It's Not Your Father's Music: Toxicology of Heavy Metals

Paul J. Jannetto, Ph.D., DABCC, FACB, MT(ASCP) Mayo Clinic Director, Toxicology & Drug Monitoring Laboratory Director, Metals Laboratory

Disclosures

- Relevant Financial Relationships: None
- · Off Label Usage:
 - None

Objectives

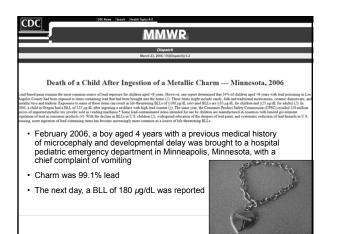
- After this session, the participant will be able to:
- Recognize and correlate the physical, clinical laboratory, and anatomic findings related to the following heavy metal exposures/toxicities:

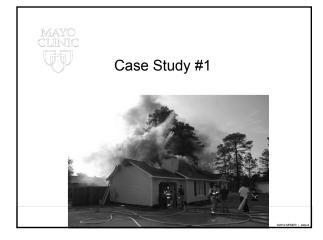
 Arsenic

 - 2. Lead
 - 3. Mercury
- 2. Identify the appropriate specimen which should be used to detect exposure to each of the metals listed above
- Correctly interpret the heavy metal test results and suggest appropriate follow-up testing 3.
- 4. Summarize the mechanism of toxicity for the metals listed above
- 5. List the appropriate treatment/management for heavy metal toxicities









Case Study #1

Background:

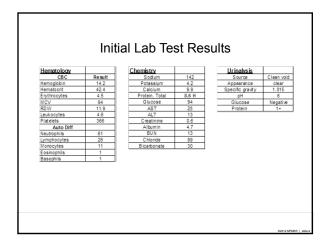
- 38 yo female presents to PCP over the course of months with multiple symptoms:
 - · Nausea and vomiting
 - · Confusion/dizziness
 - Headaches
 - Ataxia
 - Chest tightness/Shortness of breath Lethargy
 - Nosebleeds
 - · Easy bruising and bleeding gums
- · Lives w/ husband and 15 yo son
- · Occupation:
- · Homemaker/Student (on-line)

Case Study #1

Background:

- · Medical Hx:
 - · Migraines (current)
 - Past hx physical abuse by high school boyfriend
 - Anorexia/Bulimia eating disorder (in remission 10 yrs) Abnormal Pap 11 years ago
- · Hospitalizations/Surgeries:
 - Vaginal delivery x3
 - LEEP procedure

 - · Inpatient treatment for eating disorder
- Medications
 - Vicodin (hydrocodone w/ acetaminophen) for headache
 - · Relpax (eletriptan) for headache





Referral to Otolaryngology

ENT concerns/complaints:

- Nosebleeds
- Fluid in ears leading to dizziness, imbalance, nausea, and vomiting

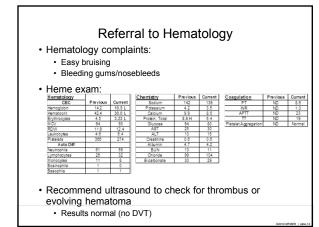
• ENT exam:

- Negative
- Dry nasal mucous membranes
- · List of complaints which don't fit ENT diagnosis
 - Nosebleeds, gum bleeding, easy bruising: possible bleeding disorder; work up through Hematology
 - Headache, nausea, imbalance, memory loss; should assess by Neurology

Referral to Neurology

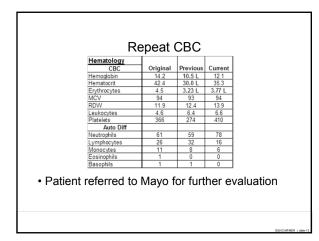
- Neurological complaints (numerous and don't localize into one portion of CNS):
 - · Confusion/forgetfulness
 - Balance is off, walks into door frames/furniture leads to
 - bruises

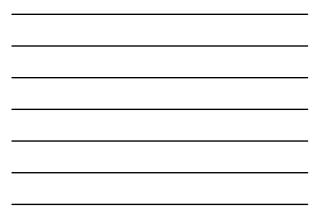
 Food tastes like "copper"
- Neuro exam:
 - Normal
 - · Gait and station are unremarkable
 - Orientation/memory: appropriate
 - Recommend MRI of head and EEG (electroencephalogram)
 Results negative for intracranial hemorrhage, mass lesion or acute infarction





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Heavy Metal Testing Performed

· 24hr urine results:

Toxicology	Result (mcg/spec)	Reference Range
Arsenic -24 hr Urine	<15	0-35
Lead- 24 hr Urine	<1	0-4
Mercury-24 hr Urine	1,817	0-9
Cadmium-24 hr Urine	<0.2	0-1.3

· Blood test result:

- Mercury: **111 μg/L** (<10 μg/L = normal)
- · Referral for Toxicology consult

Mercury

- · Forms:
 - Elemental form (Hg⁰) shiny, silver-white liquid, crosses blood-brain barrier/placenta
 - · Inorganic form (combines with Cl, S, O) is mildly toxic (Hg2+)
 - Organic (combine with C)/methylated form (HgMe₂) is extremely toxic; methylation occurs by microorganisms
- Sources:
 - <u>Environmental</u>: natural outgassing from granite rock/volcanic activity, burning coal and waste, mining ore deposits, food (shellfish/fish)
 - · Home: electrical switches, thermostats, thermometers
 - Occupational: paper & pulp industry, latex paint manufacturing (fungicide), plastic industry, jewelry making
 - <u>Miscellaneous</u>: dental amalgam
- Routes of Exposure:

 - Inhalation (75-85% Hg⁰ absorbed)
 Ingestion (Hg⁰ 0.01%, inorganic 20%, HgMe₂ 100% absorbed)
 - Dermal

Common Sources of Exposure to Mercury

- · Eating fish or shellfish contaminated with methylmercury
- · Breathing vapors in air from spills, incinerators, and industries that burn mercury-containing fuels
- · Release of mercury from dental work and medical treatments
- · Breathing contaminated workplace air or skin contact during use in the workplace (dental, health services, chemical, and other industries that use mercury)
- · Practicing rituals that include mercury.
 - Latino and Afro-Caribbean traditions use mercury to: attract luck, love, or money; protect against evil; or speed the action of spells.
 Done through a variety of uses, including wearing in amulets, sprinkling on the floor, or adding to a candle, oil lamp or cosmetic products.

What is the Source of Mercury for Case#1

· Environmental:

- · Dietary: No fish/shellfish intake
- · Dental: No fillings
- · No mercury rituals

· Occupational:

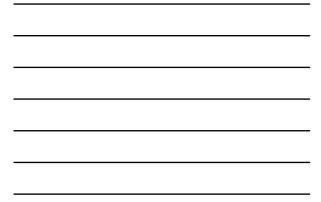
At home student/homemaker

Home:

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- Husband reports description of mercury "balling" up in furnace HEPA
- filter
- Structural house fire (March) Extensive damage/renovations
 - Out of house until September
 - · Furnace destroyed/replaced
 - Insurance company limiting what can be replaced vs. left "as is"

Target System	Acute	Chronic
Neurologic	Fatigue, Insomnia, Hearing loss, HeadacherConfusion, Lethargy, Seizures, Ataxia	Tremors, Ataxia (lower extremities), Delirium
GI tract	Metallic taste Nausea Vomiting Diarrhea	Loose teeth, blue gum
Pulmonary	Respiratory distress Pneumonitis, Edema	
Hematologic	Thrombocytopenia, Anemia	



Mercury continued

Mechanism of Action:

- Inorganic mercury (Hg⁺²) readily binds to sulfhydryl groups on a protein (which pay an integral part in the structure/function of most proteins), distorting tertiary configuration and causing loss of activity
- In addition, tertiary changes may cause some proteins to become immunogenic, eliciting T lymphocyte proliferation and Immunoglobulins to bind to the new antigen (collagen tissues are particularly sensitive)
- Hg(CH_{3)_2} species are lipophilic and avidly bind to lipid-rich tissues such as neurons (myelin is susceptible to disruption by this MOA)

Treatment/Management of Mercury Toxicity

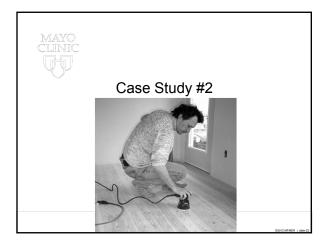
In the following order, as necessary:

- 1. Identify and remove the patient from the source of exposure
- 2. Supportive measures
- 3. Chelation therapy (reduce body burden):
 - 2,3-Dimercaptopropane-1-sulfonate (DMPS)
 - D-penicillamine
 - Dimercaprol or BAL (contraindicated for elemental and organic mercury compounds since increases brain levels)
- 4. Hemodialysis w/ infusion of a chelator (cysteine, Nacetylcysteine) in severe cases

Case Study #1 Continued

- Advised not to proceed with any chelation therapy, first identify source of mercury and remove it
- WI Dept Public Health/EPA investigation:
 - Sources of exposure:
 - · Gas Magic Chef range
 - Furnace (>40 yr old, destroyed in fire)
- Family given permission to move back home after removal
- Follow-up blood testing:
- Elimination half-life (20-65 days)
 - Toxicology
 Original (May)
 June
 July
 Aug

 Mercury-Blood
 111 µg/L
 44 µg/L
 12 µg/L
 6 µg/L





Case Study #2

Background:

- Family moved into a 1900's home 6 months ago
 - Father (29 yr)
 - Son (4 yr)
 - Son (14 months)
- Remodeling house since day 1
- Brought his kids to the family physician for a wellness check



Case Study #2 (4 year old)

• Physical Exam:

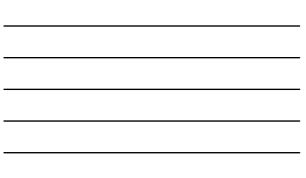
- · General: pleasant, interactive 4 yr old, no acute distress
- Skin: Warm, well perfused
- ENT: Moist mucous membranes, no oral lesions or pharyngeal erythema
- Heart: Regular rate/rhythm, no murmurs
- · Lungs: Clear, no wheezes
- Abdomen: Normal bowel sounds, soft, non-distended, non-tender to palpitation

· History:

- Father notes child has been hyperactive the past month
- Patient complains of abdominal cramping/pain; difficulty hearing
- · No change in appetite

Initial Lab Test Results (4 year old)

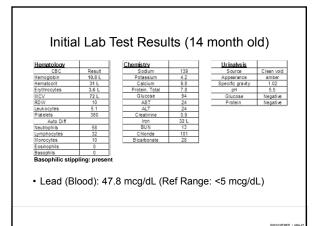
		Chemistry		Urinalysis	1
CBC	Result	Sodium	140	Source	Clean void
Hemoglobin	12.1	Potassium	4	Appearance	amber
Hematocrit	36	Calcium	10.1	Specific gravity	1.02
Erythrocytes	4.3	Protein, Total	8.2	pH	5.5
MCV	80	Glucose	88	Glucose	Negative
RDW	10	AST	25	P rotein	Negative
Leukocytes	4.6	ALT	24		
Platelets	320	Creatinine	1		
Auto Diff		Iron	59		
Neutrophils	60	BUN	13		
Lymphocytes	30	Chloride	100		
Monocytes	10	Bicarbonate	30		
Eosinophils	0				
Basophils	0				
• Lead (Bl	ood): 39	.5 mcg/dL (F	Ref Rang	ge: <5 mcg/d	lL)



Case Study #2 (14 month old)

Physical Exam:

- · General: awake, alert and in no apparent distress
- Skin: Warm, pink
- ENT: Moist mucous membranes
- · Heart: Regular rate/rhythm, no murmur
- · Lungs: Clear
- Abdomen: Normal bowel sounds, soft, non-distended, non-tender to palpitation





Lead

· Properties:

- No known biological function · Ubiquitous (air, food, water, and soil)
- · Sources:
- Environmental: paint (up to 1972), gasoline (1978), water, soil near industrial sites/freeways
- <u>Occupational</u>: battery manufacturers/foundries, plumbers, auto repair, mining Hobbies: glazes/pottery making, target shooting/slugs
- <u>Miscellaneous</u>: cigarettes, folk remedies/cosmetics, moonshine whiskey
- · Routes of exposure:
 - Inhalation:
 - Ingestion:
 - Children (~50%) / Adults (~10%)
 - Dermal: (<inhalation/ingestion)

Importance of Diet/Nutritional Status

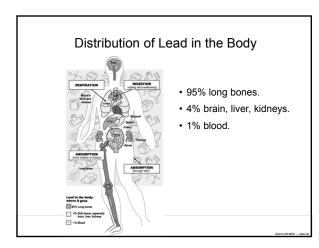
Healthy Foods to Fight Lead

Foods High in Calcium •Milk Yogurt
 Low-fat cheese •Tofu •Low-fat cottage cheese •Evaporated milk •Foods made with milk; including soups, custards, and puddings Powdered milk

Foods High in Iron •Lean red meat •Low-fat pork •Dried beans and peas •Raisins •Iron fortified cereal Iron fortified infant formula Breast milk

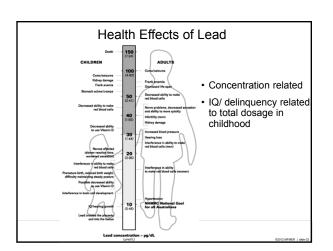
Foods High in Vitamin C •Oranges/Orange juice Grapefruit/Grapefruit •Dark green, leafy vegetables ·Potatoes cooked in the skin Broccoli •Cabbage Strawberries

http://www.health.state.mn.us/divs/eh/lead/faqs.html#Diet

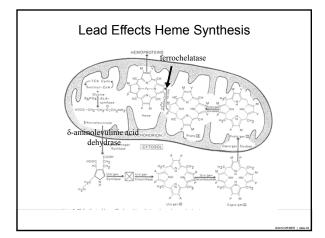


Lead Toxicity: Signs & Symptoms

- Symptomatic lead poisoning is uncommon:
 <45 µg/dL in children and <60 µg/dL in adults are usually asymptomatic
- Signs and symptoms:
 - · Severe abdominal pain
 - Fatigue
 - Mental confusion/poor concentration
 - Headache
 - Vomiting
 - Ataxia Weight loss
 - vveight loss
 Constipation
 - Constipation
 Seizures
 - Coma/Death









Laboratory Assessment

Blood lead level

- od lead level Definitive test Measured by: ICP-MS or atomic absorption spectrometry Venous (gold standard) vs. capillary blood EDTA whole blood = specimen of choice $t_{1/2} = 30.50$ days Updated reference ranges: Blood lead levels in the range of 5-9 mcg/dL have been associated with adverse health effects in children aged 6 years and younger
- Erythrocyte protoporphyrin (EP) or zinc protoporphyrin (ZPP)

 - $t_{1/2} = -68$ days Concentration >60 µg/dL is a significant indicator of exposure

- Other technologies
 Anodic stripping voltammetry (ASV)
 K-X-ray fluorescence (measure lead content of bone)
- Hematological (CBC) findings
 Normochromic/normocytic or hypochromic/microcytic
 Basophilic stippling



Case Study #2 Continued

- · Family sent to ED for follow-up testing:
 - 4 yo lead (blood):
- 33 mcg/dL (previous 39.5)
- 14 month lead (blood): · Father lead (blood):
- 55 mcg/dL (previous 47.8) 51 mcg/dL
- Toxicology consult:
 - · Local health agency contacted to evaluate home · Paint contained lead; abatement done
 - · Family stayed outside home until removal and renovations were complete
 - · Father's other labs were normal with the exception of a low iron (41 mcg/dL)

State Regulations for Laboratory Reporting of BLL (MN 144.9502)

· Reports of blood lead analysis required:

- (a) Every hospital, medical clinic, medical laboratory, other facility, or individual performing blood lead analysis shall report the results after the analysis of each specimen analyzed, for both capillary and venous specimens, and epidemiologic information required in this section to the commissioner of health, within the time frames set forth in clauses (1) and (2):
 - (1) within two working days by telephone, fax, or electronic transmission, with written or electronic confirmation within one month, for a venous blood lead level equal to or greater than 15 micrograms of lead per deciliter of whole blood; or
 (2) within one month in writing or by electronic transmission, for any capillary result or for a venous blood lead level less than 15
 - micrograms of lead per deciliter of whole blood.

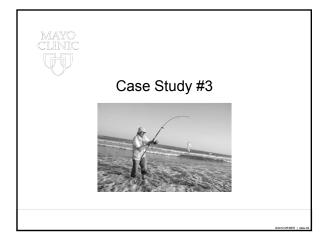
Treatment and Management

Recommendations from the Advisory Committee on Childhood Lead Poisoning Prevention

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Case Study #2 Continued

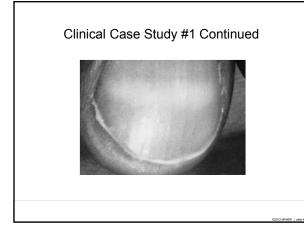
- Treatment:
 - Father (51 mcg/dL): No chelation therapy; start multi-vitamin (Fe)
 - Asymptomatic
 - · Renovations done/exposure source removed
 - 4 year old (33 mcg/dL): No chelation therapy
 - · Renovations done/exposure source removed
 - · ENT evaluation showed normal hearing
 - · Monitor blood level (declining) vs. side effects of treatment • 14 month old (55 mcg/dL): Chelation therapy
 - Oral succimer (200 mg @ 0800, 200 mg @ 1400, and 100 mg OHS)
 Iron (75 mg PO BID)
 Monitor blood lead levels, CBC, Iron, Cr, LFTs

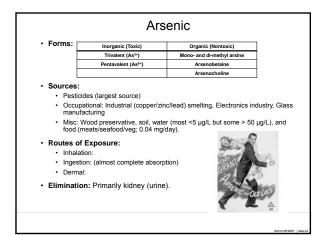


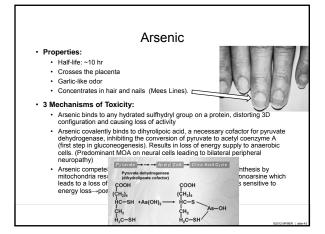
Clinical	Case	Study #	1

 50 yo man admitted to hospital 		
 Signs/Symptoms: Dry, itchy skin, nausea, vomiting, or libs-past 2 months), garlic-like breat 		s, weight loss (25
History: Multiple hospital admissions in the Nausea/vomiting but normal abd Neurologic exam: decreased mus Cyclic neutropenia, hyperpigmente	ominal exam scle strength in lower extremit	ties
Lab results: Leukocyte count: BUN: AST: ALP: LD: Creatinine:	Previous Visit_ 1.4 x 10 ³ ↓ 35 mg/dL ↑ 30 U/L N.D. N.D. N.D.	<u>Current Visit</u> N.D. 55 mg/dL ↑ 1520 U/L ↑ 550 U/L ↑ 840 U/L ↑ 2.8 mg/dL ↑
Additional findings on current	visit:	2.0 mg/dE 1









Arsenic Toxicity

- · Nervous System: Destruction of myelin
- Renal: Acute tubular necrosis
- Liver: jaundice-indicative of chronic exposure can progress to cirrhosis.
- Cardiovascular effects: Decreased contractility (arrhythmias)
 Hematopoietic effects: Anemia and leukopenia, occur a few days
- following exposure and are reversible.Cellular effects: Impairs mitochondrial enzymes and tissue respiration.
- Carcinogen: Lung cancer, and skin cancer-hyperpigmentation and hyperkeratosis.
- Death (70–180 mg)

Arsenic Toxicity: Signs & Symptoms

- Skin/Nails: Hyperpigmentation, Mee's lines
- Neurologic: Bilateral peripheral neuropathy (most common)
- Renal: Acute nephropathy with proteinuria of unexplained etiology
 Cardiovascular: Acute cardiovascular collapse of unexplained etiology, arrhythmia
- GI: Nausea, vomiting, diarrhea, weight loss
- · Hematologic: Anemia, leukopenia, thrombocytopenia

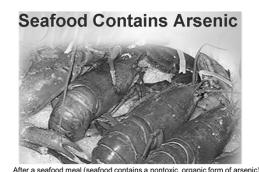
Laboratory Assessment

Specimen	Reference Range	Fatal
Whole Blood	0-12 ng/mL	100-600 ng/mL
Urine	0-35 µg/L	100-400 µg/L
Hair	0-0.9 µg/g	
Nails	0-0.9 µg/g	

Note: Urine is the best screening test to detect arsenic exposure. However, the total arsenic determination is only partially useful and fractionation testing must be done to distinguish between the toxic inorganic and nontoxic organic forms

Treatment

• BAL used to treat chronic arsenic poisoning, acute dermatitis and the pulmonary symptoms of excess arsenic exposure.



After a seafood meal (seafood contains a nontoxic, organic form of arsenic), the urine output of arsenic may increase to 300 mcg/24 hours for 1 day, after which it will decline to <25 mcg/24 hours.

Case #1 Continued

· Laboratory results:

Arsenic:

- Urine: 980 μg/L (0-35 μg/L)
- Arsenic Fractionation:
 - Urine:
 - Inorganic: 905 µg/L
 - Organic: 75 µg/L
- Patient expired before chelation therapy was begun

Heavy Metal Summary

- · Symptoms of heavy metal poisoning may be absent or Vague: - Nausea - Vomiting - Suden, unexplained weight loss - Peripheral neuropathy
- · Elevated total heavy metal results should be interpreted with caution

 - Are symptoms present?
 Are symptoms present?
 Speciation can be done to determine the presence of toxic or nontoxic species
 Rule-out contamination (venous vs capillary)
 Other sources (seafood consumption) of heavy metal
- Treatment
 - Identify and remove the source
 Chelation therapy if necessary



Self-Assessment Questions

- A 3 year-old child is brought to the Emergency department because of a week-long history of abdominal discomfort, irritability, and weakness. A complete blood count and blood smear demonstrate microcytic, hypochromic anemia with basophilic stippling of the red blood cells. Further history reveals that the family lives in a very old apartment complex with pealing paint. The most likely cause of the hematologic findings is:
 - A. Binding of carbon monoxide to hemoglobin
 - B. Inhibition of cytochrome oxidase
 - C. Inhibition of hemoglobin production caused by lead
 - D. Zinc deficiency
 - E. Iron intoxication

Self-Assessment Questions

- A 48 year-old woman with a diet rich in fish/shellfish was admitted to the hospital. Her clinical history in the previous 5 days included progressive deterioration in balance, gait, and speech. She had lost 15 pounds during the prior 2 months and had periods of nausea, diarrhea, and abdominal discomfort. She complained of a metallic taste and had a blue line along her gums.
- These findings/history are most consistent with exposure to what heavy metal?
 - A. Chromium
 - B. Lead
 - C. Mercury
 - D. Copper E. Cadmium

Self-Assessment Questions

- To screen for lead toxicity in a child, what is the preferred sample type?
 - A. Hair
 - B. Capillary EDTA whole blood
 - C. Venous EDTA whole blood
 - D. Sodium citrate plasma
 - E. Random urine