

Toxicity, Heavy Metals

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Disclosure

INTRODUCTION

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Background: Heavy metal toxicity represents an uncommon, yet clinically significant, medical condition. If unrecognized or inappropriately treated, heavy metal toxicity can result in significant morbidity and mortality. The periodic table contains 105 elements, of which 80 are considered metals. Toxic effects in humans have been described for less than 30 of these. Many metals are essential to biochemical processes, and others have found therapeutic uses in medicine. Iatrogenic metal toxicity may occur with bismuth, gold, gallium, lithium, and aluminum species. Intentional or unintentional ingestion of arsenic has been notorious as a means of suicide and homicide. However,

occupational exposure to heavy metals has accounted for the vast majority of poisonings throughout human history. Hippocrates described abdominal colic in a man who extracted metals, and the pernicious effects of arsenic and mercury among smelters were known even to Theophrastus of Erebus (370-287 BC).

The classic acute occupational heavy metal toxicity is metal fume fever (MFF), a self-limiting inhalation syndrome seen in workers exposed to metal oxide fumes. MFF, or “brass founders ague,” “zinc shakes,” “Monday morning fever” as it is variously known, is characterized by fever, headache, fatigue, dyspnea, cough, and a metallic taste occurring within 3-10 hours after exposure. The usual culprit is zinc oxide, but MFF may occur with magnesium, cobalt, and copper oxide fumes as well. A neutrophil alveolitis ensues, with hypoxia, reduced vital capacity, and diffuse bilateral infiltrates seen on radiographs.

The pathophysiology of MFF appears to be a direct toxic irritation. Treatment is supportive and effects generally resolve within 24 hours. The diagnosis of MFF is based on a history of exposure and must be clearly differentiated from the true chemical pneumonitis that occurs after exposure to metal fumes from cadmium, manganese, mercury, and nickel. These exposures are clinically indistinguishable from MFF in the early stages but tend to progress to ARDS and cause significantly more morbidity and mortality.

Toxic effects from chronic exposure to heavy metals are far more common than acute poisonings. Chronic exposure may lead to a variety of conditions depending on the route of exposure and the metabolism and storage of the specific element in question. For example, chronic exposure to cobalt dust has been associated with the development of pulmonary fibrosis that can lead to cor pulmonale. This hard metal pneumoconiosis has been described for other metal dusts. Chronic inhalation of high levels of cadmium also causes both fibrotic and emphysematous lung damage, but it also has major effects in bone and kidney. Itai-itai (ouch-ouch) disease—a syndrome of chronic renal failure and osteoporosis described in the Fuchu area of Japan—is often attributed to high levels of naturally occurring cadmium in the soil coupled with increased industrial exposures around World War II.

Exposure to copper can lead to its accumulation in liver, brain, kidney, and cornea, leading to the classic impairment and stigmata of Wilson disease and Indian childhood cirrhosis. Many of the heavy metals have been implicated as carcinogens in the setting of chronic exposure.

The most common species implicated in acute and/or chronic heavy metal toxicity are lead, arsenic, and mercury. Overall, lead is the most significant toxin of the heavy metals. Industrial decisions, such as the addition of lead to paints, dyes, and gasoline, have created an epidemic of lead poisonings. Lead is a naturally occurring substance and can be found in organic and inorganic forms. Inorganic forms of lead typically affect the CNS, peripheral nervous system (PNS), hematopoietic, renal, GI, cardiovascular, and reproductive systems. Organic lead toxicities tend to predominately affect the CNS.

The inorganic forms of lead are absorbed through ingestion or inhalation, whereas organic lead salts are absorbed through the skin. Only about 10% of an ingested dose is absorbed in adults, but the absorbed percentage may be much greater in children. Lead absorption is enhanced by deficiencies of iron, calcium, and zinc.

Under typical conditions, lead is absorbed and stored in several body compartments. Five to ten percent is found in the blood, most of which is located in erythrocytes; 80-90% is taken up in the bone and stored with the hydroxyapatite crystals, where it easily exchanges with the blood. Some authorities list the half-life of lead in the bone as long as 30 years, while others estimate the lead half-life in bone to be 105 days. Generally, excretion of lead is slow, with an estimated biologic half-life in soft tissues of 24-40 days. The remainder of the stored lead is found in soft tissue, notably the kidney and brain. The primary route of excretion is through feces (80-90%). To a lesser extent, lead is excreted in urine (10%). Lead passes the placental barrier and is found in breast milk. A correlation exists between lead toxicity and fetal wastage, premature rupture of membranes, and

sterility.

Arsenic is well known as a poison used in homicidal and suicidal attempts. Napoleon may have ultimately succumbed to its effects, albeit accidentally. His exposure is thought to have been due to a greenish pigment used in the decorative wallpaper hung in his room on St Helena during his exile. The vast majority of its victims today, however, are rats and other unsuspecting rodents. It can produce acute, subacute, and chronic toxicity.

Arsenic was the primary compound in the spray known as Lewisite that was used by the British during trench warfare in World War I. Exposure produced severe edema of the eyelids, gastrointestinal irritation, and both central and peripheral neuropathies. The first antidote to heavy metal poisoning, and the basis for chelation therapy today, was developed by the Germans during World War II in anticipation of a reinitiation of gas warfare. British Anti-Lewisite (dimercaprol) has sulfhydryl groups that bind arsenic, as well as other metals, to form stable covalent bonds in a process called complexation. The nonionic complexes can then be excreted by the body. Although a high level of suspicion for arsenic poisoning must be maintained because of its role in intentional poisoning, it is rarely seen clinically.

Mercury is receiving considerable attention today because of its ubiquity as an environmental pollutant. Ingestion of organic or inorganic mercury can precipitate protein acutely in a local reaction that causes mucosal sloughing along the GI tract and subsequent severe dehydration. This is the mechanism of death for an increasing number of water fowl along the shores of the Great Lakes. Chronic toxicity is most classically marked by neurologic effects ranging from lethargy to excitement, hyperreflexia, and tremor. The Mad Hatter, along with several of his 19th century coworkers, was a victim of chronic mercury exposure in the course of making felt hats. Chronic exposure to mercury compounds may also lead to renal and hepatic failure and deterioration of alveolar bone with loosening of the teeth.

Pathophysiology: The pathophysiology of the heavy metal toxidromes remains relatively constant. For the most part, heavy metals bind to oxygen, nitrogen, and sulfhydryl groups in proteins, resulting in alterations of enzymatic activity. This affinity of metal species for sulfhydryl groups serves a protective role in heavy metal homeostasis as well. Increased synthesis of metal binding proteins in response to elevated levels of a number of metals is the body's primary defense against poisoning. For example, the metalloproteins are induced by many metals. These molecules are rich in thiol ligands, which allow high-affinity binding with cadmium, copper, silver, and zinc among other elements. Other proteins involved in both heavy metal transport and excretion through the formation of ligands are ferritin, transferrin, albumin, and hemoglobin.

Although ligand formation is the basis for much of the transport of heavy metals throughout the body, some metals may compete with ionized species such as calcium and zinc to move through membrane channels in the free ionic form. For example, lead follows calcium pathways in the body, hence, its deposition in bone and gingivae.

Nearly all organ systems are involved in heavy metal toxicity; however, the most commonly involved organ systems include the CNS, PNS, GI, hematopoietic, renal, and cardiovascular (CV). To a lesser extent, lead toxicity involves the musculoskeletal and reproductive systems. The organ systems affected and the severity of the toxicity vary with the particular heavy metal involved, the age of the individual, and the level of toxicity.

Frequency:

- **In the US:** Of the heavy metals, toxicity by chronic lead exposure is the most commonly encountered. The National Health and Nutrition Examination Survey (NHANES III) conducted from 1988-1990 found that 0.4% of persons aged 1 year and older had blood

levels of lead of 25 mcg/dL or higher. The data also noted that, among those aged 1-5 years, an estimated 1.7 million children had blood levels greater than 10 mcg/dL. The syndrome of childhood plumbism caused by the ingestion of lead is believed to affect more than 2 million American preschool-aged children. Lead toxicity has a significantly higher prevalence among the African American population and in lower socioeconomic areas. Reliable figures for the prevalence of mercury and arsenic toxicities are not available. These toxidromes are usually encountered from industrial exposures. Arsenic exposure, however, often occurs outside the industrial realm because of its uses as a rodenticide and a commonly employed homicidal and suicidal agent.

Mortality/Morbidity: As previously noted, heavy metal toxicities are relatively uncommon. However, failure to recognize and treat heavy metal toxicities can result in significant morbidity and mortality.

Encephalopathy is a leading cause of mortality in patients with both acute and chronic heavy metal toxicity.

Race: A higher incidence of heavy metal toxicity occurs in the African American population in the US because of delays in removing lead sources from lower socioeconomic areas.

Sex:

- Little or no difference in prevalence exists.
- Occupations with heavy metal exposure that predominantly involve a particular sex are associated with higher rates of exposure in that sex.

Age: Several points are of concern in heavy metal toxicity with respect to age. Generally, children are more susceptible to the toxic effects of the heavy metals and are more prone to accidental exposures.

- Inorganic lead salts enter the body by way of ingestion or inhalation. For adults only about 10% of the ingested dose is absorbed. In contrast, children may absorb as much as 50% of an ingested dose.
- The percentage of absorbed lead is increased with deficiencies of iron, calcium, and zinc. It is also increased with a predominantly milk diet, possible due to the high lipid content.
- Children and infants are prone to developmental delays secondary to lead toxicity.

History:

- A history of ingestion or exposure is the most critical aspect of diagnosing heavy metal toxicity. A complete history, including occupational, hobby, recreational, and environmental exposure is crucial in diagnosing heavy metal toxicity.
- Most acute presentations involve industrial exposure.

- A history of ingestion often leads to the diagnosis in children.

Physical:

- Physical findings in lead toxicity vary with age and dose.
 - Any combination of GI complaints, neurologic dysfunction, and anemia should prompt a search for lead toxicity.
 - GI complaints predominate in adults.
 - Children are more prone to CNS dysfunction, including encephalopathy. Encephalopathy is rare in adults. Encephalopathy may present as an acute event with seizures, or it may develop slowly over weeks to months with variable nonspecific complaints. Closely examine the patient's history to elicit evidence of heavy metal exposure (eg, foreign body ingestions, paint chips, retained bullets).
 - Look for “lead lines” at the gingival border. These are a deep purplish to black discoloration formed by the reaction of lead secreted in saliva with the oral flora, which produces sulfides. Gingival lines of various hues may be present in chronic toxic exposure to other metals, which react to form differently colored species.
- As with lead, arsenic toxicity symptomatology varies with several factors, including concentration, rate of absorption, and the chemical form ingested.
 - GI complaints after significant lead exposure can range from anorexia and vomiting to constipation and abdominal pain ("lead colic"). Choleralike diarrhea can be seen in acute arsenic toxicity. Unlike the other heavy metals, thallium does not produce significant GI symptoms, and its hallmark is constipation.
 - Neurologic complaints ranging from neuropathy to encephalopathy have been reported in cases of acute arsenic toxicity. Arsenic toxicity presenting as ascending flaccid paralysis is often confused with Guillain-Barré syndrome.
 - Acute renal failure is not uncommon and, when observed, is often fatal.
- Mercury toxicity often presents with CNS dysfunction (eg, erethism)
 - Chronic exposure may lead to an intention tremor, the most consistent neurological finding in chronic toxicity.
 - Inorganic forms of mercury may cause severe GI complaints (eg, corrosive esophagitis, hematochezia)
 - Acrodynia (ie, Pink disease) is observed in children with mercury toxicity.
 - Physical findings include rash and desquamation of the face, palms, and soles. Gingivitis, stomatitis, and salivation are frequently noted.

Alcohol and Substance Abuse Evaluation

Anemia, Acute

Anemia, Chronic

Anemia, Sickle Cell

Encephalitis

Guillain-Barré Syndrome

Hypothyroidism and Myxedema Coma
Shock, Hypovolemic
Shock, Septic
Toxicity, Arsenic
Toxicity, Carbon Monoxide
Toxicity, Mercury

Other Problems to be Considered:

Adverse drug reaction
Thallium toxicity
Dementia
Electrolyte imbalances
Encephalopathy
Hepatic porphyrias

WORKUP

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Lab Studies:

- Lead toxicity
 - Blood lead levels
 - Diagnosis is made with venous blood lead levels in association with clinical signs and symptoms.
 - Blood lead levels higher than 10 mcg/dL are considered toxic.
 - Complete blood count (CBC) with peripheral smear
 - Findings may include basophilic stippling of the RBCs on peripheral blood smears. Basophilic stippling is not specific for lead toxicity and may be observed in arsenic toxicity, sideroblastic anemia, and thalassemia.
 - The anemia of lead toxicity may be normocytic or microcytic.
- Mercury toxicity
 - Collect a 24-hour urine specimen for measurement of mercury levels (except in short-chain alkyls).
 - Measure whole blood mercury levels for short-chain alkyls.
- Arsenic toxicity
 - Collect a 24-hour urine specimen for measurement of arsenic level.
 - Obtain a CBC.
 - Collect hair and fingernail clippings, although this is not as helpful as blood tests, unless environmental contamination of specimens can be ruled out.

Imaging Studies:

- Lead toxicity
 - Long bone x-rays in children may demonstrate the classic lead bands noted most

commonly around the knee joint.

- X-ray evaluation of the knee also may reveal lead bands, which are horizontal metaphyseal lines that represent failure of the bones to remodel, not lead.
- Lead lines are not observed in adults.
- Abdominal radiographs may demonstrate the presence of radiopacities, such as paint chips and lead weights (eg, fishing sinkers, curtain weights). Also, the presence of retained bullets, especially if near a joint, is associated with elevated lead levels in many individuals.
- Arsenic toxicity: Abdominal radiographs occasionally show metallic fragments, which indicate the need for whole bowel irrigation.
- Mercury toxicity: Chest radiographs may show pneumomediastinum or pneumothorax following elemental mercury exposure or radiodense pulmonary emboli following intravenous mercury injection.

TREATMENT

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Emergency Department Care:

- Lead toxicity
 - Treatment for acutely ill patients includes whole bowel irrigation with polyethylene glycol electrolyte solution if radiographic evidence of lead toxicity is present.
 - Perform chelation therapy and aggressive hydration.
 - Diagnosing lead toxicity can be difficult; a history of lead exposure is instrumental in the diagnosis process.
 - Anemia, in the presence of neurological and gastrointestinal symptoms, should alert the physician to the possibility of lead toxicity.
 - Consider possibility of lead toxicity in all children presenting with encephalopathy.
- Arsenic toxicity
 - Correct dysrhythmias and hypotension (significant fluid losses generally occur and require aggressive rehydration). Perform gastric lavage.
 - Perform whole bowel irrigation if radiographic evidence of arsenic toxicity is present. Administer chelation therapy.
- Mercury toxicity
 - Perform GI decontamination with activated charcoal (without a cathartic). GI decontamination should be withheld if inorganic mercury-associated corrosive effects are present in the GI tract. In such instances, upper endoscopy is indicated to detail the extent of injury and guide subsequent GI therapy.
 - Control diarrhea. Administer chelation therapy.

Consultations: If intentional ingestion or overdose is suspected, place patient in closely a monitored unit and consult a medical toxicologist and psychiatrist.

- Contact a certified poison control center or medical toxicologist.

- Consult a gastroenterologist if the possibility of corrosive GI effects is present.

Lead toxicity

The key to treating lead toxicity is removal of the offending agent and reducing the total body load of lead. Chelation agents (eg, edetate calcium disodium, dimercaprol, DMSA) are used to reduce the body stores of lead.

Arsenic toxicity

Chelation therapy with BAL, DMSA, or d-penicillamine is the primary treatment of arsenic toxicity. Removal of the offending agent and aggressive gastric decontamination aids in reducing ongoing absorption of arsenic. Hemodialysis may be beneficial in patients with acute renal failure.

Mercury toxicity

Treatment of mercury toxicity includes removing the insulting agent, gastric decontamination, and chelation therapy with BAL, DMSA, and d-penicillamine.

Drug Category: *Chelation agents* -- These drugs supply sulfhydryl groups for the heavy metals to attach and, subsequently, may be eliminated from the body.

Drug Name	Dimercaprol (British Anti-Lewisite; BAL) -- DOC in the treatment of lead, arsenic, and mercury toxicity. Administered via deep IM injection only, q4h, mixed in a peanut oil base. Chelates intracellular and extracellular lead and is excreted in urine and bile. May be given to patients with renal failure.
Adult Dose	Lead toxicity: 75 mg/m ² IM q4h for 5 d; not to exceed 24 mg/kg/d IM Arsenic toxicity: 3-5 mg/kg IM q4h for 2 d; 3-5 mg/kg IM qid on day 3; then 3-5 mg/kg IM q6-12h for 10 d (or until recovery is complete) Mercury toxicity: 3-5 mg/kg IM q4h for 2 d; followed by 3-5 mg/kg IM q6h for 2 d; followed by 3-5 mg/kg IM q12h for 7 d
Pediatric Dose	Lead toxicity: Administer as in adults Arsenic toxicity: If symptomatic without encephalopathy: 50 mg/m ² /d IM In asymptomatic children with blood lead >45 mcg/dL: 50 mg/m ² /d IM Mercury toxicity: Administer as in adults
Contraindications	Documented hypersensitivity; concurrent iron supplementation therapy
Interactions	Toxicity may increase when coadministered with selenium, uranium, iron, or cadmium

Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	May be nephrotoxic and may cause hypertension; caution with oliguria or G-6-PD deficiency; may induce hemolysis in G-6-PD deficiency
Drug Name	Edetate disodium, EDTA (Chealamide) -- Second-line for lead toxicity. Most effective when given early in the course of acute poisoning. Chelates only extracellular lead and may induce CNS toxicity if BAL therapy not initiated first. Begin therapy 4 h after BAL is given. Only given IV, and continuous infusion is recommended. Not recommended with renal failure. Because of potential for renal toxicity, patient should be well hydrated. To prevent hypocalcemia, use only calcium disodium salt of EDTA for chelation in heavy metal toxicity.
Adult Dose	Encephalopathic patient: 1500 mg/m ² /d as continuous IV infusion Symptomatic nonencephalopathic adult may be treated combined with BAL or alone
Pediatric Dose	Encephalopathic patient: 1500 mg/m ² /d continuous IV infusion Symptomatic non-encephalopathic patient: 1000 mg/m ² /d continuous IV infusion
Contraindications	Documented hypersensitivity; renal failure
Interactions	Enhances the hypoglycemic effects of insulin in diabetic patients
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Patient should be well hydrated; may worsen CNS toxicity if administered before BAL therapy
Drug Name	Succimer (Chemet) -- Metal chelator, analog of dimercaprol, used in lead poisoning. Particularly useful in children with blood levels of lead >45 mcg/dL. Repeat dosing may be necessary.
Adult Dose	Lead toxicity: 10 mg/kg PO q8h for 5 d followed by 10 mg/kg PO q12h for 14 d Arsenic toxicity: 10 mg/kg PO q8h for 5 d followed by 10 mg/kg PO q12h for 14 d
Pediatric Dose	Administer as in adults
Contraindications	Documented hypersensitivity
Interactions	Do not administer concomitantly with edetate calcium disodium or penicillamine
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Caution in renal or hepatic impairment; to prevent toxicity, patient should be well hydrated
Drug Name	Penicillamine (Cuprimine, Depen) -- Metal chelator used in treatment of arsenic poisoning. Forms soluble complexes with metals that are subsequently excreted in urine.
Adult Dose	Arsenic poisoning: 100 mg/kg PO qd; not to exceed 2 g/d divided qid for 5 d Mercury poisoning: 100 mg/kg PO qd divided qid; not to exceed 1 g/d for 3-10 d

Pediatric Dose	Arsenic poisoning: 100 mg/kg PO qd; not to exceed 1 g/d divided qid for 5 d Mercury poisoning: Administer as in adults
Contraindications	Documented hypersensitivity; renal insufficiency; previous penicillamine-related aplastic anemia
Interactions	Increases effects of immunosuppressants, phenylbutazone, and antimalarials; decreases digoxin effects; effects may decrease with coadministration of zinc salts, antacids, and iron
Pregnancy	D - Unsafe in pregnancy
Precautions	Thrombocytopenia, agranulocytosis, and aplastic anemia may occur

FOLLOW-UP

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Further Inpatient Care:

- Arsenic is frequently used for homicidal or suicidal purposes. Thoroughly scrutinize all arsenic toxicity cases for evidence of such activity. Report all cases with possible homicidal association to the proper legal authorities before discharge. Patients with suspected suicidal intent should undergo psychiatric evaluation before discharge from hospital.

Further Outpatient Care:

- Asymptomatic children and adults with elevated lead levels may be candidates for outpatient chelation therapy.
- Care must be taken to remove the source of heavy metal contamination.
- Report industrial-related toxicities to OSHA; report childhood cases to the local health department.

Complications:

- Lead toxicity
 - Children are highly sensitive to the toxic effects of lead. Encephalopathy is an indication of poor prognosis, as 85% of patients with encephalopathy develop permanent CNS dysfunction including seizures and mental retardation.
 - Abdominal symptoms are usually resolved after initiation of chelation therapy but may persist for over 15 weeks.
- Mercury toxicity
 - Complications of mercury toxicity are dose and form dependent.
 - If the toxicity is mild in cases of elemental and mercury salt toxicities, complications are few and recovery is generally good.
 - Residual CNS and neurologic deficits are common in organic mercury toxicities.
- Arsenic toxicity
 - The complications of arsenic poisoning are largely neurologic. Recovery is often

delayed for months.

- The severity of initial symptoms appears to correlate with the severity of complications and the rate of recovery.
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MISCELLANEOUS

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Medical/Legal Pitfalls:

- Failure to diagnose arsenic exposure as a homicidal or suicidal act
- Failure to report lead toxicity to the local health authorities
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