Decedent History

- **11/15:** To ER with nausea, vomiting, diarrhea, 2 hours after bowling with “friends”
  - Drank one beer in bowling alley that “tasted funny” and ate a hot dog
  - Admitted to OSH → became hypotensive → sent to ICU for pressors
  - Several labs & studies obtained during hospitalization:
    - Elevated cardiac enzymes; ESR >80; pancytopenia
    - Colonoscopy – pseudomembranous colitis; EF = 40%

- **11/21:** Transferred to UNC
  - Repeat echo shows left ventricular hypokinesis – presumed myocarditis

- **11/24:** Discharged from UNC

- **12/1:** Returns to OSH with nausea, vomiting, diarrhea, SOB, cough, sweats
  - Also complained of sleep disturbance and tingling in his feet
  - Admitted and started on succimer several hours into stay after previously ordered “heavy metals screen” returns
  - Cardiac arrest < 24 hours after admission and resuscitation efforts failed

- **12/2:** Autopsy performed at OCME
Autopsy Findings

**Internal Examination**

- No gross abnormalities

**Microscopic Examination**

- **Pulmonary**
  - Evidence of aspiration
  - Early bronchopneumonia

- **Cardiovascular**
  - Multiple foci of resolving infarction
Other Histological Findings

Peripheral Nerve

Bone Marrow

Peripheral Smear
Toxicology Findings

Serum
- Abnormal serum arsenic levels are detected for only a few hours (<4 hours) after ingestion.

Urine
- 24-hour urine collection is method of choice for diagnosis!
- Levels > 50 µg/L (0.05 mg/L) strongly suggest arsenic poisoning.
- Elevated arsenic levels may be seen with diets high in seafood, but they are comprised of primarily organic arsenic.

Hair
- Concentrations of arsenic within hair can demonstrate longer exposure.
- Hair grows 0.4 mm per day.

Interpretation
- Received arsenic at least once prior to first hospitalization.
- At least one large dose given during first hospitalization.
- Possible that another dose was given in the interim, leading to final hospitalization.

<table>
<thead>
<tr>
<th>Date</th>
<th>Blood</th>
<th>Urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>11/20</td>
<td>0.93 mg/L</td>
<td>--</td>
</tr>
<tr>
<td>11/22</td>
<td>0.46 mg/L</td>
<td>--</td>
</tr>
<tr>
<td>11/24</td>
<td>--</td>
<td>16.250 mg/L</td>
</tr>
<tr>
<td>11/30</td>
<td>0.07 mg/L</td>
<td>--</td>
</tr>
<tr>
<td>12/1</td>
<td>0.08 mg/L</td>
<td>--</td>
</tr>
<tr>
<td>12/2</td>
<td>0.07 mg/L</td>
<td>0.795 mg/L</td>
</tr>
</tbody>
</table>

Hair Arsenic Levels

![Hair Arsenic Levels Graph](image)
Arse nic

- Metalloid – chemically similar to phosphorous.
- Found in water, soil, and air, from natural and anthropogenic sources.
- Exists in inorganic and organic forms.
  - Inorganic forms are generally more toxic
  - May be ingested, inhaled, or absorbed through skin/mucous membranes
- Human exposure is possible in many ways:
  - Lumber “pressure” treated pre-2004 with CCA (Tanalith)
  - Insecticides, ant poisons, weed killers
  - Kelp supplements
  - Animal feed
  - Semiconductors
  - Wallpaper, paint, glass, ceramics
  - Metal smelting
  - Component of British Lewisite poison from WWI
  - Several medical uses
Poison of Kings

- 8th Century A.D. – arsenic trioxide first prepared
  - white tasteless, odorless powder.

- Middle Ages – “inheritance powder”


- Emerald green, a pigment used by Vincent Van Gogh (and other impressionist painters) was arsenic-based, and some theorize that chronic exposure contributed to his mental episodes.
Mechanism of Action

- Trivalent arsenic is the primary toxic moiety.
- Arsenic(III) binds avidly to enzymes and proteins with thiol (-SH) groups.
- Lipoic acid is an important enzyme cofactor that has two thiol groups.
- Multiple enzymes use lipoic acid as cofactors and are blocked as arsenic interferes with function:
  - pyruvate dehydrogenase
  - α-ketoglutarate dehydrogenase
Other Mechanisms

- Pentavalent arsenic is toxic as well because it resembles inorganic phosphate and substitutes for phosphate in metabolic pathways.
  - ATP $\rightarrow$ ADP-Arsenate
  - Bone phosphate $\rightarrow$ Bone arsenate
  - Glucose-6-phosphate $\rightarrow$ Glucose-6-arsenate

- Arsenic also alters confirmation of proteins and interferes with their function.

- Arsenic is classified as a known human carcinogen.
  - Inhalation predisposes primarily to lung cancer.
  - Oral exposure is associated with skin, bladder, liver, and kidney cancer.
  - Mechanism of carcinogenesis is unknown.
Pharmacokinetics

- Quickly and widely distributed -- peak serum levels occur 30-60 minutes after exposure.
- Excreted in urine as inorganic ion and methylated moieties.

Blood clearance of arsenic occurs in three phases:
- Phase 1 – a rapid decline occurs within 2-3 hours; up to 90% of arsenic cleared
- Phase 2 – from 3 hours to 7 days, with estimated half-life of 30 hours
- Phase 3 – a slower elimination phase, with estimated half-life of 200 hours

Steps for elimination:
- Pentavalent arsenic is reduced to trivalent arsenic
- Followed by oxidative methylation to pentavalent organic arsenic
- Stable intermediates excreted in the urine include monomethylarsonic acid (MMA\textsuperscript{V}) and dimethylarsinic acid (DMA\textsuperscript{V})
Initial Symptoms & Signs – 1h After Ingestion
- Nausea / vomiting – severe gastroenteritis from diffuse capillary damage
- Burning esophageal pain & constriction
- Watery or bloody diarrhea
- “Garlicky” odor of breath and stools

**Cardiovascular**
- Diffuse capillary injury leading to shock
- Arrhythmias

**Neurological**
- Vertigo
- Headache
- Delirium and/or mania
- Peripheral neuritis – symmetric, sensory
- Weakness

**Genitourinary**
- Oliguria
- Hematuria, albuminuria, glycosuria

**Hematological**
- Pancytopenia

**Skin**
- Numerous skin lesions
- Desquamation and hyperkeratosis
- Nail ridges (Mees’ lines)
- Subcutaneous eyelid edema
In addition to gastric lavage and fluid support, specific treatment is dimercaprol, a.k.a. BAL in oil (British Anti-Lewisite), which binds to arsenic via thiol groups and then is rapidly eliminated by the kidneys without damage to excretory organs.

- **Dose:** ~3 mg/kg by deep IM injection
  - q4h for 2 days
  - q6h for 1 d
  - q12h for 10 days

- May alternatively use D-penicillamine or succimer.

**Dimercaprol**

![Dimercaprol](image1)

**Succimer (DMSA)**

![Succimer](image2)
References


Questions?