Clinical Chemistry Trainee Council
Pearls of Laboratory Medicine
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TITLE: Heavy Metals (Lead, Arsenic, and Mercury)

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Slide 1: Title Slide

Slide 2:
It is important to recognize that there are several variables which can affect the risk of toxicity from heavy metals. For example, the interaction of toxic metals with essential metals is important when the metals share or influence the same homeostatic mechanism, which occurs for lead, calcium, and iron. Toxic metals can influence the role of essential metals as cofactors for enzymes or other metabolic processes (i.e. lead interferes with the calcium-dependent release of neurotransmitters). In addition, the formation of metal-protein complexes is important for detoxification and protection from toxicity. Metallothioneins, a family of cysteine-rich proteins, can bind/form complexes with cadmium, copper, and other metals. Extremes in ages may also be an important factor. Children and the elderly may be at increased risk for heavy metal toxicity compared to most adults. One of the main routes of exposure for heavy metals is ingestion of contaminated food. Children consume more calories per pound of body weight than adults and have higher gastrointestinal absorption of some metals (i.e. lead). Other lifestyle factors such as smoking may also have influences on toxicity since cigarette smoke contains some toxic metals (i.e. arsenic). The speciation of the metal is also important because most metals exist in both toxic and nontoxic forms and the absorption, distribution, and toxic effects are influenced by the chemical form or speciation. For metals that produce a hypersensitivity reaction, the immune status of an individual also becomes an additional toxicological variable.

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Diagnosing heavy metal toxicity is difficult because the signs and symptoms may be absent or if present, they are similar to a number of other diseases. As a result, the diagnosis of metal toxicity requires demonstration of all the following three factors:

1) A source of metal exposure must be evident,
2) the patient must demonstrate signs and symptoms typical of the metal, and
3) abnormal metal concentrations should be detected in the appropriated source.

In the end, the laboratory plays a key role in diagnosis, so obtaining the appropriate specimen and using an accurate methodology to measure the metal and provide speciation is important for the correct diagnosis.

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Lead poisoning has been recognized as a significant medical problem for thousands of years. Lead has no biological function (it isn't essential) and is commonly found in the environment (air, food, water, and soil). For most of the twentieth century, the major sources of lead exposure were lead-containing house paints and gasoline. However, the use of leaded gasoline has diminished since the introduction of unleaded gasoline which has been required in personal automobiles in the United States since 1978. In addition, the lead content of paints intended for household use has been limited to <0.5% since 1972. Nevertheless, lead is still found in paints intended for nondomestic use and in artists' pigments. Ceramic products (dishes/bowls) available from noncommercial suppliers can contain significant amounts of lead which can be leached out by weak acids (i.e. fruit juice). House dust and lead-laden paint chips produced by the weathering and wearing of exposed lead paint is one of the most common sources of exposure in young children, who are at greater risk for exposure since they spend a lot of time on the floor.

Occupations including mining, working in foundries, battery-manufacturing, and auto repair are other sources of potential exposure. Lead is also found in soil near abandoned industrial sites where lead was used. Water transported through lead or lead-soldered pipes can also be another source of exposure. Some traditional folk remedies/medicines or moonshine distilled in lead pipes are another source. Exposure to lead from any of these sources by ingestion, inhalation or dermal contact can cause significant toxicity.

In the United States, the typical diet contains ~300 µg of lead/day, of which 1-10% is absorbed. However, children and iron-deficient individuals have increased absorption of lead (up to 50%). Once absorbed, the lead rapidly incorporates into the bone (~85%), soft tissues (~10%), and erythrocytes (~5%).

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The pathological features of lead toxicity include neurological effects in adults and children. Central effects are more common in children and occur at lower concentrations, while peripheral neuropathies predominate in adults. The effects of chronic lead exposure in children include a lower intellectual capacity (lower IQ) and behavioral problems (hyperactivity and poor organizational skills).
Lead has a high affinity for sulfhydryl groups and interferes with the enzymes involved in heme synthesis, specifically amino levulinic acid dehydrogenase and delta ferrochelatase. As a result, iron incorporation into heme is impaired and a microcytic, hypochromic anemia can result. Lead also interferes with a hormonal form of vitamin D, which affects multiple processes in the body, including cell maturation and skeletal growth. Excretion of lead occurs through the kidneys, and acute exposure can cause damage to the proximal tubules and can lead to tubulointerstitial disease.

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A variety of methodologies to directly measure the lead content in various bodily specimens including blood, urine, and hair have been used to assess lead exposure. Atomic absorption methods have long been a mainstay for the measurement of heavy metals. Inductively coupled plasma mass spectroscopy can also be used to measure lead levels. A whole blood lead level is the definitive test for assessing lead toxicity. The correlation of blood lead concentrations with biological effects is well understood and it is the first compartment transversed by absorbed lead. As a result, it best reflects recent exposure. Since 99% of blood lead is associated with the erythrocyte, EDTA whole blood is the specimen of choice, not serum/plasma. The CDC currently defines lead poisoning in children as any confirmed blood lead concentration ≥10 μg/dL. In young children, capillary blood samples may be used for screening, but if positive (≥10 μg/dL), a venous sample should be drawn and tested since surface contamination may cause a false positive.

Erythrocyte protoporphyrin (EP) or zinc protoporphyrin (ZPP) can also be used as a longer term marker of lead exposure. However, EP/ZPP concentrations are not a sensitive indicator of low-concentration lead exposure and are typically elevated only when lead concentrations are >35 μg/dL. Nevertheless, EP/ZPP concentrations >60 μg/dL are indicators of significant lead exposure. The EP test is not useful for screening asymptomatic children.

Anodic stripping voltammetry (ASV) is another methodology that can be used to measure lead.
Since the majority of lead is deposited in the bones, K-X-ray fluorescence can also be used to measure the lead content of bones. It is typically used as a way to assess the total body lead burden.
Other laboratory findings/tests which may indicate lead exposure/toxicity include the CBCD. Since lead interferes with the enzymes responsible for heme synthesis, a microcytic, hypochromic anemia might be present. Another characteristic finding is basophilic stippling of erythrocytes. Neither of these findings are specific for lead toxicity (because they can also occur in iron-deficiency), but may be seen with lead toxicity.

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Symptomatic lead poisoning is uncommon in children with lead levels <45 μg/dL and adults <60 μg/dL. Nevertheless, it is still useful to recognize the signs and symptoms because not all poisonings are detected by pediatric and occupational screening programs. Acute lead exposure typically presents with severe abdominal pain and mental confusion. Acute encephalopathy is typically seen in children who may present with persistent vomiting, ataxia, and seizures. In chronic lead poisoning, adults will experience abdominal pain, fatigue, neuropsychiatric symptoms, hypertension, and constipation. Peripheral neuropathy with wrist drop may be seen with more severe exposures. Anemia is relatively uncommon in adults. In children, chronic lead poisoning signs and symptoms include anemia, abdominal pain, developmental delay, hyperactivity and other behavioral disturbances.

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The treatment for lead toxicity will typically depend on the patient's blood lead level. Asymptomatic patients with lead concentrations <25 μg/dL usually require separation from the source of exposure, or removal of the source of contamination. Children with lead concentrations >45 μg/dL should be referred for chelation therapy immediately using BAL.

Slide 9:
Arsenic is one of the best known heavy metal toxins and has been used as an antisyphilitic agent, and as a way to terminate undesirable acquaintances. Arsenic exists in a number of toxic and nontoxic forms. The toxic forms are the inorganic species denoted as As(III) and As(V). Organic arsenic is comprised of mono- and di-methyl arsine as well as arsenobetaine and arsenocholine. Only arsenobetaine and arsenocholine are non-toxic. Some of the organic forms are present in many foods.

In general, arsenic has a high affinity for keratin-rich tissues which results in high concentrations being found in hair and nails. In fact, after several weeks of exposure, transverse white striae called "Mees lines" may appear in the fingernails and are caused by the denaturation of keratin by arsenic or other heavy metals.

The largest source of exposure to arsenic in the environment is through the use of pesticides/insecticides. Other uses of arsenic and arsenic compounds include pharmaceuticals, in the glass and ceramic industry, and metallurgy. Arsenic can also be found in cigarette smoke, like many other heavy metals. Routes of exposure include inhalation, dermal and ingestion. The foods that typically contain the highest concentrations of organic arsenic include shellfish and other predators in the seafood chain (i.e. cod and haddock). As a result, the consumption of seafood before collection of a urine sample for arsenic testing is likely to result in an elevated total arsenic concentration which could be clinically misleading.

Slide 10:
A variety of methodologies (atomic absorption spectrometry and ICP-MS) have been used to directly measure the total arsenic content in various bodily specimens (blood, urine. and hair) to assess arsenic toxicity. To distinguish among toxic inorganic species and nontoxic organic species of arsenic, high-performance liquid chromatography (HPLC) or LC/MS techniques have been developed. Serum is the least useful specimen for identifying arsenic exposure because arsenic rapidly disappears to the phosphate pool (< 4hours). Whole blood specimens are useful for identifying acute exposure. However, urine samples are the preferred choice for assessing arsenic exposure because it is easy to collect. For long-term exposure (6 month-1 year), hair or fingernails can be used to assess exposure.

Note: Since seafood consumption can greatly elevate arsenic concentrations in the urine, it is important to confirm the presence of toxic vs. nontoxic species and not just treat based on the total arsenic concentration.

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Acute arsenic toxicity presents usually 30 minutes after ingestion with gastrointestinal symptoms including constriction of the throat, gastric pain, vomiting, and diarrhea. Muscle cramps, hypertension, and tachycardia follow. Chronic arsenic toxicity usually presents with dermatological, neurological, hematological, and gastrointestinal symptoms including hyperkeratosis, numbness/tingling in the extremities, leukopenia, anemia, thrombocytopenia, diarrhea, and weight loss. Multiorgan failure can also occur.

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Treatment of arsenic toxicity consists of removal of the patient from the source of exposure, supportive measures, and chelation therapy (DMSA or DMPS). In cases of severe poisoning, a catheter is generally placed and high urine output is maintained. Alkalinizing the urine helps prevent the deposition of erythrocyte breakdown products in the renal tubules.

Slide 13: Sequential and Integrated Screen Performance
Elemental mercury is a heavy, silvery, slightly volatile liquid at room temperature and is essentially nontoxic. However, once the elemental mercury is chemically modified to the ionized, inorganic species (Hg^{2+}), it becomes highly toxic. It can be bioconverted to either the divalent mercuric ion (Hg^{2+}) or alkyl mercury by microorganisms that exist both in the normal human gut and in the bottom sediment of lakes and rivers.

The single largest source of mercury in the environment is from the natural degassing of the earth's crust. Historically, mercury compounds have been found to have medicinal and fungicidal uses. Mercury is also used as a conductor in many electrical switches and home thermostats. In addition, it is used extensively in the pulp and paper industry as a whitener, and as a catalyst in the synthesis of plastics. It can also be found in latex paints because it is a potent fungicide. Finally, mercury is also used in dental amalgams.

Exposure to mercury can occur through inhalation, dermal contact, or ingestion. Dietary intake, primarily from seafood, is a major source of exposure for people who eat seafood several times a week, since methylmercury accumulates in the aquatic food chain and reach their highest level in predatory fish. While mercury has been shown to leach from dental amalgams with gum chewing, it does not seem to pose a significant threat.

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A variety of methodologies including atomic absorption spectrometry and ICP-MS have been used to directly measure the total mercury content in various bodily specimens (blood, urine, and hair). To distinguish among toxic inorganic species and nontoxic species of arsenic, HPLC or gas chromatography techniques have been developed.

Analysis of blood, urine, and hair for mercury concentrations is used to determine exposure. Plasma is not recommended because mercury concentration in plasma is about 1/20th that in erythrocytes. Urine can be used to follow the effectiveness of chelation therapy and is thought to be a better indicator of the mercury burden on the kidneys. To assess long-term exposure, hair specimens are recommended.

Key Point: Since seafood consumption can greatly influence mercury concentrations, seafood consumption should be stopped several weeks before sample collection.

Slide 15: Summary
Symptoms of mercury toxicity depend on the type of exposure (inhalation, ingestion, or dermal contact), and on the chemical form of mercury. Acute mercury toxicity can lead to mental status changes, blue-

black pigmentation of the skin, fatigue, tremors, ataxia, headache, nausea, vomiting, bloody diarrhea and a metallic taste in the mouth. In chronic exposures, lens discoloration, acrodynia, tremors, ataxia of the lower limbs, blue line along the gums, peripheral neuropathy, and renal failure can be seen.

Slide 16:

Treatment of mercury toxicity consists of removal of the patient from the source of exposure, supportive measures, and chelation therapy (DMPS or penicillamine). In severe cases, hemodialysis may be performed.

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Points to remember:

1. Symptoms of heavy metal poisoning may be absent or vague. Common GI symptoms include nausea, vomiting, diarrhea, and unexplained weight loss.
2. Elevated total heavy metal concentrations should be interpreted with caution. Speciation can determine if the elevation is due to toxic or nontoxic species. The consumption of seafood must also be considered since predator fish/shellfish can bioaccumulate heavy metals.
3. The main course of treatment for heavy metals is to identify and remove the source. Supportive care and chelation therapy can be used if necessary.

Slide 18: References