INTRODUCTION

Acute metal and metalloid toxicity is uncommon but can cause significant morbidity and mortality if unrecognized and inappropriately treated. Metals are chemical elements that possess three general properties: (1) they are a good conductor of heat and electricity, (2) they are able to form cations, and (3) they can combine with nonmetals through ionic bonds. The term heavy metal has a historical tradition in clinical medicine, but has been criticized by chemists as lacking in a precise definition or scientific merit. An alternative term, toxic metal, which also lacks firm definition, is sometimes used instead. In clinical toxicology, the following metals, noted in ascending atomic weight, are usually considered under the concept of "heavy" or "toxic" metal poisoning: beryllium, vanadium, cadmium, barium, osmium, mercury, thallium, and lead, with lead and mercury being the metals most clinically significant concerning human poisoning.

Metalloids are chemical elements with properties intermediate to those of metals and nonmetals. Although there is no precise definition, metalloids tend to have these two general properties: (1) they are semiconductors of electricity, and (2) they form amphoteric oxides. In order of ascending atomic weight, the following elements are generally considered metalloids: boron, silicon, germanium, arsenic, antimony, tellurium, and polonium; arsenic is the most clinically significant metalloid.

Exposure to either metals or nonmetals can be from (1) the pure element, (2) an organic compound containing the toxic element (defined as those compounds that contain carbon), or (3) an inorganic compound containing the element (defined as those that do not contain carbon). Depending on the metal or metalloid, potential toxicity is affected by which chemical form is responsible for the exposure.

Because of their effects on numerous enzymatic systems in the body, the metals and metalloids often present with protean manifestations primarily affecting five systems: neurologic, cardiovascular, GI, hematologic, and renal. Effects on the endocrine and reproductive systems are less clinically apparent. It is important to recognize an initial "index case" of metal poisoning to prevent others from being poisoned when the metal source is environmental or industrial (Table 203-1).
### Sources of Metal and Metalloid Poisoning

<table>
<thead>
<tr>
<th>Element</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lead</strong></td>
<td></td>
</tr>
<tr>
<td>Elemental, inorganic</td>
<td>Soldering; battery burning/reclamation; bronzing; brass-making; glassmaking; ingesting ceramic lead glaze; stripping old paint; &quot;deleading&quot; homes; &quot;moonshine&quot; whiskey; liquids in improperly glazed pottery; contaminated herbal medications and cosmetics; indoor shooting ranges; ingestion of paint chips, lead-laden floor dust, lead foreign bodies; lead bullets in abdomen or joint spaces</td>
</tr>
<tr>
<td></td>
<td>Workers at risk: jewelers, painters, lead burners and smelters, including stained glass designers, pipe cutters, pigment makers, printers, welders, pottery makers, radiator repair personnel, battery reclamation workers, construction workers</td>
</tr>
<tr>
<td>Organic</td>
<td>Leaded gasoline (tetraethyl lead)</td>
</tr>
<tr>
<td><strong>Arsenic</strong></td>
<td></td>
</tr>
<tr>
<td>Inorganic (arsenite [trivalent] or arsenate [pentavalent])</td>
<td>Insecticides, rodenticides, herbicides, mining, smelting/refining, Ayurvedic and homeopathic medicines, well water contaminated by leaching mineral ores and/or industrial waste</td>
</tr>
<tr>
<td>Organic</td>
<td>Seafood, parasitical medicines (veterinary)</td>
</tr>
<tr>
<td>Gas (arsine)</td>
<td>Mining smelting/refining, semiconductor industry; made by mixing acids with arsenic-containing insecticides</td>
</tr>
<tr>
<td><strong>Mercury</strong></td>
<td></td>
</tr>
<tr>
<td>Elemental</td>
<td>Battery and thermometer manufacture; sphygmomanometer repair; dentistry; jewelry and lamp manufacture; photography; mercury mining; manufacture of scientific instruments</td>
</tr>
<tr>
<td>Inorganic (mercury salts)</td>
<td>Cosmetic products, especially skin-lightening products; taxidermy; fur processing; tannery work; chemical laboratories; manufacture of explosives, fireworks, disinfectants, button batteries, inks, and vinyl chloride</td>
</tr>
<tr>
<td>Element</td>
<td>Source</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Organic (methyl mercury, ethyl mercury, and phenyl mercury)</td>
<td>Contaminated seafood; embalming; manufacture of drugs, fungicides, bactericides; handling of insecticides; pesticides, coated seeds; use of chlor-alkali process; working with wood preservatives</td>
</tr>
</tbody>
</table>

**LEAD**

**EPIDEMIOLOGY**

Lead is the most common cause of chronic metal poisoning and remains a major environmental contaminant, especially in developing countries. Exposure to lead can occur from inhalation or ingestion, and both inorganic and organic forms of lead produce clinical toxicity. Nonpaint sources include foreign medications, herbal and dietary supplements, Ayurvedic medications, traditional remedies, metallic charms, and cosmetics, especially products from Asia and Africa.\(^1\) Although no safe blood lead level has been identified, the Centers for Disease Control and Prevention reference value for an elevated level is ≥5 micrograms/dL (0.24 micromol/L).\(^2\)

The United States has banned lead in household paints, gasoline, plumbing systems, food, and drink cans; created lead abatement programs; and enforced standards for industrial use of lead.\(^2,^3\) Elevated blood levels in children age 1 to 5 years old are associated with residence in urban dwellings, residence in dwellings built before 1974 (especially those built before 1946), poverty, non-Hispanic black race or ethnicity, and higher population density.\(^4\) Chronic lead exposure and toxicity in children is a significant public health problem because of the effect on intellectual development.\(^5\) Worldwide, 16% of all children are estimated to have lead levels >10 micrograms/dL (0.48 micromol/L). Common sources in low-income countries are substandard or marginal living conditions near landfills and industries such as smelters, mines, and refineries, and leaded gasoline. Child labor in highly polluted conditions is another source of exposure.\(^4\) In developing countries, informal recycling of used lead-acid batteries and processing of gold ore rich in lead have caused mass lead poisonings.\(^6,^7\)

**PHARMACOLOGY**

Absorption of inorganic lead is usually via the respiratory and GI tracts; skin absorption is negligible. Dietary deficiencies in calcium, iron, copper, and zinc may contribute to increased GI absorption in children. There is
usually minimal absorption of lead from bullets or shot lodged in bone or muscle, but increased absorption and toxicity have been reported when bullets or shot are in constant contact with body fluids, such as synovial fluid or cerebrospinal fluid. Absorption of organic lead can occur after inhalation, ingestion, and dermal exposure. Exposure to organic lead can occur from sniffing gasoline (see chapter 199, "Hydrocarbons and Volatile Substances"), which may contain tetraethyl lead ("leaded gasoline"). After absorption, tetraethyl lead is metabolized to inorganic lead and triethyl lead; the latter is responsible for the neurotoxicity from leaded gasoline.

Greater than 90% of the total body lead is stored in bone, where it easily exchanges with the blood. Lead can be transferred across the placenta, a process exacerbated by increased bone turnover during pregnancy. Excretion of lead occurs slowly; the biologic half-life of lead in bone has been estimated to be 30 years.

PATHOPHYSIOLOGY

Lead toxicity primarily affects the nervous, cardiovascular, hematopoietic, and renal systems. In the CNS, the toxic effects of lead include (1) injuries to astrocytes, with secondary damage to the microvasculature and resultant disruption of the blood–brain barrier, cerebral edema, and increased intracranial pressure; (2) decreases in cyclic adenosine monophosphate and protein phosphorylation, which contribute to memory and learning deficits; and (3) alteration with calcium homeostasis, which leads to spontaneous and uncontrolled neurotransmitter release. In the peripheral nervous system, lead causes primary segmental demyelination, followed by secondary axonal degeneration, mostly of the motor nerves.

In the cardiovascular system, small but statistically significant increases in the prevalence of hypertension and atherosclerotic vascular disease are found in individuals with elevated blood lead levels.

In the hematopoietic system, lead interferes with porphyrin metabolism, which may contribute to lead-induced anemia. Coexisting iron deficiency may act synergistically with lead toxicity to produce a more profound anemia and, in children, may be more important than lead as the cause of a microcytic anemia. Hemolytic anemia also occurs as a result of inhibition of red blood cell pyrimidine 5'-nucleotidase, an enzyme responsible for clearing cellular RNA degradation products.

In the kidney, lead affects the proximal tubule, producing Fanconi’s syndrome with aminoaciduria, glycosuria, phosphaturia, and renal tubular acidosis. Chronic interstitial nephritis and increased uric acid levels are due to increased tubular reabsorption of urate. Chronic lead toxicity has been linked to gout and chronic renal failure.

Lead adversely affects osteoblast and osteoclast function in bone. With chronic lead exposure, increased calcium deposition at growth plates may be seen as "lead lines" on radiographs of long bones. Lead-induced adverse effects on the reproductive system include increased fetal wastage, premature rupture of membranes, depressed sperm counts, abnormal or nonmotile sperm, and sterility.

CLINICAL FEATURES
Signs and symptoms of lead toxicity vary according to the type of exposure (acute vs chronic) and, to a lesser extent, according to the age of the individual and type of lead (inorganic vs organic) involved (Table 203-2). Young children are more susceptible than adults to the effects of lead. Encephalopathy, a major cause of morbidity and mortality, may begin dramatically with seizures and coma or develop indolently over weeks to months with decreased alertness and memory progressing to mania and delirium. Encephalopathy due to lead poisoning typically occurs in toddlers age 15 to 30 months old with blood lead levels >100 micrograms/dL (4.8 micromol/L) but has been reported with blood lead levels of 70 micrograms/dL (3.4 micromol/L) or lower.

<table>
<thead>
<tr>
<th>System</th>
<th>Clinical Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS</td>
<td>Acute toxicity: encephalopathy, seizures, altered mental status, papilledema, optic neuritis, ataxia</td>
</tr>
<tr>
<td></td>
<td>Chronic toxicity: headache, irritability, depression, fatigue, mood and behavioral changes, memory deficit, sleep disturbance</td>
</tr>
<tr>
<td>Peripheral nervous system</td>
<td>Paresthesias, motor weakness (classic is wrist drop), depressed or absent deep tendon reflexes, sensory function intact</td>
</tr>
<tr>
<td>GI</td>
<td>Abdominal pain (mostly with acute poisoning), constipation, diarrhea, toxic hepatitis</td>
</tr>
<tr>
<td>Renal</td>
<td>Acute toxicity: Fanconi’s syndrome (renal tubular acidosis with aminoaciduria, glucosuria, and phosphaturia)</td>
</tr>
<tr>
<td></td>
<td>Chronic toxicity: interstitial nephritis, renal insufficiency, hypertension, gout</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Hypoproliferative and/or hemolytic anemia; basophilic stippling (rare and nonspecific)</td>
</tr>
<tr>
<td>Reproductive</td>
<td>Decreased libido, impotence, sterility, abortions, premature births, decreased or abnormal sperm production</td>
</tr>
</tbody>
</table>

GI and hematologic manifestations occur more frequently with acute than with chronic poisoning, and the colicky abdominal pains may be associated with concurrent hemolysis. Patients may complain of a metallic taste and, with long-term exposure, have bluish-gray gingival lead lines. Lead toxicity also causes constitutional symptoms, including arthralgias, generalized weakness, and weight loss. Delayed cognitive development can occur in infants and children whose blood lead levels are 10 micrograms/dL (0.48
Conversely, adult and pediatric patients may be asymptomatic in the face of significantly elevated blood lead levels.

With organic lead poisoning, neurologic abnormalities predominate. Symptoms range from behavioral changes, with irritability, insomnia, restlessness, and nausea and vomiting, to tremor, chorea, convulsions, and mania.

**DIAGNOSIS**

Exposure history, whether occupational or environmental, related to recent travel or immigration, a hobby, or a retained lead bullet, is the most important clue in making the diagnosis. The clinician should focus on symptoms, developmental and dietary histories (in children), pica, and any house or day care remodeling. Occupational, travel, medication, dietary supplement, cosmetic, and hobby histories should be elicited for adults being evaluated and for children who may be exposed to lead secondarily from these adult activities. Toxicity due to retained lead bullets may manifest several decades after being shot. Hyperthyroidism, pregnancy, fever, reinjury, or immobilization of the affected extremity can promote lead release from these retained objects after years of dormancy. **The combination of abdominal or neurologic dysfunction with a hemolysis should raise suspicion for lead toxicity. Consider the diagnosis in all children presenting with encephalopathy.**

The definitive diagnosis rests on finding an elevated blood lead level, with or without symptoms. The blood lead level is the best single test for evaluating lead toxicity, and levels at or >5 micrograms/dL (0.24 micromol/L) are considered elevated in children. Screening may be performed on fingerstick capillary blood, but because of the potential for environmental lead contamination, elevated levels always should be confirmed on a venous blood sample. The edetate calcium disodium provocation test and testing for erythrocyte protoporphyrin (e.g., free erythrocyte protoporphyrin, zinc protoporphyrin) are no longer recommended.

Although it is important to order a blood lead level for confirmatory diagnosis and assistance in monitoring therapy, the laboratory turnaround time for results may be days. **Diagnostic studies in the ED should therefore focus on evaluation for anemia and examination of radiographs for evidence of lead exposure.**

The anemia from lead toxicity can be normocytic or microcytic, possibly with evidence of hemolysis, such as an elevated reticulocyte count and increased serum-free hemoglobin. Basophilic stippling in red blood cells from impaired clearing of cellular RNA degradation products is sometimes seen in lead-poisoned patients. This finding is nonspecific for lead toxicity; it is also found in arsenic toxicity, sideroblastic anemia, and the thalassemias. **Anemia and basophilic stippling occur variably, and their absence does not exclude lead toxicity.**

Following acute or subacute ingestion of lead, abdominal radiographs may show radiopaque material in the GI tract. In children, radiographs of long bones, especially of the knee, may reveal horizontal, metaphyseal "lead lines," which represent failure of bone remodeling rather than deposition of lead.
The differential diagnosis of lead toxicity includes causes of encephalopathy, such as Wernicke's encephalopathy; withdrawal from ethanol and other sedative-hypnotic drugs; meningitis; encephalitis; human immunodeficiency virus infection; intracerebral hemorrhage; hypoglycemia; severe fluid and electrolyte imbalances; hypoxia; arsenic, thallium, and mercury toxicity; and poisoning with cyclic antidepressants, anticholinergic drugs, ethylene glycol, or carbon monoxide. The abdominal pains of lead toxicity can mimic sickle cell crisis, the hepatic porphyrias, and even appendicitis. Chronic lead toxicity can mimic major depression, hypothyroidism, polyneuritis, gout, iron deficiency anemia, and learning disability.

TREATMENT

Patients with appropriate signs and symptoms and an elevated blood lead level are classified as lead toxic and should be treated.

Lead-induced encephalopathy is rare but causes serious morbidity and mortality. In severely toxic patients, standard life support measures should be instituted. Seizures are treated with benzodiazepines and general anesthesia, if necessary. Lumbar puncture may precipitate cerebral herniation and should be performed carefully, if at all, with the removal of only a small amount of cerebrospinal fluid. If lead encephalopathy is suspected, initiate chelation therapy promptly (i.e., in the ED) without waiting for the results of a blood lead level (Table 203-3). If abdominal films demonstrate radiopaque flecks consistent with lead, whole-bowel irrigation with a polyethylene glycol electrolyte solution should be instituted. Larger lead bodies, such as fishing sinkers and jewelry, may require endoscopic or surgical removal.
### Guidelines for Chelation Therapy in Lead-Poisoned Patients

<table>
<thead>
<tr>
<th>Severity (blood lead level [micrograms/dL])</th>
<th>Dose</th>
</tr>
</thead>
</table>
| Encephalopathy                              | **Dimercaprol**, 75 milligrams/m\(^2\) (or 4 milligrams/kg) IM every 4 h for 5 d  
and  
Edetate calcium disodium, 1500 milligrams/m\(^2\) per day via continuous infusion or in 2-4 divided doses IV for 5 d; start 4 h after **dimercaprol** |
| Symptomatic and/or Adults: blood lead >100  
Children: blood lead >69 | **Dimercaprol**  
and  
Edetate calcium disodium (as described above)  
or  
Edetate calcium disodium (alone)  
or  
Succimer (as described below) |
| Asymptomatic Adults: blood lead 70–100  
Children: blood lead 45–69 | Succimer, 350 milligrams/m\(^2\) (or 10 milligrams/kg) PO every 8 h for 5 d, then every 12 h for 14 d |
| Asymptomatic Adults: blood lead <70  
Children: blood lead <45 | Routine chelation not indicated; remove patient from source of exposure |

*General guidelines. Consult with medical toxicologist or regional poison center for specifics and dosing.

Chelation therapy for lead toxicity uses **dimercaprol** (previously known as *British anti-Lewisite*), edetate calcium disodium (sometimes abbreviated *CaNa\(_2\)-EDTA*), and succimer (also known as *dimercaptosuccinic acid*) (Table 203-3). Another chelating agent, penicillamine, has not received approval for use in the treatment of lead toxicity by the U.S. Food and Drug Administration, but there is published experience demonstrating benefit, and penicillamine is used in Europe for lead poisoning. The chelation dosing schedules are guided by the blood lead levels, the presence or absence of symptoms, and the age of the patient. Adverse side effects from chelation therapy are common, and consultation with a medical toxicologist is recommended to assist in management.
**Dimercaprol** crosses the blood–brain barrier and is indicated when neurotoxicity or high blood lead levels are present. *Dimercaprol* is administered IM and is typically used with edetate calcium disodium to prevent lead from being transported into the brain. The diluent for *dimercaprol* includes peanut oil, and therefore, *dimercaprol* should be used with great caution in patients with peanut allergy. Side effects of *dimercaprol* include hypertension; fever, pain, and sterile abscess at injection site; nausea; vomiting; diarrhea; abdominal pain; headache; lacrimation; rhinorrhea; and hemolysis in glucose-6-phosphate dehydrogenase–deficient patients. Side effects with *dimercaprol* are dose dependent and occur in up to 65% of treated patients using recommended doses.

Edetate calcium disodium can be used as a single agent in the treatment of lead toxicity, although there is some concern that mobilization of lead from bone by this agent may lead to increased transport of lead into the brain. Edetate calcium disodium does not cross the blood–brain barrier, and therefore, *dimercaprol*, which does cross, should be given before and during the entire course of edetate calcium disodium when there are CNS symptoms. An important precaution is to not confuse this product for treatment of lead toxicity with edetate disodium, used to treat hypercalcemia. This confusion can lead to serious toxicity and even death, if the wrong drug is used. Side effects from edetate calcium disodium include renal toxicity (especially if dehydrated), dermatitis, headache, fever, chills, and myalgias.

Succimer, an oral analog of *dimercaprol*, effectively chelates lead. Although succimer does not cross the blood–brain barrier, its use as a sole agent is not associated with exacerbation of lead-induced encephalopathy. Some toxicologists consider succimer the preferred chelator for lead poisoning in all but the most severe cases. Its advantages include oral administration without increasing lead absorption from the GI tract, no serious adverse effects, and minimal chelation of essential metals. Repeat treatment may be necessary after a 2-week drug-free period. Side effects from succimer include nausea, vomiting, diarrhea, abdominal pain, rash, pruritus, sore throat, rhinorrhea, drowsiness, paresthesias, transient elevations in serum transaminases and alkaline phosphatase, thrombocytosis, and eosinophilia.

Chelation was not associated with any increased risk of birth defects in the few published cases, and pregnant women with elevated blood lead levels should be chelated following the same guidelines (Table 203-3). Neonatal blood lead levels may be elevated despite maternal chelation, and similarly, neonates should also be chelated following birth.

**DISPOSITION AND FOLLOW-UP**

Removal of the source of lead is the most important action for all individuals with lead poisoning, and patients should not be returned to their former environments until appropriate lead decontamination and abatement measures have been addressed. Family members and coworkers should be evaluated for occult lead toxicity. Hospital admission is recommended for (1) children with symptoms or with a blood lead level >70 micrograms/dL (>3.4 micromol/L), (2) adults with central neurologic symptoms, and (3) patients with suspected lead toxicity when returning to the environment is considered dangerous.
Approximately 85% of patients who suffer lead-toxic encephalopathy develop permanent central neurologic damage, including seizures, mental retardation in children, and cognitive deficits in adults. Abdominal colic usually subsides within days after beginning chelation therapy, and other acute manifestations clear within 1 to 16 weeks with therapy. Lead-induced nephropathy may be partly reversible with chelation therapy.

ARSENIC

EPIDEMIOLOGY

Arsenic is a nearly tasteless, odorless metalloid that causes significant acute and chronic toxicity worldwide. Arsenicals are found in a variety of compounds and industries (Table 203-1) and continue to be used as a means for homicide and suicide.

Arsenic exists in elemental, inorganic salts, organic salts, and gaseous forms. Elemental and organic forms have little to no toxicity, whereas inorganic compounds, including arsenite (trivalent or As\(^{3+}\)) and arsenate (pentavalent or As\(^{5+}\)), are highly toxic. Arsine is a colorless, nonirritating toxic gas encountered in the semiconductor industry, ore smelting, and refining processes and is produced when arsenic-containing insecticides are mixed with acids.

PHARMACOLOGY

Arsenic is well absorbed by GI, respiratory, and parenteral routes and may be absorbed through nonintact skin. Due to its water solubility, pentavalent arsenic (arsenate) is more readily absorbed through mucous membranes, such as the GI tract, than is trivalent arsenic (arsenite), which penetrates the skin more readily due to its increased lipid solubility. After absorption, arsenic localizes in erythrocytes and leukocytes or binds to serum proteins. Within 24 hours, redistribution into the liver, kidney, spleen, lung, GI tract, muscle, and nervous tissues occurs, with subsequent integration into hair, nails, and bone. Elimination from the blood is rapid, and excretion is predominantly renal. Toxicity of the various forms is partly determined by excretory rates, with the more toxic arsenite being excreted at a slower rate than arsenate or the organic arsenical compounds. Arsenic crosses the placenta and is teratogenic in animals and humans.

PATHOPHYSIOLOGY

Ingested or absorbed arsenic reversibly binds with sulfhydryl groups found in many tissues and enzyme systems. Acute exposure produces dilatation and increased permeability of small blood vessels, resulting in GI mucosal and submucosal inflammation and necrosis, cerebral edema and hemorrhage, myocardial tissue destruction, and fatty degeneration of the liver and kidneys. Subacute or chronic exposure can cause a primary peripheral axonal neuropathy with secondary demyelination. Inhaled arsine attaches to sulfhydryl groups of hemoglobin, producing an acute hemolytic anemia with resulting jaundice, abdominal pain, and hemoglobinuria-induced acute renal failure.
CLINICAL FEATURES

The signs and symptoms of toxicity vary with the form, amount, and concentration ingested and the rates of absorption and excretion of the various arsenical compounds (Table 203-4).

**TABLE 203-4**

Clinical Features of Arsenic Toxicity

<table>
<thead>
<tr>
<th>Onset of Symptoms</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute toxicity (10 min to several hours)</td>
<td>GI: nausea, vomiting, cholera-like diarrhea</td>
</tr>
<tr>
<td></td>
<td>Cardiovascular: hypotension; tachycardia; dysrhythmias, including torsade de pointes; secondary myocardial ischemia</td>
</tr>
<tr>
<td></td>
<td>Pulmonary: acute respiratory distress syndrome</td>
</tr>
<tr>
<td></td>
<td>Renal: acute renal failure</td>
</tr>
<tr>
<td></td>
<td>Central neurologic: encephalopathy</td>
</tr>
<tr>
<td>Subacute toxicity (1–3 wk after acute exposure or with chronic exposure)</td>
<td>Central neurologic: headache, confusion, delirium, personality changes</td>
</tr>
<tr>
<td></td>
<td>Peripheral neurologic: sensory and motor neuropathy</td>
</tr>
<tr>
<td></td>
<td>Cardiovascular: QT-interval prolongation</td>
</tr>
<tr>
<td></td>
<td>Pulmonary: cough, alveolar infiltrates</td>
</tr>
<tr>
<td></td>
<td>Dermatologic: rash, alopecia, Mees lines</td>
</tr>
<tr>
<td>Chronic toxicity (ongoing low-level occupational or environmental exposure)</td>
<td>Dermatologic: hyperpigmentation, keratoses, Bowen’s disease, squamous and basal cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>Cardiovascular: hypertension, peripheral arterial disease</td>
</tr>
<tr>
<td></td>
<td>Endocrine: diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td>Oncologic: lung and skin cancer</td>
</tr>
</tbody>
</table>

With acute toxicity, clinical effects usually develop within minutes to hours of ingestion. Severe gastroenteritis with nausea, vomiting, and cholera-like diarrhea is the hallmark of acute poisoning and may last several days to weeks, frequently necessitating hospitalization. Patients may complain of a metallic taste. Hypotension and tachycardia secondary to volume depletion, capillary leak, and myocardial dysfunction occur in moderate to severe cases. The ECG may demonstrate nonspecific ST-segment and T-wave changes with a prolonged QT interval, although these findings are more common in chronic intoxication. Ventricular tachycardia with a *torsade de pointes* morphology has been reported. Secondary myocardial ischemia may occur, leading to an erroneous diagnosis of primary myocardial infarction. Acute encephalopathy, acute respiratory distress syndrome, acute kidney injury, and rhabdomyolysis may ensue.
Survivors of acute poisonings and patients who are poisoned slowly may develop subacute toxicity, typically presenting with complaints of weakness, muscle aches, abdominal pain, memory loss, personality changes, periorbital and extremity edema, or skin rash, often with a history of gastroenteritis occurring 1 to 6 weeks earlier. Central neurologic symptoms include headache, confusion, delirium, and personality changes. Chronic encephalopathy with delirium, hallucinations, disorientation, agitation, and confabulation resembling Korsakoff’s syndrome may occur. Peripheral neuropathy develops in a stocking-glove distribution and is initially sensory, with motor symptoms developing later. Patients with severe poisoning can develop an ascending paralysis mimicking Guillain-Barré syndrome. Dermatologic manifestations vary and include morbilliform rash, alopecia, and desquamation. Mees lines (1- to 2-mm–wide transverse white lines in the nails) due to disrupted keratinization of the nail matrix may be seen 4 to 6 weeks after an acute ingestion.

Chronic toxicity from arsenic occurs with ongoing low-level occupational or environmental exposure and has been linked to the development of hypertension, peripheral vascular disease, diabetes mellitus, epidermoid cancer, respiratory tract cancer, hepatic angiosarcoma, and, possibly, leukemia. Dermatologic manifestations are prominent and include hyperpigmentation, hyperkeratosis of the palms and soles, Bowen's disease, and squamous and basal cell carcinomas. Perforation of the nasal septum has been found in workers exposed occupationally to arsenic.

**DIAGNOSIS**

The diagnosis is easily missed without a history of known exposure to arsenic. Physicians rarely encounter arsenic toxicity, and unfortunately, criminal poisonings often go undetected. The diagnosis of **acute arsenic poisoning should be considered in a patient with hypotension that was preceded by severe gastroenteritis.** The diagnosis of chronic arsenic toxicity should be considered in a patient with a peripheral neuropathy, typical skin manifestations, or recurrent bouts of unexplained gastroenteritis.

An abdominal radiograph may demonstrate intestinal radiopaque metallic flecks in cases of arsenic ingestions. The ECG often reveals a prolonged QT interval, especially in subacute poisoning. The CBC may reveal a normocytic, normochromic, or megaloblastic anemia, and/or a thrombocytopenia. The WBC count may be elevated in acute toxicity and decreased in chronic toxicity. A relative eosinophilia and red cell basophilic stippling may be observed. Elevated reticulocyte counts are found in cases with a component of hemolytic anemia.

Definitive diagnosis of acute poisoning depends on finding elevated arsenic levels in a 24-hour urine collection. All urinary measurements of metals should be collected in metal-free containers after a 5-day seafood-free diet. Normal urinary arsenic level is below 50 micrograms/L (0.67 micromol/L), and total urinary arsenic excretion in an unexposed patient typically does not exceed 100 micrograms/d (1.3 micromol/d). If the baseline urinary level is within normal limits and arsenic intoxication is still suspected, hair and nail clippings should be harvested for laboratory analysis. Due to the rapid distribution of arsenic in tissues, blood arsenic levels are unreliable.
Include arsenic toxicity in the differential diagnosis for septic shock, encephalopathy, peripheral neuropathy (including Guillain-Barré syndrome), Addison’s disease, hypo- and hyperthyroidism, patients with the previously mentioned dermatologic manifestations, Korsakoff’s syndrome, persistent gastroenteritis and/or cholera-like diarrhea, porphyria, other metal toxicities such as thallium and mercury, and unexplained, prolonged malaise and weakness.

**TREATMENT**

Acute arsenic toxicity is a life-threatening illness requiring aggressive management. The first task is to stabilize circulatory function, because hypotension and dysrhythmias are the chief causes of death. Hypotension, usually due to volume depletion, should be managed initially with crystalloid volume replacement, and vasopressor therapy with dopamine or norepinephrine may be required. Overhydration should be avoided because pulmonary and cerebral edema can occur. Ventricular tachycardia and fibrillation may be treated with lidocaine, amiodarone, and electrical defibrillation as necessary. Magnesium sulfate, isoproterenol, and overdrive pacing therapies should be considered for torsade de pointes. Drugs that prolong the QT interval, including classes IA (procainamide, quinidine, and disopyramide), IC, and III antidysrhythmics, should be avoided. Potassium, calcium, and magnesium levels should be monitored and corrected as necessary to prevent further prolongation of the QT interval and exacerbation of torsade de pointes dysrhythmias.

Gastric lavage with a large-bore orogastric tube should be performed in cases of acute ingestion, and activated charcoal, although it poorly adsorbs arsenic, may be effective if co-ingestants were taken. Whole-bowel irrigation should be considered if abdominal radiographs reveal intestinal radiopaque materials consistent with arsenic. Seizures can be treated with benzodiazepines and general anesthesia as necessary.

Initial management of chronic toxicity should be directed toward prevention of further arsenic absorption and GI decontamination, if appropriate. In cases of suspected homicidal intent, patients should be advised to avoid food and drinks prepared by others, and visitor contact with hospitalized patients should be monitored carefully.

Chelation therapy for arsenic toxicity uses dimercaprol or succimer (Table 203-5). Treat patients with acute arsenical poisoning or severe, life-threatening toxicity with dimercaprol until the clinical condition stabilizes and succimer, the less toxic oral chelating agent, can be substituted. Do not delay chelation in severely ill patients until laboratory confirmation because chelation is most effective when given within minutes to hours of exposure. Conversely, hold chelation therapy in clinically stable patients with suspected chronic arsenic toxicity pending diagnosis. Chelation with the oral agent succimer may lower the tissue content of arsenic and speed urinary excretion but does not appear to decrease morbidity or mortality in chronic arsenic poisoning. Early consultation with a regional poison control center or medical toxicologist for assistance with treatment and chelation is recommended.
Patients with acute arsine poisoning are managed with blood transfusions, exchange transfusion to remove the nondialyzable arsine, and hemodialysis for the acute kidney injury. Chelation therapy has no role in the management of arsine toxicity.

DISPOSITION AND FOLLOW-UP

Hospitalization is recommended for (1) patients with acute or life-threatening known or suspected arsenic poisoning, (2) chronically poisoned patients requiring dimercaprol therapy, and (3) patients in whom suicidal or homicidal intent is suspected. In patients with acute arsenic toxicity, prognosis may be influenced favorably by the rapid institution of dimercaprol therapy. Recovery from arsenical neuropathy appears to be related more to the initial severity of symptoms than to institution of chelation therapy, although in patients who do recover, dimercaprol appears to significantly shorten the duration of illness. Often, neurologic recovery occurs slowly over months to years. Normalization of hematologic values can occur in the absence of any specific therapy. Dermatologic manifestations of chronic toxicity are unresponsive to chelation.

MERCURY

EPIDEMIOLOGY

Mercury occurs in inorganic and organic forms. Inorganic mercury compounds are subdivided into elemental mercury (quicksilver), mercurous (Hg⁺) salts (e.g., mercurous chloride or calomel), and mercuric (Hg²⁺) salts (e.g., cinnabar or mercuric sulfide). Organic mercurials exist as short- and long-chained alkyl and aryl compounds. The short-chained alkyls, such as methyl mercury and ethyl mercury, are more toxic to humans, with dimethyl mercury being lethal in small amounts. All forms of mercury are toxic but differ in the means of exposure, routes of absorption, constellations of clinical findings, and responses to therapy (Table 203-1).

PHARMACOLOGY
**Elemental mercury** is absorbed primarily by vapor inhalation. Vacuuming elemental mercury, as from a broken thermometer or fluorescent light bulb, causes volatilization due to both the heat and the airflow through the canister. Absorption by the GI tract is usually negligible so that *swallowing mercury contained in a glass thermometer (elemental mercury) does not produce adverse effects unless the mucosa is damaged*. Elemental mercury can be absorbed dermally. IM injections of mercury can induce abscess and granuloma formation. Slow absorption and delayed systemic toxicity after IM injections of elemental mercury have been reported. IV injections have produced mercury pulmonary and systemic emboli. Elemental mercury crosses the blood–brain barrier, where it is ionized and trapped in the CNS.

**Inorganic mercury salts** are absorbed primarily through the GI tract, but they may also be absorbed across intact skin. Mercuric salts deposit in the ionized form primarily in the kidney, followed by the liver and spleen. Mercury salts do not enter the CNS in consequential amounts nor do they cross the placenta.

**Organic mercury** compounds are also primarily absorbed by the GI tract. The highly lipid-soluble short-chained alkyls easily cross membranes, accumulating in red blood cells, the CNS, liver, kidney, and fetus. Longer-chained alkyl and the aryl compounds are biotransformed into inorganic mercuric ions in the body. Therefore, toxicity with these compounds more closely resembles inorganic mercury toxicity.

Inorganic and the aryl organic mercurials are eliminated in the urine and feces. The short-chained alkyl compounds are excreted primarily in the bile, where they undergo significant enterohepatic circulation.

**PATHOPHYSIOLOGY**

Mercury binds with sulphydryl groups, affecting a diverse number of enzyme and protein systems. Methyl mercury also inhibits choline acetyl transferase, which catalyzes the final step in the production of acetylcholine and may produce symptoms of acetylcholine deficiency. Mercuric salts produce proximal renal tubular necrosis.

**CLINICAL FEATURES**

The clinical effects of mercury poisoning depend on the form and, in some cases, the route of administration. In general, the neurologic, GI, and renal systems are predominantly affected.

**Elemental Mercury**

Acute symptoms following inhalation of elemental mercury vapor include shortness of breath, fever/chills, cough, nausea, vomiting, diarrhea, metallic taste, headaches, weakness, and blurry vision. In severe cases, patients may develop acute lung injury and severe respiratory distress. Following metabolism of ingested or injected elemental mercury to inorganic salts, patients may also develop signs of inorganic mercury toxicity, including tremor and renal failure.

**Inorganic Mercury**
Mercury salts are caustic, and an acute ingestion produces a severe hemorrhagic gastroenteritis with abdominal pain often associated with a characteristic graying of the oral mucosa and metallic taste. Shock and cardiovascular collapse may rapidly ensue. Acute kidney injury results from both direct toxicity of the mercury ions and from decreased renal perfusion due to shock.

GI symptoms of chronic inorganic mercury toxicity include metallic taste, burning sensation in the mouth, loose teeth, mucosal lesions and fissures, excessive salivation, and nausea. Hallmarks of chronic neurologic toxicity include tremor, neurasthenia, and erethism. Neurasthenia is characterized by fatigue, depression, headaches, and difficulty concentrating. Erethism refers to behavioral changes characterized by shyness, emotional lability, irritability, insomnia, and delirium. Chronic renal toxicity ranges from reversible proteinuria to the nephrotic syndrome. Acrodynia, also known as pink disease, is an immune-mediated reaction characterized by a generalized rash; edema and erythema of the palms, soles, and face; excessive sweating; fever; irritability; splenomegaly; and generalized hypotonia with particular weakness of the pelvic and pectoral muscles.

**Organic Mercury**

The short-chained alkyl compounds, methyl, dimethyl, and ethyl mercury, have the most devastating effects on the CNS. After a latent period of weeks to months, orofacial paresthesias are a common initial symptom, followed by headache, tremor, and fatigue. In severe cases, patients may develop ataxia, muscle rigidity and spasticity, blindness, hearing deficits, and dementia. Although less prominent than the neurotoxicity, mild GI, renal, and pulmonary abnormalities may develop with organic mercury poisoning.

**DIAGNOSIS**

An occupational exposure history, in either the index patient or a household member, along with typical physical findings, especially tremor or a constellation of signs and symptoms suggesting erethism or acrodynia, suggests mercury toxicity. Ingestion of mercuric chloride can produce a rapidly fatal course and should be considered in a patient presenting with a corrosive gastroenteritis. Often, however, the diagnosis of mercury toxicity is subtle, arrived at only after many other diagnoses have been investigated.

For poisoning from all forms of mercury, except short-chained alkyls, a 24-hour urinary measurement of mercury should be performed after a 5-day seafood-free diet. A seafood meal (contaminated with mercury) can temporarily elevate the mercury level to the toxic range until the mercury is eliminated. Most unexposed individuals will have 24-hour urine mercury levels <10 to 15 micrograms/L (<0.05 to 0.075 micromol/L). A level >20 micrograms/L (>0.1 micromol/L) may indicate meaningful exposure.

Short-chained alkyl mercury compounds are excreted predominantly by the bile, rendering urinary measurements invalid to assess toxicity from these agents. Laboratory diagnosis after this exposure rests on finding elevated whole-blood mercury levels, because these compounds concentrate in erythrocytes. Whole-blood mercury levels are normally <5 micrograms/L (<0.025 micromol/L).
Although elevated blood or urine values are necessary to confirm the diagnosis, they correlate poorly with toxicity and are unable to distinguish the asymptomatic exposure from mercury poisoning. Furthermore, because of significant redistribution within the body, blood or urine levels do not represent total-body burden. They are most useful in confirming exposure and in following the effects of chelation therapy (see "Treatment," below).

MRI findings in methyl mercury toxicity from ingestion of contaminated seafood include marked atrophy of the visual cortex, cerebellar vermis and hemispheres, and postcentral cortex.²⁸

Behavioral changes or tremor similar to those caused by mercury can be seen with hypothyroidism, apathetic hyperthyroidism, metabolic encephalopathy, senile dementia, adverse effects of therapeutic drugs (such as lithium, theophylline, or phenytoin), Parkinson's disease, delayed neuropsychiatric sequelae of carbon monoxide poisoning, lacunar infarction, cerebellar degenerative disease or tumor, and ethanol or sedative-hypnotic drug withdrawal. Corrosive gastroenteritis can be caused by iron, arsenic, phosphorus, acids, or alkali ingestion. Cerebral palsy, intrauterine hypoxia, and teratogenic effects of therapeutic and illicit drugs and environmental contaminants should be considered when evaluating an infant thought to be affected in utero by short-chained alkyl mercury compounds.

TREATMENT

General therapeutic measures include removal from exposure and supportive therapy, including supplemental oxygen and IV hydration. Hemodialysis does not enhance mercury clearance but may be indicated for treatment of acute kidney injury.

For elemental mercury, the severe respiratory failure following inhalation of volatilized elemental mercury or aspiration of elemental mercury may require endotracheal intubation and positive-pressure ventilation.

For ingestion of inorganic mercury salts, treat with aggressive IV hydration and GI decontamination, including gastric lavage if the patient has not had significant emesis, and consider activated charcoal. Given the profuse diarrhea that may ensue, a cathartic is not indicated.

For organic mercury toxicity, institute gastric decontamination in the setting of acute ingestion. Neostigmine may improve motor function in methyl mercury–poisoned patients by improving acetylcholine levels at the neuromuscular junction.²⁶

Chelation is indicated if it can be given within a few hours after ingestion of mercury salts.²⁰ Chelation therapy for chronic exposures, especially to organic mercury, is much less effective. A history of significant mercury exposure, signs and symptoms consistent with mercury poisoning, and elevated blood or urine mercury levels may assist in the decision making and help determine duration of treatment for chronic mercury toxicity. Dimercaprol and succimer are the preferred chelators for mercury poisoning (Table 203-6).
<table>
<thead>
<tr>
<th></th>
<th>Elemental and Inorganic Mercury</th>
<th>Organic Mercury</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe acute poisoning</td>
<td>Dimercaprol, 5 milligrams/kg IM every 4 h for 2 d, followed by 2.5 milligrams/kg IM every 6 h for 2 d, followed by 2.5 milligrams/kg IM every 12–24 h until clinical improvement occurs or until able to switch to succimer therapy</td>
<td>Succimer, 10 milligrams/kg PO every 8 h for 5 d, then every 12 h for 14 d</td>
</tr>
<tr>
<td>Mild acute poisoning and chronic poisoning</td>
<td>Succimer, 10 milligrams/kg PO every 8 h for 5 d, then every 12 h for 14 d</td>
<td>No proven benefit for chelation therapy</td>
</tr>
</tbody>
</table>

The chelation regimen is adjusted according to clinical response and development of adverse reactions. Adverse reactions with dimercaprol increase with dose and include nausea, vomiting, headache, paresthesias, and diaphoresis. Fever is frequently seen in children during dimercaprol therapy. The dimercaprol-mercury complex is dialyzable, and hemodialysis may be helpful in patients receiving dimercaprol who have diminished renal function. Plasma exchange transfusion also was beneficial in a case of mercuric chloride ingestion. Dimercaprol is contraindicated in methyl mercury poisoning due to the potential for exacerbation of central neurologic symptoms. Succimer is generally well tolerated. Consultation with a poison control center or medical toxicologist is recommended for further assistance with chelation treatment.

**DISPOSITION AND FOLLOW-UP**

Hospital admission is recommended for (1) patients known or suspected to have ingested mercury salts, (2) patients known or suspected to have inhaled elemental mercury vapor with pulmonary injury, and (3) patients requiring dimercaprol therapy.

Outcome depends on the form of mercury and the severity of toxicity. Mild cases of elemental and mercury salt poisoning and very mild cases of organic mercury toxicity may have complete recovery. Death can occur in severe cases of mercuric chloride poisoning and with dimethyl mercury exposure. Most patients with symptomatic organic mercury poisoning are left with residual neurologic deficits. Environmental decontamination and removal of the patient, family members, and coworkers from a site of ongoing contamination play a critical role in preventing injury to others.
OTHER METALS AND METAL SALTS

Other metals and their salts may cause toxicity (Table 203-7). Metal salts typically cause early GI irritation (nausea, vomiting, diarrhea, cramping, and hemorrhage) with subsequent neurologic, renal, hematologic, and cutaneous abnormalities. Symptoms are often vague, and without an explicit history of metal salt exposure, patients are usually misdiagnosed. Treatment universally involves removal of the patient from the source, topical decontamination, administration of activated charcoal (if exposure involves ingestion), and supportive care, including aggressive fluid and electrolyte repletion and hemodialysis, if required. Indications for chelation and its efficacy in treating metal toxicity vary with the specific metal (Table 203-7). Consult with a medical toxicologist or a regional poison control center for specific indications and drug doses.
<table>
<thead>
<tr>
<th>Metal</th>
<th>Poisoning Source</th>
<th>Acute Clinical Manifestations</th>
<th>Chronic Clinical Manifestations</th>
<th>Specific Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bismuth</td>
<td>Antidiarrheals (bismuth subsalicylate), impregnated surgical packing paste</td>
<td>Abdominal pain, acute renal failure</td>
<td>Myoclonic encephalopathy</td>
<td>Dimercaprol (limited evidence)</td>
</tr>
<tr>
<td>Cadmium</td>
<td>Contaminated soil in cadmium-rich areas; alloys used in welding, soldering, jewelry, and batteries</td>
<td>Ingestion: hemorrhagic gastroenteritis Inhalation: pneumonitis, acute respiratory distress syndrome</td>
<td>Proteinuria, osteomalacia (itai-itai or ouch-ouch disease), lung cancer (questionable)</td>
<td>Ingestion: succimer (limited evidence; not generally indicated) Pneumonitis: chelation not indicated</td>
</tr>
<tr>
<td>Chromium</td>
<td>Corrosion inhibitors (e.g., heating systems), pigment production, leather tanning, metal finishing, dietary supplements, prosthetic joints</td>
<td>Skin irritation and ulceration, contact dermatitis; GI irritation, renal and pulmonary failure</td>
<td>Mucous membrane irritation, perforation of nasal septum, chronic cough, contact dermatitis, skin ulcers (&quot;chrome holes&quot;), lung cancer</td>
<td>Acetylcysteine (animal studies suggest efficacy as chelator)</td>
</tr>
<tr>
<td>Cobalt</td>
<td>&quot;Hard metal dust&quot; (tungsten–cobalt mixture), flexible magnets, drying agents, prosthetic joints</td>
<td>Contact dermatitis, asthma</td>
<td>Hard metal lung disease (spectrum ranging from alveolitis to fibrosis), cardiomyopathy, thyroid hyperplasia</td>
<td>Acetylcysteine (animal studies suggest efficacy as chelator)</td>
</tr>
<tr>
<td>Metal</td>
<td>Poisoning Source</td>
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<td>Specific Treatment</td>
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<tr>
<td>Copper</td>
<td>Leaching from copper pipes and containers; fungicide (copper sulfate); welding (copper oxide)</td>
<td>Ingestion: resembles iron poisoning; blue vomitus (copper salts), hepatotoxicity, hemolysis, methemoglobinemia Inhalation: metal fume fever (self-limited fever, chills, cough, dyspnea)</td>
<td>Hepatotoxicity (childhood cirrhosis or idiopathic copper toxicosis)</td>
<td>Dimercaprol for hepatic or hematologic toxicity Succimer in mild poisoning</td>
</tr>
<tr>
<td>Silver</td>
<td>Colloidal (metallic) silver used for medicinal purposes as oral solutions, aerosols, and douches; cauterizing and antiseptic agent (silver nitrate); jewelry, wire</td>
<td>Mucosal irritation (silver oxide and nitrate)</td>
<td>Argyria (permanent skin discoloration due to silver deposition and melanocyte stimulation)</td>
<td>Selenium (possible role)</td>
</tr>
<tr>
<td>Thallium</td>
<td>Rodenticides (use prohibited in the United States); contaminated herbal products; medical radioisotope (miniscule dose); most poisonings related to homicide</td>
<td>Early: nausea, vomiting, abdominal pain, tachycardia Intermediate (&gt;24 h): painful ascending neuropathy, cardiac dysrhythmias, altered mental status Delayed (2 wk): alopecia</td>
<td>Sensorimotor neuropathy, psychosis, dermatitis, hepatotoxicity</td>
<td>Multidose activated charcoal Prussian blue, 125 milligrams/kg PO every 12 h (usually dissolved in 50 mL of 15% mannitol)</td>
</tr>
<tr>
<td>Metal</td>
<td>Poisoning Source</td>
<td>Acute Clinical Manifestations</td>
<td>Chronic Clinical Manifestations</td>
<td>Specific Treatment</td>
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<tr>
<td>Zinc</td>
<td>Smelting, electroplating, military smoke bombs, zinc lozenges, welding/galvanizing (zinc oxide)</td>
<td>Ingestion: nausea, vomiting, abdominal pain (resembles iron poisoning)</td>
<td>Copper deficiency, sideroblastic anemia, neutropenia</td>
<td>Edetate calcium disodium Supportive care for metal fume fever</td>
</tr>
</tbody>
</table>

**REFERENCES**


**USEFUL WEB RESOURCES**


Mercury poisoning—[http://www.atsdr.cdc.gov/ToxProfiles/tp46.pdf](http://www.atsdr.cdc.gov/ToxProfiles/tp46.pdf), [http://www.epa.gov/hg/effects.htm](http://www.epa.gov/hg/effects.htm)