How to Recognize and Treat Heavy Metal Poisoning from Occupational and Non-occupational Exposures

A focus on Lead, Mercury and Arsenic

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Presentation Outline

- Heavy Metals
- Sources of Exposure
- Clinical Manifestation of Toxicity
- Evaluation
- Management
# Heavy Metals: Commonalities

- **Natural components of the earth’s crust**
  - Lead
  - Mercury
  - Arsenic

- **Sources of Exposure**
  - Natural sources
  - Industrial processes
  - Commercial products
  - Folk remedies
  - Contaminated food and herbals

- **All heavy metals are toxic in sufficient quantities**

- **Route of Exposure:**
  - Food
  - Water
  - Air

- **Toxicity**
  - Complexes with critical proteins and enzyme systems containing sulfur, oxygen and nitrogen
  - Cellular dysfunction and death
  - Vulnerable organs include CNS, GI, CVS, Hematopoietic, Renal and PNS

- **Toxicity Manifestations Vary**
  - Heavy metal involved
  - Exposure level
  - Chemical and valance states
  - Acute vs. Chronic
  - Age of the individual

- **Management Principles**
  - Exposure mitigation
  - Supportive Care
  - Enhanced elimination (chelation)
Lead: Characteristics

**Properties**
- Grey-silver heavy metal ~ 0.002% earth's crust
- No physiologic role
- Stored mainly in bone (95%) with half-life ~ 30 years

**History**
- Human use in paint 40,000 BC
- Industrial Revolution
  - Leaded gasoline (stopped 1990)
  - Leaded paint (banned 1972)
- Reports of toxicity
  - Ancient Egyptians
  - Leaders of Rome
    - Personality changes
    - Still births
    - Sterility

**Sources of Exposure:**
- Occupational (inhalation)
  - Battery plant workers
  - Metal Welders
  - Painters
  - Construction workers
  - Crystal glass makers
  - Firing-range operator
  - Shipbuilders
  - Lead miners
- Leaded-paint
  - Houses built before 1978
  - Lead dust
- Commercial Products
  - Retained lead bullets
  - Curtain weights
  - Lead-glazed ceramics
- Folk Remedies
  - Azarcon and greta

Lead: Chronic Toxicity in Adults

- Most commonly from occupational respiratory exposure
- Toxicity Manifestations
  - Hypertension
  - Anemia
  - Abdominal colic
  - Muscle and joint pain
  - Decreased fertility
  - Renal failure
  - Peripheral motor neuropathy (wrist drop)
  - Subtle neurological symptoms: lethargy and emotional liability
  - Encephalopathy (blood lead level > 100 mcg/dl)
- Important Considerations
  - Stored mainly in bone (95%) with half-life ~ 30 years
  - Blood lead level may increase with increased bone metabolism
  - Lead objects retained within the body releases lead
    - Acidic environment like synovial and stomach
    - Mechanical stress
Lead: Diagnosis

- Exposure History
- Unexplained Clinical Presentation
  - Hypertension, abdominal colic, wrist drop, renal failure, encephalopathy
- Blood lead level is the gold standard
- Other laboratory tests
  - CBC: hypochromic microcytic anemia and basophilic stippling
  - Basic metabolic panel
  - Urinalysis
  - X-ray fluorescence
- Occupational Monitoring
  - OSHA: periodic screening for exposure to air lead of 30 mcg/m³
  - Blood lead level check and follow up

Lead: Management

- Exposure mitigation
- Workplace
  - PPE
  - Safe work practices
  - Improving industrial engineering
- Chelation
  - Symptomatic
  - Blood lead level greater than 70 mcg/dl
- Choice of Chelating Agent
  - Oral Succimer (DMSA)
    - Mild symptoms
    - Blood lead level 70 - 100 mcg/dl
  - Intravenous CaNa₂EDTA plus oral Succimer (or IM Dimercaprol)
    - Encephalopathy
    - Blood lead level > 100 mcg/dl
Mercury: Characteristics

- **Properties**
  - Liquid silvery appearance
  - No physiologic role
  - Three distinct forms with distinct toxicities
    - Elemental
    - Inorganic
    - Organic

- **History**
  - Human use
    - Décor Egypt 1500 BC
    - Cosmetic Greece and Rome
    - Medicinal East Asia
    - Syphilitic Western Europe 1400 “two minutes with Venus, two years with Mercury”
  - Industrial Revolution
    - Workplace exposure
    - Hat makers in felt production (carroting)
  - Reports of toxicity
    - Hatters
    - “mad as a hatter”
Mercury: Elemental Mercury

- Heavy liquid that volatilize to an odorless gas at room temperature
- Sources of Exposure
  - Industrial processes and commercial applications
    - Thermometers, thermostats, barometers
    - Electronics
  - Dental amalgams
  - Home folk remedies
- Route of Exposure
  - Inhalation
  - Ingestion
- Chronic Toxicity
  - Manifestations (inhalation)
    - GI upset
    - Acrodynia (pink disease)
    - Erethism
    - Hands tremor
    - Renal failure

Mercury: Acrodynia (pink disease)

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### Mercury: Elemental Mercury

- **Diagnosis**
  - Exposure history
  - Clinical syndrome
  - 24-urine for mercury is gold standard (<50 mcg)
  - Blood mercury level has limited value (<10 mcg/L)

- **Management**
  - Exposure mitigation
  - Chelation
    - Symptomatic
    - Elevated body burden of mercury
    - Oral Succimer (DMSA)

### Mercury: Inorganic Mercury

- **Mercury salts**
  - Mercury Sulfide (HgS) Cinnabar

- **Sources of Exposure**
  - **Historic**
    - Cosmetics and skin treatments
    - Mercuric chloride in teething powder (calomel)
  - **Current**
    - Pesticides and herbicides
    - Home folk remedies

- **Route of Exposure**
  - Ingestion

- **Toxicity Manifestations (Ingestion)**
  - Corrosive to GI mucosa
  - Pink disease (calomel)
  - Renal failure
  - Nephrotic syndrome
Mercury: Inorganic Mercury

- **Diagnosis**
  - Exposure history
  - Clinical syndrome
  - 24-urine for mercury is gold standard (<50 mcg)
  - Blood mercury level has limited value (<10 mcg/L)

- **Management**
  - Exposure mitigation
  - Supportive care
  - Chelation (prompt)
    - Symptomatic
    - Elevated body burden of mercury
    - Dimercaprol IM
    - Oral Succimer (DMSA)
  - Hemodialysis
    - Renal failure

Mercury: Organic Mercury

- **Organic mercurial compounds**
  - Methyl mercury
  - Ethyl mercury (thimerosal)
  - Bioamplification
    - Microorganisms methylate inorganic and elemental mercury resulting in methylmercury
  - Well-absorbed by GI tract
  - Crosses blood-brain barrier and placenta

- **Clinical Toxicity**
  - Paresthesia (mouth area)
  - Visual fields constriction
  - Ataxia and tremor

- **Sources of Exposure**
  - Historic
    - Industrial
      - Minamata Japan 1956
      - 2263 adult poisonings
      - 63 congenital poisonings
      - Methylmercury in seafood
    - Medicinal
      - Iraq 1972
      - 6000 poisonings
      - 459 death
      - Methylmercury fungicide grain
  - Current
    - Dietary consumption of predatory fish (Tuna and sword fish)
Minamata Bay

Minamata City

- Town of 200,000
- Fishery jobs
- Fish and Shellfish main diet

Minamata Bay

Minamata Bay
Chisso Factory
1932 - 1968

“Economic” success post WWII

MINAMATA DISEASE

- 1956 Discovery of Minamata Disease
- Cat suicides
- Thousands of people affected and hundreds died
- Permanent brain damage and congenital defects “Minamata Disease”
- Methyl Mercury poisoning
- Seafood
Minamata Disease

- Acquired Minamata Disease, 1956
  - Chronic methyl mercury poisoning
  - Constricted visual fields
  - Hearing loss
  - Ataxia
  - Dysarthria
  - Tremors
  - Peripheral neuropathy

- Congenital Minamata Disease, 1962
  - Methyl mercury crosses the placenta (1ppm in cord blood)
  - Cerebral Palsy - like manifestations
  - Limb deformation

Cover up Operation

- 1959 Research Group at Kumamoto University concluded that Mercury most probable cause
- 1959 Company physician banned from revealing animal experiment results linking the plant effluent to disease
- 1965 Discovery of Minamata Disease in Niigata, Agano River Basin
- 1966 Halt of Effluent discharge into the Bay
- 1968 Official government recognition of cause-effect between Methyl mercury and Minamata
“Death Flows from the Pipe”

- Chisso chemical plant dumping Mercury waste into the bay
- Inorganic Mercury in the effluent
- Mercury was used as catalyst in PVC and Acetaldehyde production

W. Eugene Smith
Industrial Waste
from the Chisso Chemical Company 1972

Mercury Concentrations in Tissue Samples (ppm)*

<table>
<thead>
<tr>
<th>Human</th>
<th>Fish &amp; Shellfish</th>
<th>Cats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>less than 3.0</td>
<td>Control</td>
</tr>
<tr>
<td>kidney</td>
<td>3.1-144.0</td>
<td>kidney</td>
</tr>
<tr>
<td>liver</td>
<td>0.3-70.5</td>
<td>liver</td>
</tr>
<tr>
<td>brain</td>
<td>0.1-24.8</td>
<td>brain</td>
</tr>
<tr>
<td>hair</td>
<td>96-705</td>
<td>hair</td>
</tr>
<tr>
<td>Oyster</td>
<td>5.6</td>
<td></td>
</tr>
<tr>
<td>Gray mullet</td>
<td>10.6</td>
<td></td>
</tr>
<tr>
<td>Short-necked clam</td>
<td>20.0</td>
<td></td>
</tr>
<tr>
<td>China fish</td>
<td>24.1</td>
<td></td>
</tr>
<tr>
<td>Crab</td>
<td>35.7</td>
<td></td>
</tr>
</tbody>
</table>

Immediate Actions

“Quarantine” the Bay  Fishing Ban

Clean-up Operation
Removal, Reclamation and Dredging
Clean-up Operation
Removal, Reclamation and Dredging

Minamata Bay Declared Safe
July 29, 1997

1997 Removal of a net preventing mercury-polluted fish in Minamata Bay (Kumamoto Pref.) from entering the sea.
Trends in Total Mercury Levels of Fish and Shellfish

Fight goes on …

- Victims appealed their cases to District Court, the High Court, and the Supreme Court, and the latter ruled in their favor.
- ~ 10,000 people awarded payment
Health Facilities for Minamata Victims

Memories
## Mercury: Organic Mercury

### Diagnosis
- Exposure history
- Clinical syndrome
- Whole Blood mercury level is the goal standard (<10 mcg/L) since more than 90% of methylmercury is bound to Hb in RBC
- Urinary mercury is unreliable since methylmercury is eliminated primarily in the bile

### Management
- Exposure mitigation
- Supportive care
- Chelation
  - Symptomatic
  - Elevated body burden of mercury
  - Dimercaprol
  - Oral Succimer (DMSA)
# Arsenic: Characteristics

**Properties**
- Arsenic compounds occur in four chemical forms:
  - Inorganic (toxic)
  - Arsine (toxic)
  - Organic (little toxicity)
  - Elemental (non toxic)
- Toxic arsenic compounds occur in two oxidation states:
  - Arsenite is ten times more toxic than arsenate
- No physiologic role

**Sources of exposure**
- Human use:
  - Criminal Poisoning (suspected in Mozart and Napoleon deaths)
- Industry:
  - Paints
  - Pesticide, herbicide, fungicide
  - Wood preservatives
  - Semiconductors
- Medicinal:
  - Arsenic trioxide for leukemia
- Geological contamination:
  - Drinking water
- Seafood:
  - Organic arsenic (little toxicity)

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# Arsenic: Inorganic Arsenic

**Acute Toxicity**
- GI: nausea, vomiting, bloody rice watery diarrhea
- Hematologic: bone marrow suppression
- CVS: QT prolongation and torsade de pointes
- PNS: peripheral neuropathy
- CNS: encephalopathy

**Chronic Toxicity**
- Dermatologic: hyperpigmentation and keratosis on palms and soles
- Nails: Mees lines
- PNS: peripheral neuropathy
- CVA: peripheral vascular disease and HTN
Bangladesh

Arsenic

- Bangladesh. 1970 - 2005
- 3695 with arsenic poisoning
- Tube Well’s water
- Groundwater naturally contaminated with arsenic

Rahman et al. Clinical Toxicology, 39 (7), 683-700 (2001)
Bangladesh

Chronic Arsenic Toxicity

<table>
<thead>
<tr>
<th>Physical Parameters</th>
<th>Bangladesh</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area in sq km</td>
<td>148,393</td>
</tr>
<tr>
<td>Population in millions</td>
<td>120</td>
</tr>
<tr>
<td>Total number of districts</td>
<td>34</td>
</tr>
<tr>
<td>Number of arsenic-affected districts</td>
<td>252</td>
</tr>
<tr>
<td>Number of arsenic-affected districts in millions</td>
<td>178</td>
</tr>
<tr>
<td>Area of arsenic-affected districts in sq km</td>
<td>118,849</td>
</tr>
<tr>
<td>Population of arsenic-affected districts in millions</td>
<td>178</td>
</tr>
<tr>
<td>Total number of hand pump wells analyzed</td>
<td>34,000</td>
</tr>
<tr>
<td>% of samples with arsenic &gt; 10 μg/L</td>
<td>36%</td>
</tr>
<tr>
<td>% of samples with arsenic &gt; 50 μg/L</td>
<td>18%</td>
</tr>
<tr>
<td>Number of arsenic-affected blocks/police stations with arsenic &gt; 50 µg/L</td>
<td>178</td>
</tr>
<tr>
<td>Number of arsenic-affected villages (est.) with groundwater arsenic &gt; 50 µg/L</td>
<td>2000</td>
</tr>
<tr>
<td>Population drinking water with arsenic &gt; 50 µg/L</td>
<td>255</td>
</tr>
<tr>
<td>Districts surveyed for arsenic patients</td>
<td>34</td>
</tr>
<tr>
<td>Number of districts in which arsenical skin lesions were identified</td>
<td>32</td>
</tr>
<tr>
<td>Villages surveyed for arsenic patients</td>
<td>244</td>
</tr>
<tr>
<td>Number of villages in which arsenical lesions were identified</td>
<td>217</td>
</tr>
<tr>
<td>Persons from affected villages screened for arsenic patients (preliminary survey)</td>
<td>18,000</td>
</tr>
<tr>
<td>Number of patients, including children, identified as having clinical manifestations</td>
<td>3,365 (20.6%)</td>
</tr>
<tr>
<td>% of children with arsenical skin lesions of total patients</td>
<td>6.11</td>
</tr>
</tbody>
</table>

Rahman et al. Clinical Toxicology, 39 (7), 683-700 (2001)
Clinical Stages of Arsenic Chronic Toxicity

- Asymptomatic
- Dermatological manifestations
- Internal stage
  - Anemia and HTN
  - Lungs, Liver and Spleen
- Malignant stage
- Peripheral neuropathy

Rahman et al. Clinical Toxicology, 39 (7), 683-700 (2001)

Dermatologic Signs

- Keratosis
- Melanosis
- Melanokeratosis
- Leucomelanosis
- Mucous membrane pigmentation
## Arsenic Concentrations in Patients

### Bangladesh

<table>
<thead>
<tr>
<th>Parameters</th>
<th>As in Hair (µg/kg)</th>
<th>As in Nail (µg/kg)</th>
<th>As in Urine (µg/L)</th>
<th>As in Skin Scale (µg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of observations</td>
<td>4386</td>
<td>4321</td>
<td>1084</td>
<td>705</td>
</tr>
<tr>
<td>Mean</td>
<td>3390</td>
<td>8570</td>
<td>280</td>
<td>57.30</td>
</tr>
<tr>
<td>Median</td>
<td>2340</td>
<td>6400</td>
<td>1157.8</td>
<td>4800</td>
</tr>
<tr>
<td>Minimum</td>
<td>280</td>
<td>260</td>
<td>24</td>
<td>600</td>
</tr>
<tr>
<td>Maximum</td>
<td>28,060</td>
<td>79,490</td>
<td>3086</td>
<td>53,390</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>3330</td>
<td>7630</td>
<td>410</td>
<td>9790</td>
</tr>
<tr>
<td>% of samples having arsenic above normal</td>
<td>83.15</td>
<td>93.77</td>
<td>95.11</td>
<td>—</td>
</tr>
</tbody>
</table>

* Normal levels of arsenic in hair range from 60–250 µg/kg; 1500 µg/kg indicates toxicity (40).
* Normal levels of arsenic in nails range from 4300–14,000 µg/kg (41).
* Normal excretion of arsenic in urine range from 5–40 µg/1.5 L (per day) (42).
* Normal value for skin scale arsenic not defined.

Rahman et al. Clinical Toxicology, 39 (7), 683-700 (2001)
Well’s Water

Wells Water and Arsenic Level

Table 2. Range of concentration of arsenic in water from 4897 tube wells in Arokaza, Bangladesh, 2000

<table>
<thead>
<tr>
<th>Arsenic concentration (μg/l)</th>
<th>% of wells</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5-10</td>
<td>28</td>
</tr>
<tr>
<td>11-50</td>
<td>20</td>
</tr>
<tr>
<td>51-100</td>
<td>17</td>
</tr>
<tr>
<td>&gt;100</td>
<td>35</td>
</tr>
</tbody>
</table>

Well’s Depth and Arsenic Level

Arsenic

- Naturally occurring heavy metalloid
- Often associated with other metals in nature like copper, lead and gold
- Released into environment from volcanoes and erosions from mineral deposits
- Certain bacteria use arsenic salts for energy generation in the absence of oxygen and thus mobilize it from solid to aqueous phase
Contamination of Water Aquifer

Oremland: Science, Volume 300(5621). May 9, 2003. 939-944

Promotion of well-switching

Deep Well in West Bengal, LAG©
<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure history</td>
<td>Exposure mitigation</td>
</tr>
<tr>
<td>Clinical syndrome</td>
<td>Supportive care</td>
</tr>
<tr>
<td>24-urine arsenic is the gold standard (&lt;50 mcg/L)</td>
<td>Chelation</td>
</tr>
<tr>
<td>Speciation of urinary arsenic should be done to differentiate inorganic from organic forms</td>
<td>Symptomatic</td>
</tr>
<tr>
<td>Whole blood arsenic level rapidly declines in 24-48 hours (&lt;1 mcg/dl)</td>
<td>Elevated body burden of mercury</td>
</tr>
<tr>
<td>EKG</td>
<td>Dimercaprol</td>
</tr>
<tr>
<td>CBC, CMP</td>
<td>Oral Succimer (DMSA)</td>
</tr>
<tr>
<td>Nerve conduction studies</td>
<td>Hemodialysis</td>
</tr>
<tr>
<td></td>
<td>Renal failure</td>
</tr>
</tbody>
</table>