Putting it into Practice: Pediatric Environmental Health Training Resource

Mercury, Arsenic, and Cadmium Toxicity in Children

User Guide

Children's Environmental Health Network

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Editor's Note: This module covers children's exposure to mercury, arsenic and cadmium. The other toxicologically significant heavy metal, lead, is discussed in the "Childhood Lead Poisoning" module.

Mercury

I. Introduction

Mercury is a naturally occurring heavy metal that is a shiny silvery-white liquid at room temperature.[1] It is found in three forms in the environment: elemental (metallic), organic (ethyl mercury and methylmercury), and inorganic. This element has been used for many centuries for various medicinal and industrial applications and despite its limitation of use in industrialized countries it continues to be an important global pollutant in the environment. Children are particularly susceptible to adverse effects from exposure to mercury. In severe poisonings, a child's mercury body burden can be reduced through chelation. However, none of the existing treatments is effective at removing organic forms of mercury from the brain, and the chelating agents may also cause significant side effects. Therefore, considerable effort must be invested in exposure prevention, such as decreasing anthropogenic sources and reducing consumption of contaminated food and water.

II. Sources of exposure

Prenatal exposure in the United States (US) is primarily through maternal ingestion of contaminated fish. *Acute exposure* in children can typically be attributed to the inhalation of elementary mercury vapor from older broken thermometers or fluorescent light bulbs. The primary source of mercury that contributes to *chronic exposure* is the consumption of contaminated fish.[2] Chronic mercury exposure may also occur via use in folk medicines and in religious practices such as Santería and Voodoo.[3,4] Mercury is no longer used as a fungicide in the US for latex paint and its use has largely been eliminated in vaccines manufactured in the US. Mercury still exists in dental amalgam, although most new fillings do not contain mercury.[2]

III. Epidemiology

A great deal of our knowledge regarding the clinical effects of mercury poisoning stems from two historical cases in which children were exposed to high doses of methylmercury in Japan and Iraq. The first case was the result of years of industrial discharge of mercury into Minamata

bay in Japan. This extreme poisoning caused significant morbidity and mortality among the local population who consumed contaminated fish and shellfish from the bay. These effects were described in 1959 and called "Minamata Disease". The second case of extreme mass poisoning involved the ingestion of grain treated with mercury fungicides in Iraq during the 1970s.[5] However, much of the focus in recent years has been on the exposure of children to lower doses of mercury compounds, through food or other environmental exposures.

IV. Forms of Mercury

Elemental mercury is pure metallic mercury that is liquid at room temperature. It is highly volatile and can produce vapor that can easily disseminate. Some of the main sources of elemental mercury in its liquid or volatile forms include direct mining of mercury, and the production of chloralkali, fluorescent light bulbs, manometers, thermometers, and batteries. The use of mercury in small-scale gold mining is a major source of mercury exposure to adults and children in certain less developed countries.[6] In these cases, inhalation of mercury vapor or its contact with skin can lead to absorption. Mercury can also seep into the local water or food sources downstream from gold mines and enter the body through ingestion. Use of elemental and inorganic mercury in folk remedies and some religious practices such as Santería can lead to toxicity as well, but the extent of its use is unknown.

Inorganic mercury has been found in folk medicine such as Ayurvedic medicine and folk skin lightening creams. Poisoning from the other forms of inorganic mercury such as mercuric cyanide is extremely rare in children.

Organic mercury: Methylmercury is the main form of organic mercury exposure in children. Exposure is primarily through ingestion of seafood. This form of mercury is typically the product of coal and other fossil fuel power plant emissions, along with soil and sewage runoffs, that eventually deposit in rivers and various bodies of water. Anaerobic organisms in the water "bio-methylate" the inorganic mercury to the organic form, and eventually accumulate in the body of aquatic animals. In general, the larger and longer-living the animal, the more mercury they accumulate in their body. In this way, methylmercury moves up the food chain, resulting in high levels in some fish species commonly consumed by humans.

Another form of organic mercury is ethylmercury, primarily encountered as a decomposition product of thimerosal, an organomercury compound used as a preservative in vaccines. Although voluntarily abandoned by most vaccine manufacturers, thimerosal is occasionally found in some multi-dose vials. Ethylmercury, as well as other mercury salts, are still used in some cosmetic products, skin-lightening creams and soaps outside the US.

V. Clinical signs and symptoms

Much of the clinical symptoms of mercury toxicity depend on the timing of exposure (prenatal or postnatal), dosage and length of exposure (acute or chronic) and form of exposure

(elemental, organic, inorganic). Due to the importance of developmental susceptibility, the clinical signs of mercury toxicity have been categorized based on the timing of the exposure.

Prenatal exposure: Since elemental and organic mercury are both capable of passing through the placenta, any maternal exposure during pregnancy can potentially expose the fetus to these compounds. Clinical prenatal effects of methylmercury exposure date back to the mid-1800s, but were well described following the events in Japan and Iraq.[2] Mercury exposure to the high doses experienced in these poisoning events caused significant neurocognitive and physical deficits. Children born in Minamata Japan following prenatal exposure were almost uniformly reported to have mental retardation, cerebral palsy, primitive/pathological reflexes, cerebellar ataxia, failure to thrive, dysarthria, limb deformity, hyperkinesia, hypersalivation, paroxysmal symptoms, and up to 77% were born with strabismus.[7,8]

The clinical effects of low-dose prenatal methylmercury exposure have been studied in New Zealand, the Faroe Islands, and the Seychelles Islands, where the findings on neurocognitive effects from the ingestion of fish or whale meat have been mixed. Although large-scale studies in the Faroe Islands seem to indicate some loss of IQ points and decreased cognitive performance,[9] similar studies in Seychelles populations have failed to demonstrate any deficit.[10,11] Despite these mixed findings, concerns about prenatal effects of methylmercury on children's development remain, due to the importance of seafood in the diets of many populations worldwide. Unfortunately, all symptoms of prenatal exposure to mercury are irreversible.

Acute exposure: Children who are acutely exposed to mercury (e.g mercury vapor from a broken light bulb) may have both acute and chronic symptoms. The more acute symptoms may be respiratory in nature (cough, dyspnea), along with fever and headache. The longer-lasting effects of acute poisoning or vapor inhalation are similar to the symptoms associated with chronic poisoning and include central and peripheral nervous system problems. Additionally, these children may suffer from inflammation of the gums or oral mucosa, and kidney problems (proteinuria).

Chronic Exposure: This type of exposure in children can cause neurologic symptoms such as tremor (tremor mercurialis), movement disorder, ataxia, ptosis, aphasia, stupor, cachexia, and incontinence. Chronic mercury poisoning can also cause dermatologic changes. Acordynia, also known as Pink's disease, is characterized by a triad of skin findings such as exanthema, and edematous, erythematous, painful, desquamating hands and feet; neurologic symptoms that include paresthesia, irritability, photophobia, weakness, and hypertension.[12] The wide range of variability in the urine mercury level (10-50 µg/L) of children with similar dermatologic findings suggests that there may be a genetic predisposition to developing such symptoms. Anecdotal case reports suggest that these patients fully recover after the completion of their treatment.

VI. Diagnosis

Diagnosis of mercury poisoning is not unlike many other diseases; it begins with a thorough history, physical and suspicion of exposure. Unfortunately, sporadic cases of mercury poisoning clinically resemble other conditions and may be confused with gastroenteritis, Kawasaki, rheumatologic diseases, or a myriad of other conditions that may affect the skin, neurologic or gastrointestinal system. Therefore, suspicion of mercury poisoning should be complemented with laboratory testing.

Urine testing: This method is most suitable for measuring the body burden of elemental or inorganic mercury. A 24-hour mercury is preferred over a spot level; however, this may not be practical in small children. To account for dehydration and variation in kidney function, WHO has recommended that the reference values be applied to urine samples with creatinine in the range between 0.3 and 3.0 g/L.

Blood and Hair testing: Both hair and blood are most suitable for measuring organic mercury. To measure organic mercury such as methyl mercury, whole blood is placed in K-EDTA tubes (no coagulant additives). Erythrocyte analysis is particularly useful in measuring organic mercury. Hair mercury is more indicative of exposure to methylmercury at the time of hair growth. It is empiric to obtain the hair samples using a mercury-free scissors for the occipital region near the scalp and storing them in polypropylene bags.

VII. Treatment

Chelation, along with supportive care, is the mainstay of treatment for children with clinically significant mercury poisoning. Generally, water-soluble chelating agents tend to be superior to lipophilic chelators that may in fact cause redistribution of mercury and further expose the central nervous system. It is of note that use of chelators to assess the body's burden of mercury is, at best, controversial and not found to be useful or reliable. Below is a brief review of the available chelating agents. However, DMPS and DMSA are the two most effective and safest chelating agents at this time.

DMPS: Unithiol, also known as DMPS (2,3-dimercapto-1- propane sulfonic acid), is recommended as the first-line chelating agent in treating chronic and acute cases of inorganic mercury in Europe and other parts of the world, but is not approved by the US Food and Drug Administration (FDA) for use in the US.

DMSA: Succimer®, also known as DMSA (meso-2,3-dimercapto- succinic acid isomer), is otherwise similar in efficacy and redistribution properties as DMPS and is available in the US. It has been used for chelation for mercury toxicity, although it is prescribed off-label for mercury chelation, as the FDA has only approved it for chelation in cases of acute lead poisoning.[13,14] It is less effective than DMPS in removing mercury out of the kidney cells, and like DMPS, is ineffective in removing mercury from the brain.

BAL: British anti lewisite (2,3-dimercaptopropanol – dimercaprol) is effective in treating inorganic mercury poisoning (mercury salt). BAL injections are prohibitively painful in children and are ineffective against organic mercury compounds.

VIII. Prevention

To prevent mercury exposure in children, it is recommended that pregnant or lactating mothers and children avoid the ingestion of larger/predatory fish such as swordfish, shark, king mackerel, or tilefish. Alternatively, shrimp, canned light tuna, salmon, pollock, and catfish are lower in mercury than some other types of seafood such as canned albacore and fresh tuna, and can be consumed up to 12 ounces per week (two average meals) without exceeding the weekly allowable mercury. In general, the US Environmental Protection Agency (EPA) recommends that fish with less than 0.16 µg/g methyl-mercury are safe to eat once a week, fish with 0.16 to 0.65 µg/g are safe to eat once a month, and fish with more than 0.66 µg/g mercury should not be eaten. Sport fishers should check the local fish advisory before consuming their catch. Further information regarding mercury seafood advisories is available from the EPA on line. http://www.epa.gov/hg/advisories.htm

Children and pregnant women should also avoid other sources of mercury exposure such as skin lightening cosmetics, certain folk remedies or religious practices involving mercury, and industrial sources of direct contact (gold mining) or contaminated water and food.

Correct environmental abatement for accidental mercury spills is of the utmost importance. Elemental mercury should always be scooped up and never vacuumed, as the heat of a vacuum volatilizes the mercury. Mercury vapors will also be released if elemental mercury is spilled into a floor vent of a heating system.

CASE PRESENTATION

In a clinic in Lima, you are asked to consult on a 13-year-old male with hypertension. Further history taking indicates that he lives with his family in Madre de Dios, a gold mining town where small farmers supplement their income by gold mining. Your history and physical indicated that the child is developmentally delayed with ulceration and erythema of the lower extremities. In your group discussion consider the following.

Discuss with your students the following points:

1- **What are the most likely sources of mass population poisoning in gold miners?**
Mercury is the traditional means of separating gold nuggets from other impurities. Exposure to the mercury fumes and its improper disposal causes food contamination. Larger industrial companies on the other hand use cyanide to purify gold. This compound is supposed to be recycled. However, it has been known to leak or purposefully dumped into the riverbeds in Peru.

2- **What are the direct and indirect sources of mercury poisoning in this child?**
The existing population in Madere de Dios depends on seafood as one of the main sources of protein in their diet. Dumping of mercury into the soil and water causes seepage into the aquatic environment where it is converted into methylmercury by the algae.

3- **What public health measures may help prevent mercury poisoning in this population?**
There are very few means of separating gold without the use of toxic chemicals. Banning “wildcat gold mining” has been implemented in various parts of the world, however, it has met a great deal of protest from the population that it is meant to protect. Discussion surrounding this subject will allow the students to better understand the complexity of competing interests in environmental health.

PARENT QUESTIONS AND DISCUSSIONS

1- **Should I avoid fish during pregnancy and breast-feeding?**
Fish consumption seems to have many benefits and is an important source of protein for many families and cultures around the world. There is no evidence of any negative fetal effects in mothers who consume EPA recommended amount of commercially available fish in the US. Mothers should avoid the consumption of high mercury fish that include, swordfish, king mackerel, shark, and tile fish.

2- **Should I get rid of the amalgam fillings in my teeth?**
Amalgam removal may cause a spike in mercury exposure, weaken the tooth, and is costly. However, there is no evidence that amalgam fillings cause mercury poisoning. It may be reasonable to avoid any dental mercury exposure by using composites for new fillings.

3- **Should I get chelation to remove any mercury from my system?**
Chelation therapy is extremely risky and should be reserved for cases of severe poisoning. Cessation of exposure may be the best alternative for those who are not affected by life-threatening or severely symptomatic manifestations of mercury exposure.

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Arsenic

I. Introduction

Arsenic is an extremely abundant and toxic metalloid element that is found naturally in the earth's crust, where it tends to be more abundant in the southwestern states, eastern Michigan and parts of New England. Historically, arsenic has been used as a medication (treatment of syphilis, skin conditions, Chinese medicines, etc.), pesticide (primarily insecticide), and wood perseveration (copper chromium acetate (CCA) pressure-treated wood). Arsenic's modern industrial application is primarily in electronics. Odorless and tasteless, the element is linked to numerous adverse health effects, and children are particularly susceptible to its antimetabolite and carcinogenic effects.

II. Sources of Exposure

The major sources of exposure in the global population includes well water, industrial and agricultural runoff, incinerators, wood treated with copper chromium arsenate (CCA)—pressure-treated wood, and pesticides. CCA was discontinued for residential use in the US in 2003 and is now an exception use only pesticide. There has also been increasing concern in recent years due to arsenic contamination of rice. Variations in the amount of rice ingested, variations in arsenic uptake amongst different species of rice, and the type of arsenic (organic vs. inorganic), makes the possible clinical effects of arsenic exposure from rice consumption very difficult to predict.

III. Toxicology

Arsenic exists in the elemental, trivalent and pentavalent states and can form both inorganic (trivalent) and organic (pentavalent) compounds. The organic form of arsenic is far less toxic than the inorganic form and has a much higher allowable daily intake for children. Arsenic can be absorbed through ingestion or inhalation, and passes readily through the placenta. Arsenic is generally not well absorbed across the skin, although some of the inorganic trivalent compounds are lipid soluble and thus can be absorbed. Most toxicity is due to ingestion. Although the incidence of acute toxicity in developed countries has significantly dropped, arsenic poisoning from contaminated water (often shallow well water) or toxic runoff continues to be a problem in many parts of the world.

IV. Clinical Signs and Symptoms

Arsenic disrupts the metabolic processes of every organ by substituting the phosphate molecules of ATP, as well as inhibiting the function of other key metabolic enzymes (e.g. thiamine pyrophosphate). The clinical presentation of arsenic poisoning differs greatly based on the acuity of the child's exposure.

Acute poisoning: High dose acute arsenic poisoning in children (3-5mg/kg) initially presents with gastrointestinal symptoms, including vomiting within 30 minutes, and rapidly progresses to hematemesis, abdominal cramping, bloody/rice water diarrhea, and brain, liver, kidney, and heart failure. Most patients die from shock and hypovolemia. Other clinical signs of lower dose acute arsenic poisoning include facial edema, transient flushing erythema, maculopapular eruption in the intertriginous areas, hypotension, T-wave inversion, congestive heart failure leading to shock, pulmonary edema, sensorimotor peripheral axonal neuropathy, proteinuria, hematuria, and bone marrow suppression. Rhabdomyolysis and conjunctivitis may also be seen.

Chronic poisoning: Chronic exposure to arsenic during pregnancy may lead to spontaneous abortion, low birth weight, still birth, or preterm delivery. In children with chronic exposure the clinical symptoms may be as mild as low-grade bone marrow depression, generalized fatigue, and Mees lines (white line across the fingernails), or more serious, such as severe skin changes and liver and neurologic dysfunction. Arsenic is a known carcinogen and causes bladder, skin, and lung cancer later in life following prolonged exposure.

V. Diagnosis

Arsenic is mostly excreted through the kidneys. Therefore, to confirm the suspicion of arsenic poisoning in children, it is recommended that pediatricians obtain a 24-hour urine test and request fractionation of the results to distinguish inorganic, highly toxic arsenic from the organic less toxic form. Spot urine tests using arsenic to creatinine ratio is not accurate in children. In cases where fractionation is not possible, avoidance of fish (source of organic arsenic) for up to 5 days helps detect mostly the inorganic type in the urine.

VI. Prevention and Treatment

Use of clean, safe water with low arsenic content (less than 10 ppb, WHO), routine testing of well water, especially after earthquakes, and avoidance of contact or use of CCA treated wood in play grounds and wooden decks decrease the risk of poisoning. In cases of existing CCA treated structures, hand washing after exposure and removal of the contaminated soil may be both practical and effective. In cases of significant arsenic exposure, chelation using d-penicillamine, dimercaprol (BAL), or succimer (DMSA) is recommended. In cases of acute arsenic poisoning, BAL is considered the most preferred chelating agent, while in the cases of chronic poisoning, DMSA is the first choice.

CASE PRESENTATION

A five-year-old female is brought in to your office for cyclic diffuse scalp and eyebrow alopecia, fatigue, and decreased appetite every winter. She lives with her parents and two older siblings that are 16 and 18 years of age on a farm in the northern California. Her past medical history is noncontributory. However, her environmental history is significant for the use of well-water and wood burning chimney throughout the winter. None of the other family members have shown any similar signs or symptoms.

Discuss with your students the following points:

1- **What is this patient's most likely environmental poison causing her symptoms?**
Arsenic, an antimetabolite may cause subtle symptoms in cases of chronic low-dose poisoning.

2- **How do well-water and wood burning stove relate to Arsenic poisoning?**
Burning of treated wood could be responsible for the release of arsenic. Wells need to be periodically checked for arsenic, especially after an earthquake that may expose arsenic veins to well-water.

3- **What other environmental and intrinsic arsenic poisoning risk factors need to be explored?**
Exposure to leftover discontinued arsenic herbicides, and playing on old wooden decks, jungle gyms or cribs are some of the possible environmental sources of arsenic. Also, since children consume more water and food and breathe at a much higher rate, proportionately in comparison with adults, they tend to accumulate all toxins faster.

PARENT QUESTIONS AND DISCUSSIONS

1- **How can I avoid arsenic in my child?**
Educate parents that burning or sawing old treated wood should never be done. All old wooden decks and jungle gyms need to be sealed with wood finish once or twice a year. Children should wash their hands after playing on such areas, regardless. Do not use old/antique wooden cribs.

2- **Should I avoid rice or fish in my child's diet?**
Although fish contains arsenic, the amount and type of this contaminant in fish is such that it does not pose any harm to children and pregnant mothers, provided that they observe the recommended weekly amount of seafood to prevent mercury poisoning. Rice on the other hand contains a variable amount of arsenic that depends on where it has been grown, the type of rice, water source, and the amount consumed. The typical American diet does not include enough rice to be clinically significant. However, this may not be true in certain Asian countries where rice is the staple of their diet and grown in contaminated soil or water.

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Cadmium

I. Introduction

Introduction of cadmium into the environment as a pollutant began primarily as a byproduct of zinc production during the 19th century. The amount of cadmium pollution has significantly dropped in industrialized countries, while in the developing economies it continues to be an environmental burden.

II. Sources of Exposure

The major sources of cadmium exposure in the general population includes animal food sources that accumulate cadmium such as oysters and mussels caught in polluted waters, internal organs of mammals, mainly the kidneys and liver, and some species of fish. Grains such as wheat and rice that have been exposed to contaminated soil can efficiently absorb and accumulate cadmium. Tobacco smoke also serves as a significant source of cadmium exposure in the general population. Cadmium salts have also been used as fungicides, although these have been discontinued in the US.

III. Epidemiology

Cadmium is mainly absorbed through ingestion or inhalation. Cadmium does not readily cross the placenta or the blood brain barrier. While industrial workers are mainly exposed to cadmium through dust inhalation, the general public's exposure is typically through the ingestion of contaminated food and the inhalation of tobacco smoke. Children living in areas with abundant coal mining or other industrial activity are more likely to have considerably elevated cadmium levels.[1,2]

IV. Clinical Signs and Symptoms

The first reports of acute cadmium poisoning were published in the 19th century, and chronic poisoning was first discovered and documented in the late 1930s-1940s. Kidneys are the first organ to be affected by cadmium exposure and store cadmium more than other organs. Lungs can be affected in both acute and chronic poisoning, while bones are mainly affected after chronic exposure.

Acute poisoning: Acute cadmium poisoning from oral ingestion causes salivation, emesis, choking, abdominal pain, vertigo, painful spasm of the anal sphincter, and loss of consciousness. Acute cadmium inhalation can cause cough, dry throat, headache and chills, muscle weakness, leg pain, chest pain, pulmonary edema, bronchospasm and in severe cases can cause pneumonitis.

Chronic poisoning: Chronic exposure to cadmium first manifests as cortical damage in the kidneys that initially presents with microproteinuria. As the level of cadmium accumulating in the renal cortex increases, it can eventually lead to nephropathy. Cadmium may also work synergistically with lead in leading to abnormal infant neurodevelopment.[3,4,5] Bone pain and lesions are the two most common late manifestation of prolonged cadmium toxicity. This was first described in Japan and more recently observed in China where high doses of cadmium poisoning continue to occur. Although high dose cadmium inhalation has been associated with lung cancer in workers, other population studies failed to demonstrate a convincing link; nor are any mutagenic mechanisms identified. Better understanding of the clinical effects of cadmium and work conditions has led to significantly decreased pulmonary side effects of chronic exposure. Most of these pulmonary symptoms involve restrictive lung changes. However, it is almost impossible to differentiate the pulmonary effects of cadmium exposure related to tobacco smoke from the other confounding factors such as arsenic.

V. Diagnosis

Cadmium can be detected in both the blood and urine. While the blood level of cadmium mostly reflects recent exposure (half-life 75-128 days), urinary excretion of cadmium provides the best measure of the body's cadmium load.

VI. Prevention and Treatment

The primary available chelating agent in the US (DMSA) is not effective at lowering cadmium levels in children.[6] Prevention and removal of the source of exposure are the only available interventions. In cases of acute poisoning, supportive care plays a vital role. Large doses of vitamin D may help treat osteomalacia.

CASE PRESENTATION

A 7-year-old female is brought in to your office with the complaint of obsessive compulsive disorder and pica. Further history and physical indicates a child with mild cognitive deficit, and educational issues. Discuss the following;

Discuss with your students the following points:

1- **What other questions should be asked to explore poisoning risk factors in this child?**
Eating a variety of objects poses various heavy metal and chemical risk factors. A detailed history of her pica may help. Ingestion of jewelry in particular puts children at risk of cadmium and nickel poisoning.

2- **What are the long- and short-term effects of cadmium in this child?**
Cognitive deficit may be both the long- and short-term effect of her cadmium ingestion at higher doses. On the other hand, long-term exposure may lead to microproteinurea and eventually renal failure.

PARENT QUESTIONS AND DISCUSSIONS

1- **My child takes art classes. Do I need to worry about Cadmium poisoning?**
In certain states such as California, children are not allowed to work with the brands that are high in cadmium pigments and other heavy metals. Working with artist chalk is not recommended for children.

2- **Do I need to avoid any foods that are high in cadmium?**
Frequent ingestion of internal organs of mammals, particularly kidneys, may increase the burden of cadmium in children. However, due to dietary habits in the typical American household and environmental regulations, second-hand smoke remains as the main source of cadmium exposure in children.

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***Note:** This User Guide is intended to accompany the PowerPoint module of the same name. It elaborates on some studies which may require more in-depth information than what is provided on the slides. However, the contents of all slides in the module are equally important to present.*

This User Guide was developed by:

Shahram Yazdani MD
David Geffen School of Medicine, UCLA

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