laboratory abnormalities develop.

*Laboratories*

- As with any critical illness, patients may succumb to multiorgan failure, and therefore, laboratory studies should be obtained on the basis of the presentation.
- May have no lab abnormalities if present early with mild form.
- On the other hand, more severe presentations may develop complications from psychomotor agitation and muscle rigidity including elevated CK, metabolic acidosis, and an elevated lactate.
- Check BMP as renal failure may occur in the presence of rhabdomyolysis.
- Check coagulation studies as patients with hyperthermia may develop coagulopathy.

*Electrocardiography*

The typical ECG will show a sinus tachycardia; however, there are no specific diagnostic electrocardiographic criteria associated with serotonin syndrome.

**TREATMENT**

- The treatment of serotonin syndrome is largely supportive and requires the removal of the offending agent. Aggressive cooling and hydration measures should be taken in the hyperthermic patient.
• Benzodiazepines should be used liberally to treat psychomotor agitation and myoclonus. In severe cases, nondepolarizing paralytics should be used to limit the degree of rhabdomyolysis.
• In patients with mild-to-moderate symptoms, cyproheptadine, an antihistamine with 5HT<sub>1A</sub> and 5HT<sub>2A</sub> antagonism, should be considered. A 4- to 8-mg initial dose should be given orally, which often results in a rapid reversal of symptoms. If there is no response, the dose may be repeated in 2 hours. Subsequent dosing is 2 to 4 mg orally every 6 hours until the patient improves or a maximum dose of 32 mg/d is reached.

**Lithium**

**GENERAL PRINCIPLES**

Classification
Toxicity may be classified as acute, chronic, or acute on chronic. Lithium, an antidepressant, has a narrow therapeutic index, and therefore, risk of toxicity is high in patients on chronic therapy. The therapeutic range is approximately 0.6 to 1.2 mmol/L (or mEq/L).

Pathophysiology
• The mechanism by which lithium exerts its antimanic properties is not well understood. There is some evidence that lithium enhances serotonin function, which may contribute to its mood-stabilizing properties (Science 1981;213:1529).  
• Acute toxicity is associated with the development of a GI illness as lithium is a metal.  
• Chronic toxicity is primarily associated with neurologic dysfunction.  
• Although serum levels are helpful in the management of these patients, the clinical picture should be the basis for therapy.  
  ○ Generally, in chronically exposed patients, levels of less than 2.5 mEq/L are associated with tremulousness, ataxia, and nystagmus.  
  ○ Levels greater than 2.5 mEq/L are associated with a deteriorating neurologic syndrome and are an indication for aggressive intervention including dialysis.  
  ○ A serum concentration of 4.0 mEq/L in an acute overdose is also an indication for dialysis (Q J Med 1978;47:123).

Risk Factors
Lithium has peripheral effects, which may enhance its toxicity, including the development of nephrogenic diabetes insipidus. This phenomenon is thought to occur through the reduction in the binding of aquaporins in the collecting duct of the kidney (Annu Rev Physiol 1996;58:619). This development enhances toxicity by causing dehydration, which leads to an increase in proximal tubular reabsorption of lithium (J Physiol 1991;437:377). Other dehydration states may enhance toxicity as well.

Prevention
Patients on chronic lithium therapy should have serum levels monitored and regular follow-up with their psychiatrist, which should include evaluation for the clinical signs of toxicity.
Associated Conditions
Lithium therapy has been associated with the development of chronic tubulointerstitial nephropathy (J Am Soc Nephrol 2000;11:1439), thyroid dysfunction (J Toxicol Clin Toxicol 2000;38:333), serotonin syndrome (Medicine 2000;79:201), and other endocrine effects.

DIAGNOSIS

Clinical Presentation
History
Although the history is often unreliable in overdose patients, acutely intoxicated patients may present complaining of nausea and abdominal discomfort. In chronic toxicity, patients may present with worsening confusion.

Physical Examination
- Acute overdose presents with a predominately GI syndrome of nausea, vomiting, diarrhea, and abdominal pain. As the illness progresses, patients may develop signs of volume depletion with tachycardia and hypotension. Severe toxicity is associated with neurologic dysfunction including altered mental status, nystagmus, ataxia, or coma.
- Chronic toxicity is associated with tremor, nystagmus, and ataxia. Confusion, dysarthria, fasciculations, and myoclonus are frequent physical findings. Seizures are reported in the literature (Biol Psychiatry 1987;22:1184).

Diagnostic Testing
Laboratories
- Obtain serial lithium levels in patients who present with evidence of toxicity.
  - A high initial level may be due to the timing of the last dose; therefore, the clinical picture should guide therapy.
  - Obtain the serum sample in a lithium-free tube.
- Other laboratories should include a BMP to evaluate electrolyte levels, renal function, and hydration status.
- Lithium induces an elevation in the white blood cell (WBC) count.

Electrocardiography
The ECG may show nonspecific T-wave flattening or QTc prolongation; however, cardiac dysfunction is unusual in this overdose.

TREATMENT

- AC does not bind to lithium and therefore has no role in the management of these overdoses.
- Whole-bowel irrigation with polyethylene glycol at a rate of 2 L/hr is indicated for overdoses of sustained-release preparations (Ann Emerg Med 1991;20:536).
- The mainstay of therapy is the infusion of 0.9% saline solution at twice the maintenance rate. Closely monitor fluid status in these patients to avoid overload.

Other Nonpharmacologic Therapies
Consider dialysis for patients present with signs of severe toxicity with altered mental status, or other neurologic dysfunction but are unable to tolerate the required fluid
load for enhanced elimination. In patients with acute overdose and a serum lithium concentration >4.0 mEq/L or chronic overdose and a serum level >2.5 mEq/L, dialysis should be considered.

**Bupropion**

**GENERAL PRINCIPLES**

Bupropion is an atypical antidepressant of the monocyclic aminoketone class and is structurally related to amphetamines. It acts by selectively inhibiting dopamine and norepinephrine reuptake.

**DIAGNOSIS**

Bupropion has been associated with more severe symptoms than the other atypical agents. Common features of toxicity include tachycardia, drowsiness, hallucinations, and convulsions. Seizures have been reported at therapeutic doses (J Clin Psychiatry 1991;52:450). QRS prolongation has also been described in overdose. Symptoms may be delayed for up to 10 hours after ingestion of sustained-release pills.

**TREATMENT**

Treatment of bupropion overdose includes airway protection. Whole-bowel irrigation and MDAC should be considered in patients who present early with a normal mental status and ingestion of a sustained-release preparation. This modality is contraindicated in seizing patients. Seizures should be treated with benzodiazepines. Barbiturates and propofol should be considered in patients with status epilepticus.

**Antipsychotics, General**

**GENERAL PRINCIPLES**

**Epidemiology**

According to the AAPC’s 2007 report, antipsychotic/sedative hypnotic agents were the fourth leading cause of fatal overdoses in the United States (Clin Toxicol 2008;46:927).

**Pathophysiology**

Antipsychotic agents exert their therapeutic effect largely by binding to dopamine receptors in the CNS, which tends to mitigate the positive symptoms of schizophrenia. Dopamine receptor blockade is also associated with the development of movement disorders, and the newer neuroleptic agents attempt to address this by modulating serotonergic tone. Most antipsychotics affect multiple receptors in the nervous, endocrine, and cardiovascular system, which accounts for a wide range of toxic symptoms. In general, the older “typical” agents in the phenothiazine class tend to have more cardiac toxicity, with varying degrees of sodium channel blockade (wide QRS) and potassium channel blockade (QTc prolongation). Furthermore, these agents tend to have more significant extrapyramidal effects. The newer or “atypical”
antipsychotics tend to exhibit less cardiac toxicity, but they often have pronounced \( \alpha_1 \)-antagonism, causing hypotension. The atypicals are also associated with the idiosyncratic development of other medical problems. For example, olanzapine has been associated with the development of fatal diabetic ketoacidosis (DKA) (*Am J Psychiatry* 2003;160(12):2241), and clozapine was briefly withdrawn from the market as a small percentage of patients developed agranulocytosis (*J Clin Psychiatry* 2000;61:14).

**Phenothiazines**

**GENERAL PRINCIPLES**

These are the prototypic antipsychotic drugs and include chlorpromazine, thioridazine, prochlorperazine, perphenazine, trifluoperazine, fluphenazine, mesoridazine, haloperidol (a butyrophenone), and thiothixene.

**DIAGNOSIS**

**Clinical Presentation**

**History**

The history is often difficult to obtain in these patients.

**Physical Examination**

- Overdoses are characterized by agitation or delirium, which may progress rapidly to coma. Pupils may be mydriatic and deep tendon reflexes are depressed. Seizures may occur.
- Vital sign abnormalities may include hyperthermia, hypotension (due to strong \( \alpha \)-adrenergic antagonism), tachycardia, arrhythmias (including TdP), and depressed cardiac conduction.

**Diagnostic Testing**

**Laboratories**

- Serum concentrations are generally not available or useful.
- FSBG and a BMP should be checked on all patients with altered mentation.

**Imaging**

Abdominal radiographs may reveal pill concretions.

**TREATMENT**

- Assess airway and breathing, place an IV, and institute cardiac monitoring.
- Hypotensive patients should receive a 20 mL/kg bolus of normal saline (NS).
- Consider whole-bowel irrigation for ingestion of sustained-release formulations.

**Medications**

- Treat ventricular arrhythmias with lidocaine. Class Ia agents (e.g., procainamide, quinidine, disopyramide) are contraindicated; avoid sotalol.
- Treat hypotension with IV fluid administration and \( \alpha \)-adrenergic vasopressors (nor-epinephrine or phenylephrine). **Avoid epinephrine** as vasodilation may occur because of unopposed \( \beta \)-adrenergic response in the setting of strong \( \alpha \)-adrenergic antagonism.
• TdP may require magnesium, isoproterenol, or overdrive pacing (see Chapter 7, Cardiac Arrhythmias).
• Treat seizures with benzodiazepines.
• Treat dystonic reactions with benztropine, 1 to 4 mg, or diphenhydramine, 25 to 50 mg, IM or IV.
• Treat hyperthermia with cooling.

SPECIAL CONSIDERATIONS
• NMS, which may complicate use of these agents, is characterized by rigidity, hyperthermia, altered mental status, and elevated CK. NMS should be treated with aggressive cooling measures, benzodiazepines, and bromocriptine 2.5 to 10 mg IV tid until the patient improves, then taper the dose over several days to avoid recrudescence of symptoms.
• Admit those patients who have ingested a significant overdose for cardiac monitoring for at least 48 hours.

Clozapine

GENERAL PRINCIPLES
An atypical neuroleptic.

DIAGNOSIS

Clinical Presentation
• Overdose is characterized by altered mental status, ranging from somnolence to coma.
• Anticholinergic effects occur, including blurred vision, dry mouth (although hyper-salivation may occur in overdose), lethargy, delirium, and constipation. Seizures occur in a minority of overdoses. Coma may occur.
• Vital sign abnormalities include hypotension, tachycardia, fasciculations, tremor, and myoclonus.

Diagnostic Testing
• Obtain CBC and LFTs; follow the WBC counts weekly for 4 weeks.
• Clozapine levels are not useful.

TREATMENT
• As always, support ABCs. Place an IV and institute cardiac monitoring.
• Consider AC 1 g/kg if the patient presents within an hour of ingestion.
• Treat hypotension with 20 mL/kg of IVF; if resistant, treat with norepinephrine or dopamine.
• Treat seizures with benzodiazepines.
• Consider filgrastim for agranulocytosis.
• Forced diuresis, hemodialysis, or hemoperfusion are not beneficial.
• Admit and monitor patients with severely symptomatic overdoses for 24 hours or more.

**Olanzapine**

**GENERAL PRINCIPLES**

**Definition**
An atypical neuroleptic.

**DIAGNOSIS**

**Clinical Presentation**
- Overdose is characterized by somnolence, slurred speech, ataxia, vertigo, nausea, and vomiting (Ann Emerg Med 1999;34:279).
- Anticholinergic effects occur, including blurred vision, dry mouth, and tachycardia.
- Seizures are uncommon. Coma may occur.
- Vital sign abnormalities include hypotension and tachycardia. Serious dysrhythmias rarely occur.
- **Pinpoint pupils are unresponsive to naloxone.**

**TREATMENT**
- Pay attention to ABCs, place an IV, and institute cardiac monitoring.
- Give AC if presentation is within 1 hour of ingestion.
- Treat hypotension with fluids and, if ineffective, norepinephrine.
- Give benzodiazepines for seizures.
- Treat DKA aggressively, if present.

**Risperidone, Ziprasidone, and Quetiapine**

**GENERAL PRINCIPLES**

These are newer neuroleptic agents and reports of overdoses have increased significantly. Quetiapine overdose is associated with more adverse outcomes than other neuroleptic agents (Ann Emerg Med 2008;52:541) and requires aggressive therapy.

**DIAGNOSIS**

**Clinical Presentation**
- Clinical effects include CNS depression, tachycardia, hypotension, and electrolyte abnormalities.
- Clinically significant ventricular dysrhythmias are uncommon.
- Miosis is a common finding.
Diagnostic Testing
QRS and QTc prolongation have been reported (*Ann Emerg Med* 2003;42:751).

TREATMENT

- Scrupulous attention should be paid to ventilatory and circulatory support.
- Treat hypotension with 20 mL/kg fluid boluses and, if severe and persistent, consider a direct-acting pressor such as norepinephrine.
- Replete electrolytes as needed.
- Diuresis, hemodialysis, and hemoperfusion do not appear to be useful.

β-Adrenergic Antagonists

GENERAL PRINCIPLES

Definition
Of all of the agents available, propranolol tends to exhibit the most toxicity because it is lipophilic and widely distributed throughout the body and possesses significant membrane-stabilizing activity. Sotalol, which is classically thought of as a class III antiarrhythmic, also has some β-adrenergic antagonist activity and in toxic doses can result in a prolonged QTc and TdP.

Classification
Cardiovascular agents are a frequent cause of serious poisonings, and according to the 2007 annual report of the National Poison Data System, were the fifth leading cause of fatal drug exposures (*Clin Toxicol* 2008;46:927). Patients with these overdoses require aggressive intervention and close monitoring.

Pathophysiology
The toxicity associated with an overdose of β-blockers is largely due to the effects of antagonism at catecholamine receptors. In general, selectivity is lost in overdose, so bronchospasm may occur in the setting of β1-selective antagonists.

DIAGNOSIS

Clinical Presentation
- Patients with a significant ingestion of an immediate-release product will exhibit signs of toxicity within 6 hours. The exception to this rule is sotalol, which in overdose can have delayed toxicity and prolonged effects with one report of QTc prolongation persisting up to 100 hours postingestion (*Eur Clin J Pharmacol* 1981;20:85).
- With the exception of propranolol and sotalol, β-blocker overdose in healthy people tends to be benign, with significant number of patients remaining asymptomatic after ingestion (*J Toxicol Clin Toxicol* 1993;31:531).
History
Suspect β-antagonist overdose in patients with altered mental status, bradycardia, and hypotension.

Physical Examination
Patients with significant ingestions present with bradycardia and congestive heart failure (CHF). Patients with propranolol ingestions may develop coma, seizures, and hypotension. Propranolol overdoses have a high mortality (J Toxicol Clin Toxicol 1997;35:353).

Differential Diagnosis
In patients with symptomatic bradycardia, also consider overdose of CCB, clonidine, or digoxin.

Diagnostic Testing
Laboratories
Patients with β-antagonist overdoses occasionally become hypoglycemic; therefore, a FSBG should be obtained. Likewise, any patient with an altered mental status should have a BMP sent. Consider obtaining a lactate as patients with profound hypotension may develop mesenteric ischemia.

Electrocardiography
The ECG may reveal sinus bradycardia or AV block. In propranolol ingestions, a wide QRS manifesting sodium channel blockade may be present. With sotalol, QTc prolongation may appear as a delayed presentation and TdP may develop.

TREATMENT
The treatment of β-blocker overdose is largely supportive in mild-to-moderate cases. The patient should have an IV placed, and continuous cardiac monitoring should be instituted. Hypoglycemia should be treated with 50 mL of 50% dextrose (D50). Consider AC if patients present within 1 hour of ingestion. Intubation and ventilation should be instituted in patients with altered mental status. Likewise, consider orogastric lavage in patients with potential for severe toxicity such as propranolol overdoses.

Medications
• Patients with significant toxicity, propranolol, or sotalol ingestions should be treated more aggressively.
• Atropine 1 mg IV may be given up to 3 mg for symptomatic bradycardia; however, this is usually ineffective as the bradycardia is not vagally mediated.
• A fluid bolus of 20 mL/kg should be given and may be repeated; monitor for the development of fluid overload.
• Glucagon 2 to 4 mg IV may be given over 1 to 2 minutes. Then start infusion of 2 to 5 mg/hr, not to exceed 10 mg/hr. One of the significant side effects of glucagon administration is nausea and vomiting; monitor for vagally mediated bradycardia.
• Calcium gluconate 3 to 9 g IV may be given through a peripheral line in patients with hypotension. Alternatively, consider calcium chloride 1 to 3 g through a central line slow IV push over 10 minutes. Calcium chloride is sclerosing and can cause severe extravasation injury.
• Any patient with hypotension is a candidate for high-dose insulin euglycemia therapy. Although the mechanism for improvement is unclear, this is routinely used in the management of severe CCB overdose (J Toxicol Clin Toxicol 1999;37:463). Animal studies of severe propranolol overdose have shown a survival benefit (Ann Emerg Med 1997;29:748). This involves a bolus of 1 U/kg of regular insulin, followed by an infusion of 0.5 to 1.0 U/kg/hr of regular insulin. This should be accompanied by a dose of 50 mL of D$_{50}$ and a dextrose drip at 1 g/kg/hr of dextrose. That calculates to 10 mL/kg/hr of D$_{10}$ or 2 mL/kg/hr of D$_{50}$ (Goldfrank’s Toxicologic Emergencies. 8th ed. New York: McGraw-Hill, 2006:933). FSBG should be obtained every 30 minutes, and potassium levels should be followed every 2 hours with repletion as profound hypokalemia may complicate this treatment modality. The BP response tends to be delayed by 15 to 30 minutes.

• Lipid therapy is emerging as a promising treatment modality in these often fatal poisonings. Theoretically, lipid administration causes lipophilic drugs to partition into the plasma and away from the heart. The current protocol, which can be found at http://www.lipidrescue.org, starts with 1.5 mL/kg of 20% intralipid administration over 1 minute, followed by an infusion rate of 0.25 mL/kg/min. If there is no response, the patient may have repeat boluses every 3 to 5 minutes until a 3 mL/kg total dose, and the infusion rate may be increased to 0.5 mL/kg/min. The maximum total dose recommended is 8 mL/kg (J Med Toxicol 2011;7(2):151).

• Catecholamines should be approached with caution in these patients because α-stimulation in conjunction with β-blockade may precipitate acute heart failure. Therefore, hemodynamic monitoring should be instituted with careful titration of epinephrine at 0.02 μg/kg/min or norepinephrine at 0.10 μg/kg/min. Isoproterenol at 0.10 μg/kg/min may be useful as well; however, monitor closely for the development of hypotension. It is important to note that high doses of these agents may be required.

Other Nonpharmacologic Therapies

• In cases of refractory hypotension and bradycardia, it is reasonable to consider intra-aortic balloon pump (IABP) (Ann Emerg Med 1987;16:1381) and ECMO (Arch Mal Coeur Vaiss 2001;94:1386).

• Transvenous pacing may be attempted, but it is generally difficult to achieve capture, given the degree of myocardial depression.

Calcium Channel Blockers

GENERAL PRINCIPLES

Definition

CCBs are widely used for the management of tachyarrhythmias and hypertension. Generally speaking, the overdoses of dihydropyridines, such as amlodipine, nimodipine, nicardipine, and nifedipine, tend to be more benign; although in massive overdose, selectivity may be lost and may result in significant symptoms. Nondihydropyridines, verapamil and diltiazem, can produce severe toxicity, even in the setting of a small overdose.
Pathophysiology
CCBs exert their effects by blocking L-type calcium channels on the smooth muscle of the vasculature and the myocardium. This decreases inotropy and chronotropy and results in a decrement of BP and heart rate. In overdose, these effects are accentuated. L-type calcium channels are also involved in the release of insulin from the β-islet cells of the pancreas. In CCB overdose, patients will often present with elevated blood sugars.

**DIAGNOSIS**

**Clinical Presentation**
Patients with diltiazem or verapamil overdoses should be considered critically ill and require aggressive intervention.

**History**
Patients will often present with an unintentional ingestion where they missed a dose and attempt to “catch up” by doubling their next dose. Intentional ingestions will often not be accurately reported.

**Physical Examination**
Patients with verapamil or diltiazem overdoses will present with profound hypotension, bradycardia, and generally have a normal mental status until they arrest. It is thought that CCBs have somewhat of a neuroprotective effect that may explain the preservation of mentation. In the setting of dihydropyridine overdoses, patients usually present with hypotension and a reflex tachycardia.

**Differential Diagnosis**
CCB toxicity may resemble β-antagonist or clonidine overdoses.

**Diagnostic Testing**
This is a clinical diagnosis; serum concentrations are not useful in the management of CCB overdose.

**Laboratories**
- **FSBG** should be checked and is elevated in the setting of CCB toxicity. This is part of the toxidrome associated with this particular overdose.
- **A BMP** should be obtained as well to follow serum calcium levels. In patients on a calcium drip, ionized calcium should be followed.

**Electrocardiography**
The ECG may show sinus bradycardia, conduction delays, or even complete heart block. With dihydropyridine overdose, a sinus tachycardia may be present.

**TREATMENT**
The treatment of dihydropyridine CCB overdose is largely supportive in mild-to-moderate cases. The patient should have an IV placed, and continuous cardiac monitoring should be instituted. Consider **ACi** if patients present within 1 hour of ingestion. Intubation and ventilation should be instituted in unstable patients. Likewise, consider **orogastric lavage** in patients with potential for severe toxicity. **Whole-bowel**
Irrigation with polyethylene glycol should be instituted for sustained-release preparations.

**Medications**

Patients with significant toxicity, such as verapamil or diltiazem ingestions, should be treated more aggressively.

- **Atropine** 1 mg IV may be given up to 3 mg for symptomatic bradycardia; however, this is usually ineffective as the bradycardia is not vagally mediated.
- **A fluid bolus** of 20 mL/kg should be given and may be repeated; monitor for the development of fluid overload.
- **Calcium gluconate** or **calcium chloride** may be given as described in the treatment section of β-blocker overdose. In addition, a calcium gluconate drip may be started and run up to 2 g/hr. Close monitoring of calcium is required.
- Any patient with hypotension is a candidate for **high-dose insulin euglycemia therapy**. See discussion of this topic under treatment of β-blocker overdose.
- **Lipid therapy** as described in the treatment section of β-blocker overdose should be initiated early.
- **Catecholamines** should be approached with caution in these patients because α stimulation may precipitate acute heart failure. Therefore, **hemodynamic monitoring** should be instituted with careful titration of epinephrine starting at 0.02 μg/kg/min or norepinephrine at 0.10 μg/kg/min.

**Other Nonpharmacologic Therapies**

- In cases of refractory hypotension and bradycardia, it is reasonable to consider IABP (Clin Cardiol 1991;14:933) and cardiopulmonary bypass (Ann Emerg Med 1989;18:984).
- Transvenous pacing may be attempted but it is generally difficult to achieve capture, given the degree of myocardial depression.

**SPECIAL CONSIDERATIONS**

Patients with ingestions of a sustained-release preparation should be monitored in an intensive care setting. Immediate-release preparations should be monitored for 6 to 8 hours prior to discharge or psychiatric evaluation.

**Clonidine**

**GENERAL PRINCIPLES**

- Clonidine is an orally administered agent used in the management of hypertension.
- Clonidine is an imidazoline drug with centrally acting antihypertensive effects related to α2-agonism, which decreases sympathetic outflow from the CNS (N Engl J Med 1975;293:1179). Other drugs in this family include oxymetazoline and tetrahydrozoline, nasal decongestants that exhibit similar toxicity when orally administered. In overdose, peripheral effects include an initial release of norepinephrine with a **transient increase** in BP, followed by hypotension (Clin Pharmacol Ther 1976;21:593).
DIAGNOSIS

Clinical Presentation
Although the clinical presentation of these overdoses can be quite concerning, most patients recover with supportive care. Patients tend to develop symptoms within 30 minutes to an hour after their overdose.

History
The history is unreliable in these patients as they are often somnolent or comatose on arrival to the hospital.

Physical Examination
Suspect clonidine overdose in patients with hypotension, bradycardia, and CNS depression. Occasionally, patients may develop hypoventilation, which is usually responsive to vocal or tactile stimulation (Ann Emerg Med 1981;10:107). Pupillary examination reveals miosis, and this finding in the setting of hypotension and bradycardia is highly suggestive of clonidine overdose.

Differential Diagnosis
β-Antagonists, digoxin, and CCB overdose should be included in the differential.

Diagnostic Testing
Laboratories
Serum clonidine concentrations are not routinely used in the management of these patients. An FSBG and BMP should be obtained on any patient with altered mental status.

Electrocardiography
The ECG generally shows a sinus bradycardia.

TREATMENT

• Patients generally respond with supportive care. In severely poisoned patients, consider intubation and ventilation; however, this is rarely needed.
• Avoid GI decontamination and AC in these patients as they tend to develop altered mental status quickly.
• Atropine 1 mg IV may be given up to 3 mg for symptomatic bradycardia; however, this is usually not necessary as the bradycardia tends to resolve on its own.
• A fluid bolus of 20 mL/kg should be given and may be repeated; monitor for the development of fluid overload.
• An initial dose of 0.4 mg of naloxone may be useful in reversing the hypotension and bradycardia associated with clonidine overdose (Hypertension 1984;69:461). Occasionally, high doses may be required with redosing every 2 to 3 hours as naloxone has a shorter duration of action than clonidine.

SPECIAL CONSIDERATIONS
Withdrawal syndromes have been reported in patients who have stopped taking clonidine. It is usually manifested as rebound severe hypertension, agitation, and
palpitations. Treatment is to administer clonidine, and taper the dose gradually. Benzodiazepines are also useful in this situation.

**Other Antihypertensives**

**GENERAL PRINCIPLES**

- These agents include **diuretics**, **α₁-antagonists**, **angiotensin converting enzyme (ACE) inhibitors**, and **angiotensin II receptor blockers (ARBs)**.
- **Diuretics** tend to be benign in overdose. Occasionally, they cause dehydration and electrolyte imbalances. Laboratory studies should include a BMP. Management usually only requires gentle fluid hydration.
- **α₁-Antagonists** cause peripheral vasodilation, which usually responds to hydration. Occasionally, they cause enough hypotension to require vasopressors. In these cases, norepinephrine should be administered.
- **ACE inhibitors** rarely cause significant toxicity, although there are case reports of fatal overdoses. Treatment is supportive. In patients with hypotension, naloxone may be useful (*Clin Pharmacol Ther* 1985;38:560).
- **ARBs** may cause hypotension in overdose. Treatment is supportive.

**Parasympathetic Agents**

**GENERAL PRINCIPLES**

*ACh* is a common neurotransmitter of the peripheral and central nervous systems, acting on nicotinic and muscarinic receptors.

**Anticholinergics**

**GENERAL PRINCIPLES**

Anticholinergic effects are primarily due to blockade of muscarinic receptors (i.e., antimuscarinic effects), and therefore mainly affect parasympathetic functions.

**Epidemiology**

Anticholinergic poisoning occurs either from intentional ingestion of certain plants or over-the-counter medications (e.g., Jimson weed, diphenhydramine) (*Can J Emerg Med* 2007;9(6):467), or from accidental overdosing (e.g., medical noncompliance, polypharmaceutical regimens) (*Rev Neurol* 2006;43(10):603).

**Etiology**

Drugs and medications with anticholinergic effects include the following:

- **Anticholinergics**: Atropine, scopolamine, benztpine, glycopyrrolate, ipratropium
- **Antihistamines**: Diphenhydramine, promethazine, doxylamine
- **Antipsychotics**: Chlorpromazine, clozapine, olanzapine, quetiapine
- **Antidepressants**: Amitriptyline, nortriptyline, imipramine, desipramine
- **Antiparkinson drugs**: Benztpine, trihexyphenidyl
- **Mydriatics**: Cyclopentolate, homatropine, tropicamide
- **Muscle relaxants**: Cyclobenzaprine
- **Plants**: Belladonna, Jimson weed, *Amanita* mushrooms
Pathophysiology

- Blockade of muscarinic receptors (i.e., parasympathetic autonomic nervous system [ANS], except for the sympathetically innervated sweat glands) leads to the so-called **anticholinergic toxidrome**.
- **Tachycardia** is one of the main symptoms in anticholinergic poisoning. Vagal blockade of cardiac muscarinic receptors leads to unopposed sympathetic stimulation of the myocardium.
- Some anticholinergic drugs can also cross the blood–brain barrier and interact with muscarinic receptors in the cortex and subcortical regions of the brain causing anticholinergic **CNS manifestations**.

Associated Conditions

- Antihistamines and cyclic antidepressants also block sodium channels and cause additional cardiac symptoms such as dysrhythmias and QRS prolongations.
- Potassium channel blockade may result in QTc prolongation and TdP.

**DIAGNOSIS**

Clinical Presentation

**Anticholinergic Toxidrome**

- **Central effects**: Confusion, agitation, euphoria/dysphoria, hallucinations, incoherent thoughts and speech, lethargy, ataxia, choreoathetoid movements, rarely, seizures or coma
- **Peripheral effects**: Tachycardia, mouth dryness, decreased perspiration with flushed skin and hyperthermia, dilated pupils with photophobia and blurred vision, decreased bowel sounds, urinary retention
- A helpful mnemonic for antimuscarinic effects is “RED as a beet, DRY as a bone, BLIND as a bat, MAD as a hatter, and HOT as a hare.”

**TREATMENT**

- All patients presenting with an anticholinergic toxidrome need **cardiovascular monitoring**. Serial evaluation of vital signs and serial physical exams are essential to address sudden worsening of the patient’s condition (dysrhythmia, seizure).
- GI decontamination is only indicated if the patient is fully awake and cooperative due to the high risk of aspiration or loss of airway control in unconscious or combative patients. **Gastric lavage** for GI decontamination may be appropriate, given decreased stomach emptying and slowed GI motility from the anticholinergic effect.
- Patients with hyperthermia may benefit from cooling measures.

Medications

- **Physostigmine** is a reversible **anticholinesterase**, which leads to increased ACh in synapses to overcome receptor blockade. It is useful in the management of severe anticholinergic poisoning with delirium, hallucinations, and seizures (*Int J Clin Pharmacol Ther Toxicol* 1980;18(12):523).
Chapter 28 • Toxicology

- In the emergency department setting, the use of physostigmine as a diagnostic tool in patients with high suspicion of anticholinergic agitation or delirium has been found to be relatively safe (Ann Emerg Med 2003;42(1):14).
- **Contraindications:** underlying cardiovascular disease, wide QRS complex or AV block on ECG, asthma, bowel or bladder obstruction, peripheral vascular disease (PVD), or gangrene. Its use is also contraindicated in the setting of cyclic antidepressant overdose.
- **Adult dosing:** 0.5 mg IV over 5 minutes every 5 minutes up to 2 mg total or until improved level of consciousness.
- Physostigmine has a short duration of action (20 to 60 minutes) and redosing might be necessary if agitation recurs.
- **NOTE:** Always have atropine at bedside for reversal if needed, that is, in case of severe bradycardia or asystole from unopposed cholinergic stimulation, or other dysrhythmias from sodium channel blockade (e.g., in TCA overdose) (J Emerg Med 2003;25(2):185).

**Benzodiazepines** should be used as adjuncts to treat anticholinergic agitation or delirium. There is no benefit in benzodiazepine monotherapy in anticholinergic central symptoms (Ann Emerg Med 2000;35(4):374).

### Cholinesterase Inhibitors

#### GENERAL PRINCIPLES

**Definition**

Cholinesterase inhibitors are chemical compounds that inhibit the enzyme cholinesterase. Blockade of AChE function leads to excess ACh in synapses of the ANS and sympathetic nervous system (SNS).

**Classification**

Cholinesterase inhibitors are divided into two classes:
- Organophosphates
- Carbamates

### Organophosphates

#### GENERAL PRINCIPLES

**Epidemiology**

- Organophosphates (OPs) are commonly used as pesticides and insecticides. Some also have medical indications (e.g., malathion in lice shampoo).
- In the developing world, OP and other pesticide poisonings represent the most common cause of overdose deaths (QJM 2000;93(11):715).
- OPs are also potent chemical terrorism and warfare agents (“nerve gas” agents) (e.g., sarin in the Tokyo subway attack, tabun in the Iraq–Iran war) (Anesthesiology 2002;97(4):989).
- Although self-inflicted OP poisoning with suicidal intent occurs, exposure is primarily occupational or accidental (Intern Med 2007;46(13):965). Since absorption occurs through skin and airways, the handling of OPs requires appropriate protective gear.
**Pathophysiology**

- Inhibition of AChE leads to accumulation of ACh at nicotinic and muscarinic receptors, resulting in **excessive cholinergic stimulation**.
- The severity of symptoms varies depending on the route of exposure (dermal, inhalation, oral, parenteral), dose, lipid solubility of OP, and enzyme affinity (*Lancet* 2008;371(9612):597).
- Initially, most OPs bind AChE reversibly. Some OPs, however, become permanently bound over time, a phenomenon known as “aging.” If aging occurs, the only way to overcome the inhibitory effect is for the body to synthesize new enzyme.
- OPs are heptatically metabolized. Some OPs become active toxins after liver metabolism (e.g., Parathion) (*Bull World Health Organ* 1971;44(1):289).
- In severe poisoning, symptoms occur usually within 6 hours after exposure and are unlikely to occur if an exposed person remains free of symptoms for 12 hours or more (*Bull World Health Organ* 1971;44(1):289).

**DIAGNOSIS**

**Clinical Presentation**


- **Muscarinic effects**
  - SLUDGE syndrome: Salivation, Lacrimation, Urination, Diarrhea, GI cramping, Emesis.
  - Bradycardia, bronchorrhea, bronchoconstriction (NOTE: Asphyxia and cardiovascular collapse are lethal features of OP poisoning).
  - Other effects: Miosis, diaphoresis.
  - NOTE: Intoxicated patients may present with tachycardia instead of bradycardia due to hypoxia (bronchoconstriction, bronchorrhea).

- **Nicotinic effects**
  - Ganglionic: Tachycardia, hypertension, diaphoresis, mydriasis.
  - Neuromuscular: Neuromuscular depolarization, fasciculations, motor weakness, paralysis with respiratory failure (analogous to succinylcholine, which is related to ACh).
  - Central: Confusion, agitation, lethargy, seizures, coma.

**Diagnostic Testing**

- **Cholinesterase levels:** There are two different cholinesterases that are routinely measured in red blood cells and plasma (*Bull World Health Organ* 1971;44(1):289).
- Both assays are relatively useless in assessing the severity of exposure in acute intoxications because of their wide ranges of normal values.
- They are mostly used as sensitivity markers to compare changes from baseline enzyme activity (e.g., in chronic occupational exposure or after OP elimination) (*Lancet* 2008;371(9612):597).

**TREATMENT**

- **Protection:** OP-intoxicated patients pose a significant risk for further contamination of others through direct contact. Health care personnel should use special
personal protective equipment (PPE) (gowns, gloves, masks) until the patient is properly externally decontaminated (Lancet 2008;371(9612):597). PPE should not consist of latex or vinyl, since OPs are lipophilic and may penetrate such materials.

- **Decontamination:**
  - Gastric lavage might be indicated in stable patients who ingested contaminated fluids (Clin Toxicol 2009;47(3):179).
  - NOTE: All lavaged/aspirated fluids need to be safely discarded.

- **Stabilization:**
  - ABCs: Have a low threshold for early intubation in order to obtain airway protection.
  - AVOID mouth-to-mouth resuscitation because of contamination risk.
  - Start IV fluids as an initial bolus of 20 mL/kg (Crit Care 2004;8(6):R391).

- **Atropine** is an antimuscarinic agent, which competes with ACh for receptor binding.
  - GOAL: Atropinization (i.e., drying of bronchial secretions with normalized oxygen saturation [which may require 10 to 100 times the usual atropine doses]), heart rate >80 bpm, and systolic BP >80 mm Hg (Lancet 2008;371(9612):597).
  - The initial adult dose is 1 to 3 mg IV bolus. Then titrate according to persistence of bronchorrhea by giving the double of the previously used dose every 5 minutes until atropinization is achieved (Lancet 2008;371(9612):597).
  - The initial pediatric dose is 0.02 mg/kg IV. Titrate as in adults (BMJ 2007;334(7594):629).
  - Once the patient is stabilized, an infusion of atropine should be started with 10% to 20% of the initial atropinization dose per hour and should be held once anticholinergic effects occur (absent bowel sounds, urinary retention, agitation) (Lancet 2008;371(9612):597). Adults and children may develop paradoxical bradycardia through central anticholinergic mechanisms. NOTE: Atropine has no effect on NMJs; therefore, pralidoxime needs to be added as early as possible in order to reverse muscle weakness.

- **Pralidoxime** (2-PAM): Pralidoxime forms a complex with OPs that are bound to AChE. The pralidoxime–OP complex is then released from the enzyme and thus regenerates AChE function.
  - Once the AChE bound OPs start aging, pralidoxime is rendered ineffective. Therefore, it is crucial to start pralidoxime therapy early.
  - Pralidoxime also binds to some degree to free OPs and so prevents further AChE binding.

- **Adult dosing** used to be administered as boluses given over time. New evidence, however, is favoring an infusion regimen (Lancet 2006;368(9553):2136): 1 to 2 g of pralidoxime in 100 mL NS IV over 20 minutes, then infusion of 500 mg/hr (Lancet 2008;371(9612):597).
  - NOTE: Pralidoxime use longer than 24 hours might be indicated if unaged OPs are redistributed from fat tissue. In such cases, infusions should be continued
Overdoses • Carbamates

until patient remains symptom free for at least 12 hours without additional atropine doses, or until the patient is extubated (Lancet 2008;371(9612):597).

- Cardiac and respiratory failure have been reported after administration of pralidoxime (Crit Care Med 2006;34(2):502).
- Though pralidoxime might not be effective in all cases of OP poisoning due to the aging effect, it is still recommended to be used routinely in order to decrease the total atropine requirements (Crit Care Med 2002;30(10):2346).

- Benzodiazepines are the first-line agents for OP-induced seizures (BMJ 2007;334(7594):629).

COMPLICATIONS

- Intermediate syndrome (IMS):
  - This syndrome is a postacute paralysis from persistent ACh excess after the acute cholinergic phase has been controlled.
  - Weakness of proximal extremity muscles and muscles supplied by cranial nerves that occurs hours to days after treatment of acute OP poisoning and often leads to respiratory failure if unnoticed (PLoS Med 2008;5(7):e147).

- OP-induced delayed neurotoxicity (OPIDN):
  - Besides AChE some OPs also inhibit other neurotoxic esterases, resulting in polyneuropathy or spinal cord damage due to demyelination of the long nerve fibers.
  - OPIDN usually occurs several days to weeks after acute OP poisoning leading to temporary, chronic, or recurrent motor or sensory dysfunctions (Annu Rev Pharmacol Toxicol 1990;30:405).

MONITORING/FOLLOW-UP

- All patients with severe or moderate poisoning should be admitted to an ICU after initial stabilization for further monitoring and treatment (Crit Care 2004;8(6):R391).
- Asymptomatic patients presenting with a history of unintentional poisoning or patients with only mild symptoms do not always require hospital admission but should be observed for 6 to 12 hours. In these patients, consider measuring cholinesterase activity 6 hours after ingestion to evaluate for major ingestion (BMJ 2007;334(7594):629).

Carbamates

GENERAL PRINCIPLES

Epidemiology

Carbamates are reversible AChE inhibitors that also lead to ACh excess in the synaptic junction. They are occasionally found in pesticides. However, their most common use in this country is medicinal.

- Physostigmine is a naturally occurring methyl carbamate found in the Calabar bean. Other common carbamates are pyridostigmine and neostigmine.
Pyridostigmine has been administered to U.S. soldiers while under nerve agent attack to prevent anticholinergic symptoms after possible exposure (JAMA 1991;266(5):693).

**Pathophysiology**
- Inhibition of ACh breakdown through AChE block leads to accumulation of ACh at nicotinic and muscarinic receptors with **excess cholinergic stimulation**.
- Carbamates are reversible enzyme inhibitors; they release AChE spontaneously. There is no “aging” phenomenon with carbamates.

**DIAGNOSIS**

**Clinical Presentation**
The clinical picture of the carbamate-induced cholinergic toxidrome is analogous to the one seen in OP poisoning since nicotinic and muscarinic receptors of the ANS and SNS are affected.
- Look for **SLUDGE syndrome**, **bradycardia**, **bronchorrhea**, and **bronchoconstriction** as well as neuromuscular depolarization, and be aware of the risk of cardiovascular or respiratory failure.
- Symptoms from carbamate poisoning are generally milder compared to OP poisoning and of shorter duration.

**Diagnostic Testing**
Cholinesterase levels are used to compare changes from baseline enzyme activity in mild exposures or to assess treatment success after acute exposure (Clin Chem 1995;41:1814).

**TREATMENT**
- The same measures of **protection** and **decontamination** as with OP poisoning apply to carbamates.
- **Stabilization**:
  - ABCs: Have a low threshold for early intubation in order to obtain airway protection.
  - Avoid mouth-to-mouth resuscitation because of contamination risk.

**Medications**

**First Line**
- **Atropine** is an antimuscarinic agent that competes with ACh for receptor binding.
  - **GOAL**: **Atropinization**. See Treatment under Organophosphates section for dosing guidelines.
  - Adults and children may develop paradoxical bradycardia through central anticholinergic mechanisms.

**Second Line**
Given the reversible action of carbamates, pralidoxime should only be given if more than 2 mg atropine has been required for bronchorrhea control (Am J Emerg Med 1990;8(1):68).
• Pralidoxime should be given if there is no clear evidence for isolated carbamate poisoning since additional OP exposure should always be suspected.
• Benzdiazepines are the first-line agents for carbamate-induced seizures.

Barbiturates

GENERAL PRINCIPLES

The use of barbiturates has largely fallen by the wayside as safer drugs are now available. Barbiturates are still used as induction agents for anesthesia as well as second-line agents for seizure control.

DIAGNOSIS

Suspect barbiturate overdose in patients who present with CNS and respiratory depression.

Clinical Presentation

History
It is often difficult to elicit a history as these patients are generally comatose on arrival.

Physical Examination
Typical examination findings include respiratory depression and coma. Other vital sign abnormalities may include hypothermia. Patients may develop cutaneous bullae known as “barb blisters” (Cutis 1990;45:43). Miosis may be present.

Differential Diagnosis
The differential diagnosis includes benzodiazepine overdose, hypoglycemia, ethanol intoxication, CNS, and other metabolic causes of coma.

Diagnostic Testing

Laboratories
This should include routine testing for any presentation of coma: blood glucose, BMP, LFTs, and thyroid function tests.

Electroencephalography
In barbiturate overdose, Electroencephalography (EEG) recordings may show no electrical activity.

Imaging
• A CXR should be obtained on all of these patients to evaluate for aspiration.
• Head CT may help evaluate for the presence of CNS lesions contributing to coma.

Diagnostic Procedures
Consider lumbar puncture (LP) in patients with undifferentiated coma to evaluate for meningitis or subarachnoid hemorrhage.

TREATMENT

The most important management strategy in barbiturate overdose is airway and breathing protection. Patients with respiratory depression should be intubated.
Medications

First Line
- Consider MDAC in patients with a protected airway and bowel sounds.
- Hypotension should be treated with 20 mL/kg bolus of NS. If this fails, consider a direct-acting vasopressor such as norepinephrine.

Second Line
Urine alkalinization with sodium bicarbonate is reserved for phenobarbital overdoses refractory to MDAC. It is inferior to MDAC (J Toxicol Clin Toxicol 2004;42:1).

Other Nonpharmacologic Therapies
Consider hemoperfusion in the setting of life-threatening phenobarbital overdose that is refractory to conventional management (Chest 2003;123:897). Hemodialysis has been reported to be useful as well (Am J Kidney 2000;36:640).

Benzodiazepines

GENERAL PRINCIPLES

In general, benzodiazepines have a wide safety margin. Deaths are usually related to the presence of a coingestant or ethanol.

DIAGNOSIS

Clinical Presentation
History
This is often difficult to elicit as patients are frequently comatose.

Physical Examination
The typical presentation of a pure oral benzodiazepine overdose is coma with normal vital signs. Respiratory depression is exceedingly unusual in oral overdose of benzodiazepines.

Differential Diagnosis
The differential diagnosis includes barbiturate overdose, hypoglycemia, ethanol intoxication, CNS, and other metabolic causes of coma.

Diagnostic Testing
Laboratories
- This should include routine testing for any presentation of coma: blood glucose, BMP, LFTs, and thyroid function tests. Consider LP in patients with undifferentiated coma to evaluate for meningitis or subarachnoid hemorrhage.
- Urine drug screens are unreliable in the setting of benzodiazepine overdose as the target metabolite, oxazepam or desmethyldiazepam, is not produced by the metabolism of many of the benzodiazepines. Classically, clonazepam, flunitrazepam, alprazolam, and lorazepam are not detected. Therefore, routine screening is not recommended (Clin Chem 2003;49:357).

Imaging
- A CXR should be obtained on all of these patients to evaluate for aspiration.
- A head CT may help evaluate for the presence of CNS lesions contributing to coma.
TREATMENT

Supportive care with observation is the mainstay of therapy. In patients with coingestions and respiratory depression, intubation and ventilation may be required. Since this is a benign overdose, **gastric lavage and AC are not necessary.** These interventions may cause aspiration in an otherwise stable patient.

Medications

- Traditional recommendations include the use of flumazenil; however, given the propensity to precipitate seizures and acute benzodiazepine withdrawal in patients on long-term benzodiazepine therapy, this therapy should be **avoided.** Other **contraindications** include a seizure history, coingestion of a cardiotoxic or epileptogenic drug, or ECG evidence of cyclic antidepressant ingestion.
- In **special cases** such as reversal of iatrogenically induced respiratory depression, reversal of sedation, or pediatric benzodiazepine ingestion, flumazenil may be given as a 0.1 mg/min dose intravenously. Repeat injections may be given, as resedation occasionally reoccurs.

**Sympathomimetics, General**

**GENERAL PRINCIPLES**

Definition

Patients who overdose on sympathomimetic agents exhibit a syndrome of excess adrenergic tone due to direct stimulation of adrenergic receptors or the effects of norepinephrine and epinephrine. Many of the agents in this category are drugs of abuse; although, several therapeutic agents can produce a similar toxidrome.

Classification

Agents that fall into this category include amphetamines, cocaine, vasopressors, methylxanthines, and \( \beta \)-agonists.

Epidemiology

Stimulants and street drugs were the sixth leading cause of fatal exposures according to the AAPCC in 2007, with 188 fatalities reported (Clin Toxicol 2007;46(10): 927).

Pathophysiology

- Agents that stimulate the sympathetic nervous system generally do so by either causing the release or preventing the reuptake of **endogenous catecholamines**, or **directly stimulating** \( \alpha \)- and/or **\( \beta \)-receptors.**
- **Methylxanthines** (theophylline, caffeine) and **\( \beta \)-agonists** (albuterol, dobutamine, isoproterenol) enhance chronotropy and inotropy by **facilitating calcium entry into the myocardium.** They also enhance the function of \( \beta_2 \)-receptors leading to bronchodilatation. Stimulation of the \( \beta_2 \)-rich vascular beds to skeletal muscle results in **vasodilatation** as well. Therefore, in a pure \( \beta \)-agonist overdose, **hypotension and tachycardia** predominate.
- **Epinephrine, norepinephrine, cocaine, and amphetamines** have both \( \alpha \)- and \( \beta \)- effects resulting in **hypertension and tachycardia.**
Other α-receptors are found on the iris, which when stimulated, results in pupillary dilatation. Sympathetic stimulation of sweat glands is a cholinergic effect.

Amphetamines

GENERAL PRINCIPLES

Drugs of abuse in this class include amphetamine, methamphetamine, and 3,4-methylenedioxymethamphetamine (MDMA). MDMA is a potent inducer and/or reuptake inhibitor of presynaptic serotonin, dopamine, and norepinephrine.

DIAGNOSIS

Clinical Presentation
- Suspect amphetamines in any patient presenting with a sympathomimetic toxidrome of hypertension, tachycardia, dilated pupils, and diaphoresis.
- Severely intoxicated patients may develop hyperthermia, seizures, coma, and cardiovascular collapse.

History
Drug abusers will often deny illicit use; therefore, the history is often unreliable.

Physical Examination
Patients may have agitation and altered mental status depending on the degree of intoxication.

Differential Diagnosis
The differential includes anything that may result in a sympathomimetic toxidrome including cocaine, ephedrine, pseudoephedrine, and various amphetamine-derived designer drugs.

Diagnostic Testing

Laboratories
Patients with a sympathomimetic toxidrome should be evaluated for end-organ dysfunction.
- A BMP is useful to assess the degree of hydration and renal function. MDMA is also associated with the development of hyponatremia due to either SIADH or ingestion of large quantity of water.
- A CK should be checked to evaluate for rhabdomyolysis in agitated patients.
- Patients complaining of chest pain should have a troponin drawn.
- Urine drug screens are often associated with false-negative and false-positive results, are expensive, and do not contribute to the management of this syndrome.

Electrocardiography
An ECG should be obtained to evaluate for ischemia and electrolyte disturbances.

Imaging
In select cases, imaging may be useful.
- Obtain a head CT in patients complaining of a headache or altered mental status.
• Obtain a CXR in patients complaining of chest pain.
• In patients with severe chest pain that radiates to the back or is associated with marked agitation, consider obtaining a chest CT to evaluate for aortic dissection.

**TREATMENT**

Mild-to-moderate cases usually respond to supportive care, including IV hydration. In hyperthermic cases, aggressive cooling measures should be taken. As always, priority should be given to airway protection, breathing, and circulation.

**Medications**

*First Line*
- Treat agitation and seizures with benzodiazepines. In refractory seizures, consider barbiturates and propofol.
- Hypertension and tachycardia may be managed with CCBs. AVOID β-antagonists as they may be associated with the development of a hypertensive crisis.
- Nitroglycerin, nitroprusside, and phentolamine may be used in the setting of severe hypertension.
- Ventricular arrhythmias should be treated with lidocaine or amiodarone.

*Second Line*
- Some data suggest that antipsychotics are useful in the management of agitated delirium in these patients (N Engl J Med 1968;278:1361). Consider administration of haloperidol 5.0 mg IV or droperidol 2.5 mg IV in patients with hallucinations (Eur J Emerg Med 1997;4:130).
- In hyperthermic-agitated patients, consider paralysis with a nondepolarizing agent to prevent rhabdomyolysis.

**Other Nonpharmacologic Therapies**

Patients with renal failure and rhabdomyolysis may require hemodialysis.

**SPECIAL CONSIDERATIONS**

MDMA may cause hyponatremia and serotonin syndrome (see earlier discussion).

**REFERRAL**

Obtain a chemical dependency consult in patients hospitalized as a result of drug abuse.

**Cocaine**

**GENERAL PRINCIPLES**

• Cocaine exerts its effects by inhibiting the reuptake of norepinephrine, serotonin, epinephrine, and dopamine. Excess adrenergic tone in the setting of toxicity is reflected by the development of hypertension and tachycardia. Drug-seeking behavior is likely modulated by dopaminergic effects in the ventral tegmental area of the brain.
Cocaine has also been implicated in the development of early cardiovascular disease (Circulation 2001;103:502), likely due to a combination of vasospastic (N Engl J Med 1989;321:1557), prothrombotic (Heart 2000;83:688), and atherogenic effects (J Am Coll Cardiol 2006;47:2120).

**DIAGNOSIS**

**Clinical Presentation**
- Patients with cocaine intoxication often present with complaints of ischemic chest pain.
- Suspect cocaine in any patient presenting with a sympathomimetic toxidrome of hypertension, tachycardia, dilated pupils, and diaphoresis.
- Severely intoxicated patients may develop hyperthermia, seizures, coma, and cardiovascular collapse.

**History**
Drug abusers will often deny illicit use; therefore, the history is often unreliable.

**Physical Examination**
Patients may have agitation and altered mental status depending on the degree of intoxication.

**Differential Diagnosis**
The differential includes anything that may result in a sympathomimetic toxidrome, including amphetamines, ephedrine, pseudoephedrine, and various amphetamine-derived designer drugs.

**Diagnostic Testing**

**Laboratories**
Patients with a sympathomimetic toxidrome should be evaluated for end-organ dysfunction.
- A BMP is useful to assess the degree of hydration and renal function.
- A CK should be checked to evaluate for rhabdomyolysis in agitated patients.
- Patients complaining of chest pain should have a troponin drawn.
- Urine drug screens, although reliable in determining recent use, should not modify the acute management of these patients.

**Electrocardiography**
- An ECG should be obtained to evaluate for ischemia and electrolyte disturbances.
- Cocaine is a known sodium channel blocker, which may be reflected as a wide complex rhythm on the ECG (J Pharmacol Exp Ther 1992;261:910).
- Cocaine has been reported to increase the QTc (Emerg Med J 2004;21:252).

**Imaging**
In select cases, imaging may be useful:
- Obtain a head CT in patients complaining of a headache or altered mental status.
- Obtain a CXR in patients complaining of chest pain.
- In patients with severe chest pain that radiates to the back or is associated with marked agitation, consider obtaining a chest CT to evaluate for aortic dissection.
TREATMENT
Mild-to-moderate cases usually respond to supportive care, including IV hydration. In hyperthermic cases, aggressive cooling measures should be taken. As always, priority should be given to airway protection, breathing, and circulation.

Medications
First Line
- Treat agitation and seizures with benzodiazepines. In refractory seizures, consider barbiturates and propofol.
- Hypertension and tachycardia may be managed with CCBs.
- AVOID β-antagonists as they may be associated with the development of a hypertensive crisis.
- Nitroglycerin, nitroprusside, and phentolamine may be used in the setting of severe hypertension.
- Sodium channel blockade should be treated with sodium bicarbonate (Circulation 1991;83:1799). Give 1 to 2 mEq/kg as an IV bolus; may repeat. Monitor for QRS narrowing.
- Ventricular arrhythmias should be treated with lidocaine.

Second Line
In hyperthermic-agitated patients, consider paralysis with a nondepolarizing agent to prevent rhabdomyolysis.

Other Nonpharmacologic Therapies
Patients with renal failure and rhabdomyolysis may require hemodialysis.

SPECIAL CONSIDERATIONS
- Body packers with suspected cocaine toxicity or obstructive symptoms should have emergent surgical intervention.
- Consider whole-bowel irrigation in patients who present without signs of toxicity. Increasingly, cocaine has been found to be adulterated with levamisole. This veterinary dewormer has been demonstrated to cause agranulocytosis and vasculitis, which reverse with cessation of cocaine use. Any patient who presents with an unexpected decrease in their WBC or necrotic skin rash should be counseled to stop using cocaine. G-CSF may be used to treat serious neutropenia (Semin Arthritis Rheum 2011;41(3):445).

Theophylline
GENERAL PRINCIPLES
Definition
Theophylline is a methylxanthine agent used in the treatment of obstructive pulmonary diseases such as asthma and emphysema. Its use has largely fallen by the wayside as alternative, less toxic medications have been developed. However, patients with refractory pulmonary disease may still be prescribed this drug.
Classification
Toxicity is classified as acute or chronic. The management strategy is different depending on whether the drug is an immediate- or sustained-release preparation.

Pathophysiology
Theophylline exerts its therapeutic effects by promoting catecholamine release, which results in enhanced $\beta$-agonism (Circulation 1983;67:162). Additionally, at high doses, theophylline is a phosphodiesterase inhibitor, which prolongs the effects of $\beta$-agonism by preventing the breakdown of cyclic adenosine monophosphate (cAMP). Theophylline is also an adenosine antagonist, which in therapeutic doses, enhances bronchodilation. However, in toxic doses, adenosine antagonism is associated with the development of tachydysrhythmias and seizures.

DIAGNOSIS

Clinical Presentation
- **Acute toxicity**: Patients with serum concentrations $>20$ $\mu$g/mL will present complaining of nausea and multiple episodes of vomiting. On examination, the patient will be tremulous and tachycardic. Hyperventilation is often present. In more severe cases, hypotension and seizures occur. Refractory status epilepticus is due to adenosine antagonism in the CNS (Neuroscience 1994;58:245). These effects are most often present at serum concentrations $>90$ $\mu$g/mL in the acutely intoxicated patient.
- **Chronic toxicity** usually occurs in patients with a large body burden of theophylline who develop a concurrent illness or are administered a drug that delays the P450 metabolism and theophylline clearance. Subtle symptoms such as nausea and anorexia may occur; tachycardia is usually present. Severe toxicity may occur at serum levels of 40 to 60 $\mu$g/mL. Patients with these serum concentrations may present with seizures.

Diagnostic Testing

Laboratories
- **Acute toxicity** usually occurs at levels $>90$ to 100 $\mu$g/mL and is associated with the development of hypokalemia and hyperglycemia. In severe cases, expect a metabolic acidosis. Obtain a BMP and blood glucose.
- **Serial theophylline** concentrations should be obtained every 1 to 2 hours until a downward trend is present; remember, with sustained-release preparations, a peak may not be evident for 16 hours or later post ingestion.
- **Calcium, magnesium, and CK** should be checked as well.
- **Chronic toxicity** may occur at levels $>40$ $\mu$g/mL and is usually associated with normal laboratory values unless seizures are present. In these cases, obtain the laboratories mentioned earlier. Serial theophylline concentrations are also warranted in these patients.

Electrocardiography
Adenosine antagonism and increased catecholamines may result in a sinus tachycardia or supraventricular tachycardia (SVT) on the ECG. In overdose, premature ventricular contractions (PVCs) may be apparent.
TREATMENT

Patients with theophylline toxicity do not require gastric lavage as they tend to vomit. Sustained-release preparations occasionally form bezoars. Severely intoxicated patients require intubation and ventilation. Sustained-release formulations should be treated with whole-bowel irrigation. Replete potassium and electrolytes as needed.

Medications

- Administer AC 1 g/kg. Consider MDAC as theophylline clearance is increased by this modality (Clin Pharmacol Ther 1983;33:351). Ensure patients have adequate airway protection as vomiting and aspiration may occur.
- Vomiting should be managed with ondansetron or metoclopramide. Phenothiazines are contraindicated as they lower the seizure threshold.
- Seizures are often refractory and should initially be treated with benzodiazepines. If this modality fails, consider moving to phenobarbital as a 10 mg/kg loading dose at a rate of 50 mg/min, followed by up to a total of 30 mg/kg at a rate of 50 mg/min, followed by 1 to 5 mg/kg/d to maintain therapeutic plasma levels. Propofol is a reasonable alternative if these fail. Monitor for hypotension.
- Hypotension should be treated with 20 mL/kg bolus of IVF, which may be repeated. Direct pressors such as phenylephrine and norepinephrine may be added if fluid boluses are not sufficient. Since much of the hypotension is mediated by $\beta_2$-agonism, avoid epinephrine. Consider using short-acting $\beta$-antagonists such as esmolol, which although counterintuitive, may reverse $\beta_2$-mediated vasodilation. Monitor for bronchospasm.
- Arrhythmias should be treated with $\beta$-antagonists. Use short-acting agents such as esmolol and monitor for bronchospasm.

Other Nonpharmacologic Therapies

Hemoperfusion (charcoal or resin) or hemodialysis is indicated for the following:
- Intractable seizures or life-threatening cardiovascular complications, regardless of drug level.
- A theophylline level of $\geq 100$ mg/mL after an acute overdose.
- A theophylline level $>60$ mg/mL in acute intoxication, with worsening symptoms, or inability to tolerate oral charcoal administration.
- A theophylline level $>60$ mg/mL in chronic intoxication without life-threatening symptoms.
- A theophylline level $>40$ mg/mL in a patient with chronic intoxication and CHF, respiratory insufficiency, hepatic failure, or age older than 60 years (J Emerg Med 1993;11:415).

Toxic Alcohol, General

GENERAL PRINCIPLES

- High alcohol concentrations increase the measured plasma osmolality and subsequently widen the osmolar gap. A normal gap is $<10$ mmol/dL and varies from $-14$ to $+10$ mmol/dL (N Engl J Med 1984;310(2):102).
In presence of a widened gap, the actual serum alcohol level can be estimated if done early after ingestion (BMC Emerg Med 2008;8:5) with the following calculation:

\[
\text{Osmol gap} \times \frac{\text{Molecular weight of alcohol}}{10} = [\text{Serum alcohol}(\text{mg/dL})]
\]

Soon after ingestion, alcohol metabolization begins, the osmolar gap falls, and the anion gap rises (Clin J Am Soc Nephrol 2008;3(1):208). Therefore, the osmolar gap should only be used to support the diagnosis of toxic alcohol poisoning and not to draw conclusions about the actual amount of ingested toxin.

\[
\text{Calculated osmolarity} = 2\text{Na}^+ + \frac{\text{BUN}}{2.8} + \frac{\text{Glucose}}{18} + \frac{\text{Alcohol/Molecular weight of alcohol}}{10}
\]

The specific molecular weights for each alcohol can be found in the following sections below.

**TREATMENT**

The general approach to toxic alcohol ingestions is to (Clin Toxicol 2002;40(4):415):

- Prevent the formation of toxic metabolites by inhibiting alcohol dehydrogenase (ADH) (in methanol and ethylene glycol poisoning only).
- Eliminate the toxic alcohol and toxic metabolites from the blood.
- Correct acid–base imbalance.
- Replenish cofactors.

**Methanol**

**GENERAL PRINCIPLES**

**Definition**
Methanol is used in gasoline antifreeze, deicers, windshield washer fluid, paint and varnish removers, fuel, photocopy fluid, embalming fluids; is found in “moonshine” liquor; and is used as a denaturant for ethanol.

**Etiology**
- Ingestions are mostly intentional as suicide attempts.
- Another common cause of poisoning is the use of methanol as ethanol substitute.

**Pathophysiology**
Methanol is oxidized to toxic formic acid and this product is responsible for the anion gap metabolic acidosis in methanol poisoning (Intern Med 2004;43(8):750).
DIAGNOSIS

Clinical Presentation

• Early stage:
  ◦ Early after ingestion, mild CNS depression or headache evolves, but profound obtundation or inebriation can occur as well.
  ◦ These early symptoms are directly caused by methanol prior to metabolization.

• Late stage:
  ◦ After a latent period of about 14 to 18 hours, severe anion gap metabolic acidosis without significant lactate or ketone concentrations develops.
  ◦ Formate accumulation within the retina and optic nerve fibers causes “snow field vision,” blurred vision, visual field defects, or blindness (Arch Ophthalmol 1991;109(7):1012).
  ◦ Other CNS symptoms during the late phase are lethargy, convulsion, delirium, and coma. Basal ganglia hemorrhage with dyskinesia or hypokinesia has been observed (Int J Clin Pract 2004;58(11):1042).
  ◦ Abdominal complaints include nausea, vomiting, pain, and acute pancreatitis (Clin Toxicol 2000;38(3):297).

History

Obtain history of what, when, how, and how much of the toxic substance was ingested.

Physical Examination

• Assess mental status and respiratory and cardiovascular stability.
• Kussmaul respirations may indicate underlying metabolic acidosis.
• Visual field testing may reveal central scotoma or other visual field defects. A thorough funduscopic exam may show hyperemia, disk edema, or atrophy (Med J Aust 1978;2(10):483).

Diagnostic Testing

Laboratories

• Address possible causes of an anion gap acidosis:
  ◦ BMP: Acidosis, anion gap, renal function
  ◦ Urinalysis (UA): Ketones
  ◦ Serum lactate

• Accu-Cheks.

• Obtain serum osmolality, if toxic alcohol ingestion is suspected. Molecular weight of methanol is 32.04 g/mol.

• ABG or VBG: To assess acid/base status and treatment success.

• Ethanol level: If elevated, toxic methanol manifestations may be delayed; if elevated in presence of acidosis, the acidosis is unlikely to be related to a toxic alcohol ingestion, since ethanol blocks the metabolism of the parent compound (unless the toxic alcohol ingestion occurred hours before ethanol ingestion).

• Serum methanol level: Usually not readily available; therefore, clinically not useful.

TREATMENT

• ABCs and supportive care, monitor urine output.
• GI decontamination: Nasogastric lavage is only indicated in patients who present <30 minutes after ingestion or who ingested large amounts of methanol while maintaining a normal mental status.
• Do not use AC since the GI tract rapidly absorbs methanol. AC bears a high risk of aspiration in acutely intoxicated patients.

  o Serum alkalinization limits the amount of undissociated formic acid, which prevents CNS toxicity.
  o Urine alkalinization enhances clearance of formate. CAVEAT: Watch for fluid overload if giving large amounts of bicarbonate.

• Ethanol therapy: EtOH serum levels of 100 mg/dL block ADH sufficiently to inhibit formation of toxic metabolites.
  o Loading dose of 7.6 mL/kg of 10% ethanol solution IV (correlates with an EtOH serum level of 100 to 200 mg/dL).
  o Maintenance dose of 0.8 mL/kg/hr (nondrinker), or 2.0 mL/kg/hr (drinker), or 2.0 to 3.3 mL/kg/hr (on hemodialysis) of 10% ethanol solution IV (Clin J Am Soc Nephrol 2008;3(1):208).

• Fomepizole therapy: 4-Methylpyrazole (Antizol) is an FDA-approved competitive inhibitor of ADH for the treatment of methanol poisoning (Intensive Care Med 2005;31(2):189).
  o Loading dose of 15 mg/kg IV, maintenance dose of 10 mg/kg IV every 12 hours for 48 hours, then 15 mg/kg IV every 12 hours until methanol level <20 mg/dL.
  o Dose adjustment may be needed for patients on hemodialysis (N Engl J Med 2009;360(21):2216).
  o Continue treatment until methanol levels <20 mg/dL and acidosis resolves (Curr Opin Nephrol Hypertens 2000;9(6):695).

• Indication: Ethanol or fomepizole therapy should be started early if:
  o Strong evidence of methanol ingestion
  o Methanol serum level >20 mg/dL
  o Osmolar gap >10 mmol/dL
  o Arterial pH <7.3
  o Serum CO₂ <20 mmol/L
  o Or unexplained anion gap metabolic acidosis is present (N Engl J Med 2009;360(21):2216)

Other Nonpharmacologic Therapies

• Hemodialysis should be used in addition to the aforementioned therapies in order to prevent end-organ toxicity.

• Hemodialysis corrects metabolic abnormalities and eliminates nonmetabolized methanol. Indications for hemodialysis are a methanol level >50 mg/dL, severe acidemia (bicarbonate <15 mmol/L, pH <7.30), and/or optic injury from toxicity (Hum Exp Toxicol 2005;24(2):55).

• Folic acid 1 mg/kg (up to 50 mg) IV every 4 to 6 hours and folinic acid (leucovorin) 1 mg/kg (up to 50 mg) IV every 4 to 6 hours enhance formate metabolism and should be given until metabolic acidosis resolves (Alcoholism 1980;4(4):378).

SPECIAL CONSIDERATIONS

• Coingestion of ethanol might delay the onset of initial symptoms because of ethanol’s higher affinity to ADH.

• Ethanol therapy has significant disadvantages; for example, complex dosing regimen, hard to titrate therapeutic levels, intensive care requirements, and severe side-

- Admit all patients on ethanol infusions to the ICU (risk of hypotension, tachycardia, hypoglycemia, CNS and respiratory depression).
- Stable patients on fomepizole infusion can be safely admitted to the floor. Adverse effects of fomepizole are usually mild and include headache, nausea, dizziness but not sedation (Alcoholism 1988;12(4):516; Lancet 1999;354(9181):831).
- Report all cases of methanol intoxication to the local poison control center (1-800-222-1222).
- Get a clinical toxicologist involved early.
- Consult ophthalmology or neurology service if signs of optic injury or other neurologic deficits present.

**Ethylene Glycol**

**GENERAL PRINCIPLES**

**Etiology**

- Ingestions are mostly intentional suicide attempts.
- Another common cause of poisoning is the use of ethylene glycol as ethanol substitute.

**Pathophysiology**

- Ethylene glycol is oxidized to glycolic acid and oxalic acid.
- Glycolate accumulation is responsible for the anion gap metabolic acidosis in ethylene glycol poisoning.
- Oxalate accumulation is responsible for the development of acute renal failure in ethylene glycol poisoning (Clin Toxicol 1986;24(5):389).

**DIAGNOSIS**

**Clinical Presentation**

- Neurologic stage (30 minutes to 12 hours):
  - CNS depression with altered mental status, hallucinations, ataxia, slurred speech, and cranial nerve palsies are directly caused by ethylene glycol prior to metabolization.
  - Seizures, coma, and respiratory depression can occur in severe intoxications.
- Cardiovascular stage (12 to 24 hours): Glycolate affects the cardiopulmonary system and causes tachycardia, hypotension, heart failure, pulmonary edema, and ARDS.
- Renal stage (24 to 72 hours postingestion):
  - Glycolic acid is further metabolized to oxalic acid. Oxalate is a calcium chelator, and accumulation of oxalate leads to hypocalcemia.
  - Calcium oxalate can precipitate in the renal tubules, which subsequently causes acute tubular necrosis with flank pain and acute renal failure (Acta Clin Belg 1999;54(6):351).
- Within 4 to 6 hours after ingestion, development of an anion gap metabolic acidosis with absence of significant lactate or ketone concentrations occurs.
- Abdominal complaints (nausea, vomiting, pain) are also common.
History
Obtain history of what, when, how, and how much of the toxic substance was ingested.

Physical Examination
- Assess mental status and respiratory and cardiovascular stability.
- Kussmaul respiration may indicate severe metabolic acidosis.

Diagnostic Testing

Laboratories
- Address causes of a high anion gap metabolic acidosis:
  - BMP: Acidosis, anion gap, renal function.
  - UA: Ketones, oxalate crystals (usually a late sign during intoxication).
  - Serum lactate.
  - **Glycolic acid may also be misinterpreted as a high lactic acid on a point-of-care blood gas analyzer.** Serum levels should be obtained in these cases.
- Obtain serum osmolality if toxic alcohol ingestion is suspected. Molecular weight of ethylene glycol is 62.07 g/mol.
- ABG or VBG to assess acid/base status and treatment success.
- Ethanol level: If elevated, toxic ethylene glycol manifestations may be delayed; if elevated in presence of acidosis, unlikely to be toxic alcohol ingestion (unless toxic alcohol ingestion occurred hours before ethanol ingestion).
- Obtain serum ethylene glycol level: Usually not readily available, therefore clinically often not useful.
- Serum calcium level: Low if increased formation of calcium oxalate.
- Repeated renal function testing: Increased risk of acute kidney injury (AKI).

TREATMENT

- ABCs and supportive care, monitor urine output.
- GI decontamination: Nasogastric lavage is only indicated in patients who present <30 minutes after ingestion or who ingested large amounts of ethylene glycol while maintaining a normal mental status.
- **Do not use AC** since the GI tract rapidly absorbs ethylene glycol. AC bears a high risk of aspiration in acutely intoxicated patients.
- **Thiamine** (Vitamin B1) 100 mg IV every 4 to 6 hours and **pyridoxine** (Vitamin B6) 50 mg IV every 6 to 12 hours enhance glycolate metabolism and should be given until metabolic acidosis resolves (*Eur J Emerg Med* 2005;12(2):78).
  - Serum alkalization limits the amount of undissociated glycolic acid, which prevents CNS toxicity.
  - Urine alkalization enhances clearance of glycolate. CAVEAT: Watch for fluid overload if giving large amounts of bicarbonate.
• Ethanol therapy: EtOH serum levels of 100 mg/dL block ADH sufficiently to inhibit formation of toxic metabolites. See discussion of methanol overdose treatment for dosing.
• **Fomepizole** therapy: See discussion of methanol overdose treatment for dosing.
• **Indications:** Ethanol or fomepizole therapy should be started early if:
  ○ Strong evidence of ethylene glycol ingestion
  ○ Ethylene glycol serum level >20 mg/dL
  ○ Osmolar gap >10 mmol/dL
  ○ Arterial pH <7.3
  ○ Serum CO₂ <20 mmol/L

**Other Nonpharmacologic Therapies**
• **Hemodialysis** should be used in addition to the aforementioned therapies in order to prevent end-organ toxicity.
• **Hemodialysis** corrects metabolic abnormalities and eliminates nonmetabolized ethylene glycol. Indications for hemodialysis are an ethylene glycol level >50 mg/dL, severe acidemia (bicarbonate <15 mmol/L, pH <7.30), and/or optic injury from toxicity (*Hum Exp Toxicol* 2005;24(2):55).

**Ethanol**

**GENERAL PRINCIPLES**

• Elimination rate: 20 to 25 mg/dL/hr (zero-order kinetics, faster in chronic alcoholics).
• Ethanol is present in all alcoholic beverages, some food extracts, mouthwash, cold syrups, but is also industrially used as a solvent in its denatured form.

**Pathophysiology**
Ethanol is oxidized to acetic acid (acetate), which is further metabolized to nontoxic intermediates.

**DIAGNOSIS**

**Clinical Presentation**
• CNS depression with ataxia, drowsiness, and confusion are common symptoms at blood levels >100 mg/dL. Respiratory depression can occur at higher concentrations (*Emerg Med 1984;2(1):47*).
• Chronic alcohol abuse induces tolerance, and patients appear asymptomatic even with high blood levels (*J Emerg Med 1997;15(5):687*).
• Hypoglycemia is due to an altered NADH/NAD⁺ ratio with the development of a reduced state. Pyruvate is then shunted off the gluconeogenesis pathway, and lactate production is favored due to increased NADH. Severe hypoglycemia is common in chronic alcoholics and in children.
• Chronic intoxication causes further gluconeogenesis disturbances, an increase in ketogenesis (β-hydroxybutyrate), and eventually the development of alcoholic ketoacidosis (AKA) (*Hum Exp Toxicol 1996;15(6):482*).
Diagnostic Testing

- Obtain glucose levels and BMP (especially in chronic alcoholics).
- Serum ethanol levels are only relevant to rule out poisoning with other alcohols, in presence of coma or altered mental status, or to prove incapacity in an intoxicated patient.
- Serum osmolality (if coingestion with other alcohols is suspected). Molecular weight of ethanol is 46.07 g/mol.
- May also have mild lactic acidosis.

TREATMENT

Treatment is mainly supportive; however, hemodialysis may be indicated in severe poisoning. Administer 100 mg thiamine IV followed by 50 mL of D$_5$W in water IV to any comatose alcoholic patient.

SPECIAL CONSIDERATIONS

- Increased morbidity and mortality result from chronic toxicity (liver and GI injuries) and AKA.
- Traumatic injuries and severe hypothermia are frequent findings due to risky behavior or decreased judgment capability during acute intoxication.
- Ethanol withdrawal can lead to life-threatening conditions and requires special attention.
- Patients should be observed until signs of clinical intoxication resolve.

Cyanide

GENERAL PRINCIPLES

Cyanide is one of the most rapidly acting and lethal poisons in existence. Cyanide has an odor of bitter almonds; however, only 50% of the population can detect it (Clin Toxicol 1981;18(3):367).

Etiology

- Inhalation of smoke from structural fires is the most common source of cyanide exposure in the United States and Western countries.
- Other etiologies include artificial nail remover, older rodenticides, electroplating solutions, photographic developer solutions, laboratory reagents, laetrile, plants (such as pits from the *Prunus* species), food such as cassava, and from the metabolism of sodium nitroprusside.

Pathophysiology

- Cyanide is a chemical asphyxiant. It induces cellular hypoxia by inhibiting Complex IV (also known as cytochrome c oxidase or cytochrome oxidase aa$_3$) in the electron transport chain and thus preventing the formation of adenosine triphosphate (ATP).
- Hyperlactemia occurs from inhibition of aerobic metabolism.
**DIAGNOSIS**

**Clinical Presentation**

- The dose, duration of exposure, route of exposure, and etiology of the exposure all contribute to the severity of the illness. Signs and symptoms can be nonspecific, so physicians must have a high degree of clinical suspicion to avoid missing the diagnosis (*Hum Exp Toxicol* 2007;26:191).

- Transient increases in heart rate, BP, and respiratory rate can be followed by cardiovascular collapse and respiratory failure. Initially, patients can present with bradycardia and hypertension; this is followed by tachycardia and hypotension before they experience cardiovascular collapse.

- The heart and CNS have high demands for oxygen and are commonly affected. Signs and symptoms include headache, anxiety, lethargy, seizures, coma, respiratory failure, and cardiovascular collapse. Cyanide does not cause cyanosis.

- The cherry-red skin that is classically associated with cyanide toxicity is an uncommon finding. Retinal veins may be bright red.

**Laboratories**

- Blood and serum levels are available. However due to lengthy delays in obtaining them, they are not clinically useful in treating the acutely ill patient. Smokers may have a slightly elevated baseline level compared to nonsmokers.

- Due to inhibition of aerobic metabolism, patients can have an elevated lactate levels. In smoke inhalation victims, a lactate greater than 10 mmol/L was suggestive of cyanide toxicity (*N Engl J Med* 2007;26(3):191).

- Patients may have an “arterialization” of their venous blood as the venous oxygen saturation may be very elevated due to inhibition of aerobic metabolism. This can be seen when comparing arterial and venous blood gasses that are drawn simultaneously.

**TREATMENT**

Two antidotes are available for patients with cyanide toxicity.

- The cyanide antidote kit contains amyl nitrite pearls and sodium nitrite. The pearls can be broken and placed under the patient’s nose while IV access is obtained. Sodium nitrite (300 mg) is administered as a 3% solution given over 2 to 4 minutes IV in adults. Nitrites are given to induce a methemoglobinemia so that the cyanide will preferentially bind to them instead of the electron transport chain. However, in patients with smoke inhalation, this can be dangerous as they may already have elevated levels of carboxyhemoglobin and the combination can cause a very severe functional anemia. Nitrites can also cause or exacerbate hypotension. The second part of the antidote is sodium thiosulfate administered as 12.5 g IV in adults. Its time of onset is slower than the nitrites; at times, it is given prophylactically to patients on nitroprusside infusions (*Ann Pharmacother* 1992;26(4):515).

- Hydroxocobalamin (5 g IV) is another antidote. It combines with cyanide to form cyanocobalamin (vitamin B<sub>12</sub>). It has few side effects. It turns the urine red and causes skin discoloration, which negatively interferes with co-oximetry. It will also interfere with certain laboratory tests such as bilirubin, creatinine, and serum glucose (*Crit Rev Toxicol* 2009;39(7):541).
The rest of care is supportive, including adequate volume resuscitation, airway support, and vasopressor and inotropic support as needed (Hum Exp Toxicol 2007;26:191).

**Carbon Monoxide**

**GENERAL PRINCIPLES**

Carbon monoxide (CO) is a colorless, odorless, and tasteless gas that is produced during incomplete combustion of carbon-containing fuels. It is the leading cause of poisoning morbidity and mortality in the United States (JAMA 1991;266:659).

**Etiology**

Common sources of exposure include smoke inhalation in house fires, malfunctioning heaters and electric generators, automobile exhaust, smoking, forklifts, and chemicals such as methylene chloride (Emerg Med Clin N Am 2004;22:985).

**Pathophysiology**

- CO binds with hemoglobin to form carboxyhemoglobin, which causes a functional anemia and shifts the oxyhemoglobin dissociation curve to the left.
- CO inhibits cellular respiration by binding to mitochondrial cytochrome oxidase and disrupting the electron transport chain (J Toxicol Clin Toxicol 1989;27(3):141).
- Nitric oxide levels, which cause vasodilation, are also increased (likely secondary to activation of nitric oxide synthase) (Emerg Med Clin N Am 2004;22:985).

**DIAGNOSIS**

The diagnosis of CO poisoning is challenging due to its many vague signs and symptoms that can wax and wane depending on the patient’s source of exposure.

**Clinical Presentation**

- Patients may present with flu- or viral-like symptoms, which include headache, myalgias, fatigue, lethargy, nausea, vomiting, and dizziness. If these patients remove themselves from the exposure, such as when they leave their house to seek medical attention, the symptoms may improve before they are evaluated by a physician.
- The heart and CNS have higher oxygen demands and so patients can present with chest pain, myocardial infarctions, cardiac dysrhythmias, syncope, stroke-like symptoms, seizures, coma, and other psychoneurologic symptoms.
- Patients may present with persistent neurologic sequelae (PNS), which occur at the time of exposure or delayed neurologic sequelae (DNS), which can occur anywhere between 2 and 40 days after the exposure (Ann Emerg Med 1995; 25:474).

**Diagnostic Testing**

- Carboxyhemoglobin (CO-Hgb) levels are readily available. They can be obtained on either arterial or venous specimens (Ann Emerg Med 1995;25:4813). Levels greater than 5% in nonsmokers and greater than 10% in smokers generally confirm
an exogenous exposure. However, levels do not correlate well with a patient’s symptoms or prognosis.

- New handheld pulse co-oximeters can be used to noninvasively measure CO-Hgb. Standard pulse oximeters may falsely reassure as they cannot detect a difference between oxyhemoglobin and CO-Hgb. This results in a “gap” between the measured pulse oximetry using a finger probe and the true value found by using co-oximetry.
- Levels need to be interpreted in the context of how long it has been since the exposure and when oxygen therapy was initiated. Both will cause the level to be “falsely low.”
- Head CTs may show bilateral lesions in the globus pallidus.
- A lactic acidosis may be present due to the disruption of aerobic respiration.

**TREATMENT**

- Treatment involves administering oxygen. One hundred percent oxygen administered through a non-rebreather will decrease the half-life of CO to 60 to 90 minutes. Hyperbaric oxygen (HBO) will decrease it to 20 to 30 minutes. Most patients will need to be transported to tertiary centers to receive HBO, hence, improving PNS or preventing DNS and not just decreasing the half-life of CO is the rationale for the use of HBO.
  - Indications for and the benefit of HBO are controversial and more research is needed (Cochrane Database Syst Rev 2011 April 13;(4):CD002041). Suggested indications include syncope, coma, neurologic deficits, PNS, cardiac ischemia, severe metabolic acidosis, pregnancy, and CO >25%.
  - HBO carries risks including oxygen-induced seizures, barotraumas, Claustrophobia, and tympanic membrane rupture. Also, once in the chamber, access to the patient is limited and cardioversion and defibrillation cannot be performed.
- Additional care is supportive including airway and ventilator support, vasopressors for hypotension, and treating any additional concurrent injury such as if the patient has a burn from a house fire.

**COMPLICATIONS**

- If the patient survives the exposure, DNS and PNS are the most feared long-term complications after CO poisoning.
- The signs and symptoms of DNS are variable and a standard definition does not exist. They can include malaise, fatigue, headache, memory problems, paralysis, dementia, neuropathy, psychosis, and cortical blindness (Ann Emerg Med 1995; 25:474).