ACUTE IRON INTOXICATION
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OBJECTIVES
1. Be familiar with the various forms of iron containing products available. Know how to calculate the amount of elemental iron ingested given the amount and type of iron salt ingested.
2. Be able to characterize or estimate the risk of toxicity given the amount of iron ingested.
3. Understand the pathophysiology of acute iron intoxication.
4. Be familiar with the clinical manifestations of iron toxicity, especially in terms of the four stages of toxicity that may be seen with severe iron intoxication.
5. Be able to describe how to evaluate a patient with a potential iron overdose utilizing data obtained from physical exam, laboratory testing, and radiology.
6. Be able to describe how to medically manage (treatment and monitoring) a patient with evidence of iron intoxication.

INCIDENCE AND SEVERITY
• Approximately 22,000 cases of acute iron ingestion/poisoning occur each year in the US.
• Approximately 80% of acute iron poisoning cases involve children < 6 years of age.

• Case disposition:
  Home management without ipecac induced emesis----->50%
  Home management with ipecac induced emesis-------->30%
  Emergency department management---------------------->20%
  Cases involving admission from ED-----------------------> 7%
  Cases with fatal outcome------------------------------------> <1%

IRON CONTAINING PRODUCTS
• Over 200 prescription and OTC products available.

• Iron content:
  Childrens preparations 12-18 mg of elemental Fe.
  Adult preparations 50-100 mg of elemental Fe.

<table>
<thead>
<tr>
<th>IRON SALT</th>
<th>PERCENT ELEMENTAL IRON</th>
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<tbody>
<tr>
<td>Ferrous sulfate*</td>
<td>20†</td>
</tr>
<tr>
<td>Ferrous gluconate*</td>
<td>12</td>
</tr>
<tr>
<td>Ferrous fumarate*</td>
<td>33</td>
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*Most common; †325 mg = 65 mg elemental Fe

ESTIMATE OF TOXICITY
**Ingested dose (mg/kg elemental iron) = (number of tablets x amount of iron salt x % elemental iron) ÷ weight (kg)
20 mg/kg------------------> nontoxic or minimally toxic
20-60 mg/kg----------> mild to moderate toxicity
> 60 mg/kg--------------> potentially serious or life threatening.
IMMEDIATE HOSPITAL REFERRAL FOR GI DECONTAMINATION AND INITIAL EVALUATION; (the usual estimate for a lethal dose without prompt and specific intervention is in the range of 200 to 250 mg per kg)

NOTE: It is important to remember that the history and circumstances surrounding an iron exposure as well as the appearance of any symptoms must be carefully elucidated. Initial reports may be dangerously underestimated.

PHYSIOLOGY

• Approximately 10% of dietary iron is absorbed in the ferrous form.

• The body contains approximately 3.5 grams of iron: 2.5 gm are present in hemoglobin, the remainder as stores. Only a small fraction is present in plasma----> 50 to 150 mcg/dl----> almost all is bound to transferrin.

• Humans excrete approximately 1 mg of iron per day (about two thirds from the GI tract, exfoliated intestinal cells, and iron loss in bile, and the other third due to losses in the urine and desquamated skin). These pathways may increase total iron secretion to a maximum of 2 mg, even in large iron excess states.

• An average of 10 mg elemental iron is required in our daily diet to account for the 1mg excreted each day. Women may require as much as 20 mg per day during menstruation.

PHARMACOKINETICS

1. Iron is absorbed in the ferrous (2+) state, and is converted to the ferric (3+) states in vivo. Iron has a direct corrosive effect on the mucosal lining of the GI tract that may result in an increase in the rate and extent of iron absorption.

2. No good mechanism for iron excretion exists. Iron may be cleared renally or by dialysis if it is complexed with the chelator, deferoxamine.

PATHOPHYSIOLOGY

1. Gastrointestinal----> Vomiting and diarrhea, melena, and abdominal pain may occur and may progress to life threatening hemorrhagic gastritis, perforation, and peritonitis.

   • Acute intestinal necrosis may lead to perforation and peritonitis.

   • Survivors of severe gastritis may develop scarring and obstruction four to six weeks after ingestion.

   • Acute gastroenteritis may contribute to early cardiovascular toxicity through fluid and blood loss.

2. Cardiovascular----> (↓BP, ↑HR) Iron toxicity may lead to decreased cardiac output, cardiac arrest and shock. The first stage is probably a direct effect of iron, or ferritin, in causing massive postarteriolar dilatation leading to venous pooling, with a compensatory increase in total peripheral resistance and tachycardia to maintain normal blood pressure. This is followed by capillary leakage and plasma loss with a rising hematocrit and blood viscosity as blood volume and central venous pressure decrease.

   **Hypovolemia/hypoperfusion --> Lactic acidosis/tissue ischemia --> multiple system organ failure and shock

01/11/04
3. **Metabolic** --> **Metabolic acidosis** is commonly seen with severe iron overdose. There are two primary mechanisms by which severe metabolic acidosis may occur.

   a. Following absorption, ferrous iron is converted to ferric iron resulting in the liberation of a free unbuffered hydrogen ion.

   b. Intracellular iron impairs mitochondrial metabolism by disrupting oxidative phosphorylation and results in free radical formation and lipid peroxidation.

4. **Central Nervous System** --> (_CNS)_ depressed sensorium, ranging from mild obtundation to profound coma.
   
   - Coma early in the postingestion period carries a grave prognosis.

5. **Hepatic** --> Liver damage occurs infrequently but may result in hepatocellular damage and necrosis. Laboratory evidence of such damage includes elevated SGPT levels, hypoglycemia, prolonged prothrombin time, and elevated bilirubin values. May see evidence of jaundice, coagulopathy and disseminated intravascular coagulogulation (DIC) in patients with impending liver failure.

### CLINICAL MANIFESTATIONS

<table>
<thead>
<tr>
<th>PHASE</th>
<th>Time Post-Ingest</th>
<th>GI</th>
<th>CNS</th>
<th>CV</th>
<th>OTHER</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (early acute)</td>
<td>0-6 hours</td>
<td>Nausea, vomiting, diarrhea, abdominal pain, melena, hematemesis</td>
<td>Lethargy, Coma</td>
<td>Pallor, tachycardia, hypotension</td>
<td></td>
</tr>
<tr>
<td>II (quiescent)</td>
<td>6 to 24 hours</td>
<td>(Not always present. May go directly to III)</td>
<td>Intermittent lethargy</td>
<td></td>
<td></td>
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<tr>
<td>III (systemic toxicity)</td>
<td>12-48 hours</td>
<td>Hematemesis, melena</td>
<td>Lethargy, Coma, Seizures</td>
<td>Cyanosis, CO, Vasomotor collapse, Shock Pulmonary edema</td>
<td>Metabolic acidosis, Coagulopathy, Renal Failure</td>
</tr>
<tr>
<td>IV</td>
<td>2-3 Days</td>
<td></td>
<td></td>
<td></td>
<td>Hepatic Failure</td>
</tr>
<tr>
<td>V (late)</td>
<td>2-8 weeks</td>
<td>Gastric scarring, Pyloric obstruction</td>
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**Diagnostic Testing, Laboratory Evaluation, and Predictors of Toxicity**
THE TWO LEADING DIAGNOSTIC TOOLS FOR VERIFYING SIGNIFICANT IRON POISONING IN THE ASYMPTOMATIC OR MILDLY SYMPTOMATIC PATIENT ARE SERUM IRON CONCENTRATIONS AND AN ABDOMINAL X-RAY.

1. PEAK SERUM IRON CONCENTRATIONS------> MEASURE 3 TO 5 HOURS POST-INGESTION

- Verify peak iron concentrations with follow-up levels. Chewable preparations may peak 2 to 4 hours post-ingestion; Sustained-release preparations may have delayed peaks > 6 hours post-ingestion.

- After six hours post-ingestion, concentrations may fall owing to the rapid distribution of iron from the blood into soft tissues and the liver.

- Recently, the usefulness of a serum total iron-binding capacity (TIBC) has been questioned. Theoretically, if the TIBC is greater than the serum iron concentration, then all the serum iron in the blood should be in the non-toxic bound form. Traditionally, serum TIBC has been routinely measured in iron overdose cases and if the serum iron conc. > TIBC then chelation therapy is started to bind and eliminate the potentially toxic unbound iron. However, the TIBC may become falsely elevated as serum iron concentrations exceed 400 to 500 µg/dl such that the serum iron concentrations "chase" but never surpass the TIBC despite potentially serious elevations in serum iron. **The TIBC must not be considered a reliable tool for clinical decision making when managing a potential iron poisoning.**

<table>
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<tr>
<th>IRON CONCENTRATION ( µg/dL )</th>
<th>POTENTIAL SEVERITY</th>
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<tbody>
<tr>
<td>Under 150</td>
<td>Normal</td>
</tr>
<tr>
<td>150 - 350</td>
<td>Minimum toxicity (mild phase I symptoms)</td>
</tr>
<tr>
<td>350 - 500</td>
<td>Moderate toxicity ; chelation may not be necessary(risk of serious hepatic or metabolic aberrations is slight)</td>
</tr>
<tr>
<td>500 - 1000</td>
<td>Serious toxicity: start chelation immediately</td>
</tr>
<tr>
<td>Over 1000</td>
<td>Potentially lethal poisoning: start maximum chelation immediately</td>
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2. ABDOMINAL RADIOGRAPH

- Intact adult iron supplement tablets are radiopaque and may be easily seen on an abdominal X-ray. **The presence of a large number of tablets in the stomach and intestine may help verify a significant potentially life-threatening exposure.**

- Must specify abdominal radiograph (aka. KUB or abdominal flat-plate) when ordering the radiological evaluation. A chest x-ray may not effectively capture radiopaque material present in the bowels.

- Ingested Childrens Chewable Multivitamins with iron do not effectively appear on abdominal X-rays, most likely because of the relatively lower iron content and the fact that the tablets have been readily chewed, crushed, and dissolved.

- A negative abdominal X-ray does not rule out the possibility that a significant iron exposure has occurred.

- Abdominal X-ray also is useful as a guide to determine the effectiveness of gastrointestinal decontamination therapy, particular with regard to whole bowel irrigation.

3. **Other predictors of potentially serious iron toxicity when serum iron concentrations are not available.**
• Presence of severe gastroenteritis, hematemesis, hypotension, shock, decreased mental status, or coma.

• Presence of reddish brown ("vin rose") urine following administration of deferoxamine
  If any unbound iron is present, the chelated complex should theoretically turn the urine to a light orange to dark, reddish brown ("vin rose") color. However, a negative challenge test does not rule out the possibility of potentially serious iron intoxication.

4. Other laboratory tests useful for patient assessment and monitoring:
   • Electrolytes and arterial blood gases for fluid/electrolyte abnormalities and metabolic acidosis.
   • Complete Blood Count (CBC), coagulation studies (PT and APTT), liver (AST, ALT, T.bili) and renal function tests (serum creatinine, BUN, baseline urinalysis, urine output)

5. Type and crossmatch patient's blood.

TREATMENT

1. Supportive measures ——> Airway, Breathing and Circulation (ABCs) ——> Establish dual IV access!! Patients who report with severe gastrointestinal symptoms such as hematemesis, melena, profound vomiting and/or diarrhea, shock, or coma, require urgent intensive care. The first priority is to insure an airway and establish reliable venous access. Such patients will need intravenous chelation therapy and may need massive fluid resuscitation: thus, it will be necessary to place at least one large gauge (preferably central) catheter for volume replacement and a second line for deferoxamime infusion.

   Hemodynamic Compromise: (ÿBP, hypovolemia/hypoperfusion, shock)

   • Volume replacement/fluid resuscitation
   • Vasopressors and/or inotropes (eg. dopamine, dobutamine, norepinephrine)
   • Respiratory support
   • Blood transfusion
   • Correction of metabolic acidosis
   • Place on cardiac monitor

2. Gastrointestinal Decontamination
   a) Whole bowel irrigation (polyethylene glycol electrolyte lavage solution or GoLytely)
      • The most effective means of GI decontamination in the setting of significant iron overdose.

   INDICATION: Any case involving > 60 mg/kg elemental iron ingestion and/or iron opacities are visualized on abdominal X-RAY.

   DOSE
   • Adult WBI = 2 liters per hour
   • Pediatric WBI = 0.5 Liters per hour (20-25 ml/kg/hour)
   • Antiemetics, preferably ondansetron (Zofran) or ganisetron (Kytril) should be used to control vomiting that invariably occurs with WBI.

   Endpoint of Treatment with WBI: Administer until a clear rectal effluent is achieved and abdominal x-ray is negative for tablet fragments. WBI may be required for extended periods of time in some cases (1-3 days) in order to clear tablet fragments from the GI tract.
**IT IS IMPORTANT THAT X-RAY MONITORING AND TABLET COUNTS BE USED TO VERIFY THAT IRON TABLETS HAVE BEEN REMOVED, PASSED (OR DISSOLVED).**

b) **Ipecac** induced emesis—> Routine use in iron overdose cases has fallen out of favor in recent years. Some poison centers still use SOI in home management (<40 mg/kg) of iron overdose and some ER clinicians still consider it a potentially useful means of gastric decontamination. A drawback to using SOI is that it eliminates the ability to observe for iron-induced emesis, one of the primary initial symptoms or iron poisoning.

c) **Gastric lavage** with a large-bore orogastric tube (30-40 F for adults and 16-26 F for children). Gastric lavage frequently fails to remove iron tablet fragments in the stomach, primarily due to bezoar formation and the ability of the iron tablets to adhere to the lining of the stomach wall.

d) GI chelation—> CONTROVERSIAL!!!
   - Phosphate and bicarbonate solutions as well as orally administered deferoxamine have been used in the past to theoretically decrease iron absorption. The efficacy and safety of orally administered complexation agents are as yet to be demonstrated by a well designed clinical study. Many poison control centers and emergency departments will routinely recommend lavage with a 2-5% sodium bicarbonate solution then leave 50 to 100 ml in the stomach after emesis or lavage. **At present, there is not enough evidence to indicate that any of the above solutions are better than conventional methods.**

e) Activated charcoal—> iron does not significantly adsorb to charcoal. **Give AC if suspect co-ingestants!!**

f) Surgery
   - Heroic cases of gastrotomy procedures to remove tablet fragments and iron bezoars have been reported but this intervention is highly discouraged due to the high degree of morbidity associated with gastrotomy, and the success reported with use of Whole Bowel Irrigation.
   - A recent potentially life-threatening iron overdose case in Minnesota resulted in a successful outcome after a novel procedure (gastroscopy) was employed to manually remove iron tablets from a 2-yo child's stomach. This child never had iron concentrations exceeding 500 mcg/dL.

3. Chelation Therapy—> **DEFEROXAMINE**
   - 100 mg deferoxamine will bind 9 mg iron (exclusively binds ferric ion in vivo) to form a water-soluble complex, ferrioxamine, which is excreted renally (also hemodialyzable).
   - Deferoxamine inactivates cytoplasmic and mitochondrial iron, preventing the disruption of mitochondrial function and cell injury.
Indications for DEFFEROXAMINE:

- Serum iron > 500 µg/dl
- Serum iron > 350 µg/dl and patient showing symptoms of mild iron toxicity (vomiting).
- Positive deferoxamine challenge test and/or symptoms.
- Severe systemic toxicity (hypotension, shock) and/or severe GI symptoms (protracted vomiting, diarrhea, melana, hematemesis)
- Definitive evidence of a serious exposure (i.e. abdominal x-ray demonstrates numerous tablets in GI tract)

a.) Initial IV dose = 15 mg/kg/hr maximum (more rapid IV infusions have led to hypotension and tachycardia).
   - Start at 10 mg/kg/hour and titrate up to 15 mg/kg/hour. Watch for hypotension or rashes during infusion!!
   - IM Dose: 90 mg/kg Q6-8 hours up to a maximum of 1000 mg per dose in a child; 2000 mg per dose in an adult.

b.) As the patient improves, the dose may be reduced to 10 mg/kg/hr x 8 hours, then 5 mg/kg/hr until serum iron <100 µg/dl or urine is no longer red

c.) Maximum daily dose listed by the manufacturer is 6 gm. Higher daily doses have been used but reports of pulmonary toxicity and ocular toxicity may warrant a more cautious approach to daily dosing.

d.) Deferoxamine/adverse reactions
   - Hypotension and rash----> generally associated with infusion rates > 15 mg/kg/hr
   - Ocular toxicity----> visual disturbances and vision loss.
   - Pulmonary----->Acute Respiratory Distress Syndrome ( ARDS)

e.) Drug/lab interactions
   - Presence of deferoxamine in serum can give falsely low serum iron concentrations. This may be circumvented by adding a reducing agent (0.5 ml of a 10% thioglycolic acid solution) to the test pack solutions.

4. Exchange transfusion
   - Difficult to set up and clinical experience is limited.
   - Human and animal studies have shown favorable results.

5. Hemodialysis
   - In the event of acute renal failure, chelation may be continued with concurrent hemodialysis since the complex is dialyzable.

SUGGESTED READINGS